Effects Of A Novel, High-Intensity Aerobic Interval Training Program on Diastolic And Cardiovascular Function In Patients With Heart Failure With Preserved Ejection Fraction.

by

Siddhartha Angadi

A Dissertation Presented in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

Approved April 2012 by the
Graduate Supervisory Committee:

Glenn Gaesser, Chair
Chong Lee
Farouk Mookadam
Sonia Vega-López
Pamela Swan

ARIZONA STATE UNIVERSITY

May 2012

ABSTRACT

Heart failure is a major worldwide health concern and is the leading cause of hospitalization among elderly Americans. Approximately 50% of those diagnosed with heart failure have heart failure with preserved ejection fraction (HFPEF). HFPEF presents a therapeutic dilemma because pharmacological strategies that are effective for the treatment of heart failure and reduced ejection fraction have failed to show benefit in HFPEF. Long term moderate intensity exercise programs have been shown to improve diastolic function in patients HFPEF. High intensity interval training (HIIT) has been shown to improve diastolic function in patients with heart failure and reduced ejection fraction. However, the effects of high intensity interval training in patients with HFPEF are unknown. Fourteen patients with HFPEF were randomized to either: (1) a novel program of high-intensity aerobic interval training (n = 8), or (2) a commonly prescribed program of moderate-intensity (MOD) aerobic exercise training (n = 6). Before and after four weeks of exercise training, patients underwent a treadmill graded exercise test for the determination of peak oxygen uptake (VO_2peak), a brachial artery reactivity test for assessment of endothelium-dependent flow-mediated dilation (BAFMD), aortic pulse wave velocity assessment as an index of vascular stiffness and two-dimensional echocardiography for assessment of left ventricular diastolic and systolic function. I hypothesized that (1) high-intensity aerobic interval training would result in superior improvements in FMD, aortic pulse wave velocity, VO_2peak, diastolic function and, (2) changes in these parameters would be correlated with changes in

VO_2peak. The principal findings of the study were that a one month long high intensity interval training program resulted in significant improvements in diastolic function as measured by two-dimensional echocardiography [pre diastolic dysfunction (DD) grade – 2.13 $\pm$ 0.4 vs. post DD grade – 1.25 $\pm$ 0.7, p = 0.03]. The left atrial volume index was reduced in the HIIT group compared to MOD (- 4.4 $\pm$ 6.2 ml/m^2 vs. 5.8 $\pm$ 10.7 ml/m^2, p = 0.02). Early mitral flow (E) improved in the HIIT group (pre - 0.93 $\pm$ 0.2 m/s vs. post - 0.78 $\pm$ 0.3 m/s, p = 0.03). A significant inverse correlation was observed between change in BAFMD and change in diastolic dysfunction grade (r = - 0.585, p = 0.028) when all the data were pooled. HIIT appears to be a time-efficient and safe strategy for improving diastolic function in patients with heart failure and preserved ejection fraction. These data may have implications for cardiovascular risk reduction in this population.

ACKNOWLEDGMENTS

I would like to thank the ASU-Mayo seed grant program. Without the funding provided through this mechanism this study would have been impossible. I would also like to thank our patients for their patience when things did not go exactly as planned as well as their diligence in following through with the study and for ensuring that the trial would come to fruition.

Barbara Knight who was the clinical coordinator for the study deserves praise for her deft patient handling/scheduling skills and well as her ability to sort out the occasional and troublesome billing issues that constantly raised their heads at the clinic. The fine folks in the department of cardiac rehabilitation (Holly, Ann, Jean, Dimitra, Jenelle and Christy) were instrumental towards the completion of the study as they handled a lot of the minor day to day issues associated with exercise training in this aged population. Their patience and attentiveness contributed in no small way to the success of this study.

I would like to thank Farouk Mookadam who helped me navigate the complex corridors of the Mayo Clinic both literally and figuratively. The training he imparted to me with regard to 2D echocardiography and arterial stiffness testing was invaluable and helped me improve my skillset. His sagely advice whenever things went for a loop was invaluable.

Glenn Gaesser was a terrific mentor and friend. He has consistently challenged me throughout my tenure as his graduate student. I have learned a plethora of invaluable skills from him. He taught me to question everything. I will

miss being a fellow intellectual mercenary with him and it was honor to work with him these past years.

Thank you to all my friends. You kept me sane along the way. And finally, my deepest gratitude goes to Mom, Dad and my sister, Chinka. Putting up with me for all these years was no mean task. My journey from precocious brat to a doctoral candidate was a long one. Thanks for all the support and love.

TABLE OF CONTENTS

Page

LIST OF TABLES vi

LIST OF FIGURES vii

CHAPTER

1 INTRODUCTION 1

Hypothesis and Specific Aims 5

2 REVIEW OF LITERATURE 6

HFPEF: Risk factors, diagnosis and pathophysiology 6

Grading and prognosis in patients with diastolic dysfunction 12

Ventricular-vascular coupling in HFPEF 13

Exercise and vascular compliance in HF 15

Heart failure and endothelial function 17

VO_2peak: A predictor of disease risk and target of therapy in heartfailure 21

Pathophysiology of ventilatory abnormalities in congestive heart failure 24

Health related quality of life and depression in the setting of congestive heart failure 26

3 METHODS AND MATERIALS 29

Sample size and analysis 37

Statistical analysis 39

CHAPTER Page

4 RESULTS 40

Within-group effects 40

Between-group effects 46

Relationship between vascular function and left ventricular diastolic function 49

5 DISCUSSION 51

6 CONCLUSION 55

REFERENCES 56

APPENDICES

A Short form – 12 quality of life questionnaire 71

B Beck Depression Inventory 74

C Institutional Review Board Approval 77

LIST OF TABLES

Table		Page
1.	Sample size estimation	38
2.	Baseline characteristics of subjects	41
3.	Within-group effects of high intensity interval training	43
4.	Within-group effects of moderate intensity training	45

LIST OF FIGURES

Figure		Page
1.	CONSORT Diagram	30
2.	Changes in diastolic function in both exercise training groups	47
3.	Changes in left atrial volume index after training	48
4.	Relationship between BAFMD and diastolic function	50

Chapter 1

INTRODUCTION

Heart failure is a major worldwide health concern and is the leading cause of hospitalization among elderly Americans. Currently 5.7 million Americans are estimated to have heart failure and the estimated direct and indirect costs of treating heart failure are approximately $37.2 billion (Lloyd-Jones et al., 2009). Approximately 40-50% of those diagnosed with heart failure will have heart failure with preserved ejection fraction (HFPEF) and the remainder will display reduced ejection fraction (HFREF) (Borlaug & Redfield, 2011a; Vasan, Benjamin, & Levy, 1995).

The heart failure phenotype across these two clinical conditions is very similar. Patients with heart failure typically present with a constellation of symptoms such as dyspnea, fatigue, exercise intolerance, peripheral / pulmonary edema, rales and gallops. From a hemodynamic standpoint heart failure is best defined as the inability of the heart to "provide adequate cardiac output to the body at rest or with exertion, or to do so only in the setting of elevated cardiac filling pressures."(Borlaug & Redfield, 2011a) Although, phenotypically the two heart failure syndromes are similar, mechanistically they behave rather differently. This is made abundantly clear by the fact that state of the art pharmacotherapy has improved morbidity and mortality in patients with heart failure and reduced ejection fraction but failed to do so in patients with heart failure and preserved ejection fraction (Borlaug & Redfield, 2011a). It is important to note that individuals with heart failure have significant restrictions in

their ability to carry out activities of daily living and the condition places a significant burden on patients, families and long-term care systems due to higher rates of disability, geriatric conditions and nursing home admissions (Gure, Kabeto, Blaum, & Langa, 2008).

Exercise training has been established as adjuvant therapy in heart failure (Tabet et al., 2008). Although aerobic exercise training guidelines for treatment of heart failure with reduced ejection fraction (HFREF) are well established, no consensus exercise guidelines exist for management of HFPEF (Pina et al., 2003). Exercise training increases VO_2peak, thus improving prognosis for patients with heart failure (Tabet et al., 2009). Indeed, VO_2peak has been reported to be the single best predictor of mortality in those with cardiac disease (Kavanagh et al., 2002). Exercise training also improves endothelial function and reduces arterial stiffness, as well as enhancing quality of life (Hambrecht et al., 2000; Wisloff et al., 2007). This is critical because HFPEF is associated with significant diastolic dysfunction, a loss of compensatory systemic vasodilator reserves, arterial stiffness and endothelial dysfunction (Borlaug et al., 2006).

Aerobic and cardiovascular adaptations are generally greater after high-intensity exercise training; interval-type exercise facilitates this type of training because it allows for rest periods that make it possible for patients with heart failure to perform short (e.g., 1-4 minutes) work periods at intensities that are higher than would be possible during continuous exercise (Wisloff et al., 2007). For example, Wisloff *et al.* demonstrated the superiority of high-intensity aerobic interval training, as compared to continuous, moderate-intensity exercise training,

in patients with stable post-infarction heart failure (with reduced ejection fraction) (Wisloff et al., 2007). Not only were VO_2peak and FMD improved by a greater extent, patients tolerated the high-intensity program without reported incidents. Furthermore, they found it "motivating to have a varied procedure to follow," whereas patients found the continuous exercise group training sessions to be "quite boring."

High-intensity aerobic interval training presents a unique, yet untested, therapeutic modality for the exercise training of patients with heart failure with preserved ejection fraction. Interestingly, current exercise training guidelines for HF state, "training intensity does not seem to directly influence the magnitude of the increase in exercise tolerance (Pina et al., 2003)." However, there are compelling published data to suggest that high-intensity interval training may be a superior and time-efficient training strategy in patients with heart failure and reduced ejection fraction (Wisloff et al., 2007). The authors also presented convincing data that showed significant improvements in diastolic function that may be relevant to patients with HFPEF.

Pilot testing of high-intensity interval training in patients with heart failure with preserved ejection fraction is warranted. Results of pilot testing may have important implications for reducing cardiovascular risk, increasing short- and long-term quality of life and survival, and reducing healthcare costs in this patient population (Georgiou et al., 2001; M. F. Piepoli, Davos, Francis, & Coats, 2004). Patients with heart failure that undergo moderate-intensity exercise training live on average 2.16 years longer at the extremely low cost-effectiveness ratio of

$1494 per life year saved (Georgiou et al., 2001). It is important to note that the majority of the HF patient population belongs to the Medicare age group. Thus, this intervention has significant potential to reduce healthcare costs. From the viewpoint of patient safety, present data from Wisloff and colleagues states that there have been no significant adverse events associated with high intensity interval training in over 2000 patient hours (U. Wisloff, Ellingsen, & Kemi, 2009). The primary goal of this proposed study was to examine the efficacy of a novel, short-term, high intensity interval training program to a more traditional moderate intensity training program in patients with HFPEF.

Hypotheses and Specific Aims

The primary specific aim was to determine the efficacy of a novel, high-intensity aerobic interval exercise training program for improving VO_2peak, endothelial function, arterial stiffness and left ventricular diastolic function in patients with HFPEF. A secondary aim was to determine whether the vascular changes are correlated with the changes in VO_2peak.

I hypothesized that improvements in VO_2peak, endothelial function, arterial stiffness and diastolic function would be greater after the high-intensity aerobic interval training program compared to traditional moderate intensity exercise and that, these adaptations would be correlated with changes in VO_2peak.

Chapter 2

REVIEW OF LITERATURE

Heart failure with preserved ejection fraction: Risk factors, diagnosis and pathophysiology

The major risk factor responsible for the development of heart failure regardless of ejection fraction is hypertension. The prevalence of hypertension is greater in HFPEF, nevertheless it is common to both forms of heart failure (Levy, Larson, Vasan, Kannel, & Ho, 1996). Many of the pathophysiological derangements that are observed in HFPEF appear to present as a continuum with hypertensive heart disease (Borlaug, Lam, Roger, Rodeheffer, & Redfield, 2009; Borlaug, Olson et al., 2010; Lam et al., 2007; Melenovsky et al., 2007). These factors when coupled with the loss of contractile reserve, impaired vasodilation, endothelial dysfunction and reduced diastolic reserve appear to promote the transition to heart failure with preserved ejection fraction (Borlaug et al., 2006; Borlaug, Nishimura, Sorajja, Lam, & Redfield, 2010; Borlaug, Olson et al., 2010; Brubaker et al., 2006).

Heart failure with preserved ejection fraction can be diagnosed invasively through cardiac catheterization (relatively uncommon) or utilizing non-invasive modalities such as two-dimensional echocardiography and plasma levels of natriuretic peptides (Nagueh et al., 2009; Paulus et al., 2007). Echocardiography plays a central role in the non-invasive assessment of left ventricular diastolic function. Its low cost and ease of accessibility make it the ideal modality for the routine evaluation of diastolic function / dysfunction.

Optimal performance of the left ventricle depends upon its ability to cycle between two states, namely: 1) diastolic filling which is dependent upon a compliant chamber that allows the left ventricle to fill from low left atrial pressure and, 2) systolic ejection which is the rapid ejection of the stroke volume from the left ventricle. The stroke volume (i.e. the volume of blood ejected by the left ventricle during ventricular systole) must increase in response to demands such as exercise without a concomitant rise in left atrial pressures (Brutsaert, Sys, & Gillebert, 1993).

In the setting of diastolic dysfunction the main physiological consequence is an elevation of left ventricular (LV) filling pressures which has been demonstrated invasively (Brutsaert et al., 1993) and can be measured using echocardiography as well (Nagueh et al., 2009). Typically exercise results in minimal elevations in filling pressures. Exercise induced elevations in filling pressure can however limit exercise capacity and indicate diastolic dysfunction. In subjects with occult diastolic dysfunction, measuring diastolic function in the setting of an exercise test can help unmask it.

Left ventricular filling is largely determined by the interplay between LV filling pressures and filling properties (viz., end-diastolic properties such as compliance and stiffness) (Nagueh et al., 2009). Both intrinsic and extrinsic factors can affect these. Extrinsic factors include pericardial restraint and its ventricular interaction. Intrinsic factors include myocardial stiffness, myocardial tone, chamber geometry (concentric vs. eccentric remodeling) and wall thickness (Leite-Moreira, 2006).

Some important morphological correlates of diastolic function are: 1) left ventricular hypertrophy, 2) left atrial volume and, 3) pulmonary artery systolic and diastolic pressures. These are typically quantified with two-dimensional echocardiography (2D-Echo).

1. Left ventricular hypertrophy is amongst the important reasons for diastolic dysfunction. In HFPEF, concentric hypertrophy (increased left ventricular mass and thickness) or remodeling (normal mass but increased relative wall thickness) are typically observed. In case of pathological left ventricular hypertrophy, LV relaxation is slowed which results in reduced early diastolic filling (E). As a result, this shift a greater proportion of LV filling to late diastole after atrial contraction (A) which results in changes that are observed in the E/A ratio that are observed with diastolic dysfunction. The lowering of the E/A ratio (<0.8) is one of the important diagnostic features of early stage diastolic dysfunction, although with worsening disease severity a pseudonormalization is typically observed.
2. Left atrial (LA) volume can be reliably and accurately measured with 2D-echo (Nagueh et al., 2009). An LA volume index of $\geq$ 34 ml/m^2 is an important predictor of death, heart failure, atrial fibrillation and ischemic stroke (Abhayaratna et al., 2006).
3. Pulmonary artery systolic and diastolic pressures are important functional correlates of diastolic dysfunction as well. Patients with signs of HF and diastolic dysfunction typically have elevated

pulmonary artery pressures. Once, pulmonary disease is ruled out it becomes safe to infer that elevated pulmonary arterial pressures are a direct consequence of elevated left ventricular filling pressures.

Systolic pulmonary arterial pressures (S) are non-invasively determined by isolating the physiological tricuspid regurgitation (TR) jet using continuous-wave Doppler together with systolic right atrial pressure. The formula used is as follows:

$4 * (\text{velocity of TR jet})^2$ = pulmonary arterial systolic pressure – right atrial pressure.

Similarly, pulmonary artery diastolic pressure (D) can be calculated by estimating the velocity of the pulmonary regurgitation (PR) jet and applying the formula:

$4 * (\text{end-diastolic velocity of PR jet})^2$ = pulmonary arterial diastolic pressure – right atrial pressure.

Other important correlates of diastolic function include inflow patterns specifically at the mitral valve and their associated hemodynamics. Mitral inflow patterns are identified by the mitral E/A ratio, deceleration time and the isovolumetric relaxation time. They can help determine if normal, impaired LV relaxation, pseudonormal or restrictive filling patterns exist which correspond to worsening degrees of diastolic dysfunction. These patterns are very valuable from a clinical standpoint as they are correlated better with cardiac filling pressures, New York Heart Association Functional (NYHA) class, and prognosis as compared to left ventricular ejection fraction (Nagueh et al., 2009). Age-

appropriate values for all variables have been reported previously and are considered when grading and diagnosing diastolic dysfunction (Nagueh et al., 2009). Mitral valve flow patterns can be difficult to accurately quantify in the setting of elevated heart rates (sinus tachycardia, atrial fibrillation, atrial flutter) and present a fair bit of diagnostic difficulty. In case a pseudonormalized filling pattern is present the patient is asked to perform a Valsalva maneuver (forceful expiration ~ 40 mmHg against a closed nose and mouth) which can help differentiate a pseudonormal E/A ratio from a normal one. A fall in the E/A ratio by $\geq$50% is highly specific for elevated left ventricular filling pressures (Hurrell, Nishimura, Ilstrup, & Appleton, 1997).

Pulmonary venous flow is another important physiological variable that needs to be assessed for the accurate assessment of diastolic function. Principle measurements that are recorded are the peak systolic velocity (S), peak antegrade diastolic velocity (D) and peak atrial reversal velocity in late diastole. Peak systolic velocity is composed of two components, S1 and S2. S1 is related to atrial relaxation and hence, S2 (which is related to stroke volume and pulse wave propogation down the pulmonary arterial tree) is used to compute the ratio of peak systolic to peak diastolic velocity.

Diastolic velocity (D) is affected by changes in left ventricular filling and compliance and changes synchronously along with changes in mitral E velocity. Pulmonary venous atrial reversal velocity and duration are influence by left ventricular late diastolic pressures, atrial preload and left atrial contractility. A reduction in left atrial compliance along with an in increase in left atrial pressure

results in a reduction of S velocity and increases the D resulting in an S/D ratio < 1. Increased left ventricular end-diastolic pressure results in increased atrial reversal velocity and duration. Pulmonary venous inflow velocities are influenced by age and that is taken into consideration when the values obtained are evaluated.

Another important variable that is obtained via echocardiography using tissue Doppler imaging is e'. This is the early diastolic annular velocity and it's typically viewed in the context of the ratio between E and e'. The E/e' ratio plays an important role in the estimation of left ventricular filling pressures which are typically adjusted for age. In the presence of impaired left ventricular relaxation the e' velocity is reduced and delayed which can lead to an elevated value for the E/e' ratio. A septal E/e' ratio < 8 is usually associated with normal left ventricular filling pressures whereas a ratio > 15 is associated with elevated filling pressures. A value between 8-15 is considered indeterminate and other echocardiographic indices need to be used. E/e' is highly predictive of adverse events in patients with hypertensive heart disease, mitral regurgitation, end-stage renal disease, atrial fibrillation and cardiomyopathic disorders (Bruch, Klem, Breithardt, Wichter, & Gradaus, 2007; Dokainish et al., 2005; Hillis et al., 2004; Okura et al., 2006; Redfield et al., 2003; Sharma et al., 2006; Troughton et al., 2005; Wang, Yip, Yu et al., 2005; Wang et al., 2003; Wang, Yip, Wang et al., 2005; Yamamoto et al., 2003). The E/e' ratio is one of the most reproducible echocardiographic parameters that can be used to estimate pulmonary capillary wedge pressure and is the preferred prognostic parameter in a host of cardiac conditions.

All of the above Doppler and echocardiographic measurements are crucial to the accurate estimation of diastolic function and current guidelines for assessing and staging left ventricular diastolic function are built around them.

Grading and Prognosis in patients with diastolic dysfunction

Diastolic dysfunction is graded as: 1) Grade I (mild) – Impaired relaxation pattern, 2) Grade II (moderate) – pseudonormalized filling and, 3) Grade III (severe) – restrictive filling. This grading scheme was an important predictor of all-cause mortality. Even patients with grade I diastolic dysfunction have a five-fold higher 3-5 year mortality in comparison to subjects with normal diastolic function (Redfield et al., 2003).

It is important to note that while neurohumoral antagonism (ß-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers) has been shown to improve morbidity and mortality in heart failure with reduced ejection fraction, similar improvements in patients with HFPEF have not been reported (Borlaug & Redfield, 2011a). Mortality rates are higher in patients with HFPEF as opposed to asymptomatic diastolic dysfunction (87 vs. 154 deaths per 1000 person-years; hazard ratios – 1.48 and 1.88 respectively as compared to patients with no heart failure and normal systolic function) (Gottdiener et al., 2002). HFPEF also appears to be associated with similar rates of mortality as heart failure with reduced ejection fraction (Senni et al., 1998). Other predictors of mortality in patients with HFPEF are incident diastolic dysfunction grade, peripheral artery disease, diabetes, male gender, New York Heart Association

class, older age extent of coronary artery disease and impaired renal function (Ahmed, Aronow, & Fleg, 2006; Hillege et al., 2006; Jones, Francis, & Lauer, 2004; O'Connor, Gattis, Shaw, Cuffe, & Califf, 2000; Persson et al., 2007).

Ventricular-vascular coupling in heart failure with preserved ejection fraction

Ventricular and arterial stiffening is common in patients with heart failure and preserved ejection fraction (Borlaug & Kass, 2008). This typically occurs through a combination of factors such as age, hypertension, diabetes mellitus and renal dysfunction. A stiff vascular tree is detrimental from the standpoint of late systolic load as wave reflections (e.g. from arterial bifurcations) are greater. This increase in net systolic afterload alters systolic and diastolic function and increases cardiac workload leading to a net increase in myocardial oxygen consumption. This in turn leads to an impaired cardiovascular reserve. Arterial afterload has a profound impact on ventricular diastolic relaxation and compliance (Borlaug & Kass, 2008).

Good cardiovascular function is dependent upon effective ventricular-vascular coupling. Cardiac afterload is defined in several ways. It is often considered to be equivalent to systolic blood pressure but that ignores several important variables and often results in erroneous estimations. Systemic blood pressure is determined by ventricular-vascular coupling as well as preload, contractility and heart rate (Kass & Kelly, 1992). Coupling of the heart and the vasculature is typically expressed using the ratio Ea/Ees (Ea – effecteive arterial

elastance; Ees – end systolic elastance) (Kass & Kelly, 1992; Sunagawa, Maughan, Burkhoff, & Sagawa, 1983; Sunagawa, Maughan, & Sagawa, 1985). In essence, Ees is a measure of ventricular stiffness and the numerator represents vascular load. With normal aging the Ea/Ees ratio is preserved in men but declines somewhat in women because the Ees appears to rise out of proportion to increases in Ea.

Increases in ventricular and vascular stiffness affect cardiac reserve and that is especially evident in the setting of exercise stress. Warner and colleagues studied the acute effects of angiotensin receptor blockade using losartan in asymptomatic patients with echo evidence of diastolic dysfunction (Warner, Metzger, Kitzman, Wesley, & Little, 1999). Losartan administration resulted in blunted peak systolic pressures during exercise, increased time to BP >190 mmHg and resulted in a 10% increase in peak oxygen consumption. This effect on peak exercise oxygen uptake may not be due to the BP lowering aspect of losartan administration. Recently Little *et al* examined the effects of losartan administration and compared them to hydrochlorothiazide administration in patients with diastolic dysfunction (Little et al., 2006). Although, blood pressures were equivalently lowered in the losartan and hydrochlorothiazide groups, only the losartan group showed improved exercise performance and improvements in quality of life. This suggests that the ventricular and vascular effects of angiotensin receptor blockade rather than blood pressure reduction may be responsible for the improvement in VO_2peak, thus, highlighting the critical role that ventricular and vascular stiffness play in determining cardiovascular reserve.

Additionally, it is also important to note that stiff arteries often have compromised endothelium-dependent vasodilation. *In vitro* studies have demonstrated that both the shear stress and vessel distension that occur with pulsatile perfusion influence nitric oxide production. Interestingly, when vessel distension is compromised, Akt (a cytoprotectant regulator of cellular apoptosis and oxidative stress) activation is compromised leading to less activation of nitric oxide synthase (Li, Chiou, Bugayenko, Irani, & Kass, 2005). Since, endothelium dependent vasodilation is a major component of vasodilator reserves it may help explain the poor vasodilator reserves observed in patients with HFPEF. At present however, this remains to be observed *in vivo* studies.

Exercise and Vascular compliance in the context of heart failure

As mentioned in the prior section, arterial compliance is reduced in patients with congestive heart failure (Giannattasio et al., 1995; Lage et al., 1994). Systemic arterial compliance is a significant contributor to cardiac afterload and an important determinant of left ventricular work (Parnell, Holst, & Kaye, 2002) and acute reductions in arterial compliance have also been shown to greatly increase myocardial oxygen demand, reduce diastolic pressure and lower coronary blood flow (since diastolic pressure is essentially equal to coronary perfusion pressure) (Parnell et al., 2002). Vasodilator therapy has been shown to improve the symptomatology of heart failure. Aerobic exercise has considerable effects on vascular compliance as well and may serve as an important adjunct to drug therapy in patients with congestive heart failure (Cameron & Dart, 1994;

Guimaraes et al., 2010; Kelly, Tunin, & Kass, 1992; Rakobowchuk, Stuckey, Millar, Gurr, & Macdonald, 2009; Rakobowchuk et al., 2008).

Acute sprint interval exercise and interval training have been shown to improve central arterial compliance in young healthy subjects (Rakobowchuk et al., 2009; Rakobowchuk et al., 2008). Improvements in arterial compliance have been reported following moderate intensity exercise in healthy subjects and in patients with HF (Cameron & Dart, 1994; Parnell et al., 2002). Parnell and colleagues studied the effects of moderate intensity exercise on systemic arterial compliance in patients with congestive heart failure (Parnell et al., 2002). Twenty-one patients were randomized to either a usual care or a moderate intensity exercise group. Subjects exercised for 8-weeks at 50-60% of their maximum heart rate and progressively increased exercise from three 30 minute sessions per week to 60 minutes 5-7 days/week. Systemic arterial compliance was determined before and after exercise training using applanation tonometry and Doppler aortic velocimetry. Significant improvements were observed in arterial compliance (0.57 $\pm$ 0.11 to 0.77 $\pm$ 0.14 arbitrary compliance units).

At present the effects of interval training on arterial compliance in patients with heart failure and preserved ejection fraction are unknown.

Heart failure and endothelial function

Endothelial function is an emerging risk marker that can potentially be used for risk assessment in patients with congestive heart failure (Katz et al., 2005). Katz et al demonstrated that a 1% reduction in endothelial function (as measured by brachial artery flow mediated dilation) in adults with CHF was associated with a 20% increase in mortality risk in adults with congestive heart failure (CHF) even after adjustment for prognostic indicators such as age, etiology of CHF, New York heart association functional class and ejection fraction.

Endothelial function has been observed to be impaired in subjects with congestive heart failure and may be responsible for significant impairments in systemic and coronary perfusion whilst resulting in increased systemic vascular resistance that places an elevated afterload upon a failing heart (Bauersachs & Schafer, 2004). Impairments in coronary perfusion are analogous to impaired myocardial perfusion and can lead to significant reductions in ventricular performance.

Systemic endothelial dysfunction is observed as soon as 2 hours after a myocardial infarction (Wagner et al., 2001) in animal models of CHF and has significant pathophysiological implications. Impaired left ventricular function in patients with CHF leads to reduced blood flow through conductance and resistance vessels which in turn results in reduced shear stress that results in lowered eNOS expression on the luminal surface of the endothelial cells. Effective nitric oxide (NO) release in these patients may also be significantly

lowered as a consequence of scavenging by reactive oxygen species (ROS) since patients with CHF exhibit increased vascular release of ROS. ROS also appear to be responsible for endothelial cell apoptosis which destroys endothelial cell integrity (Agnoletti et al., 1999; Valgimigli et al., 2003). This damage is typically repaired by marrow derived endothelial progenitor cells; however, it appears that systemic inflammation that accompanies CHF appears to impair the functional capacity of the same (Agnoletti et al., 1999).

Thus it appears that endothelial dysfunction in the setting of CHF is largely a result of reduced vascular NO production and increased production of reactive oxygen species which in turn results in apoptotic destruction of endothelial cells. The systemic inflammation in turn affects the ability of the endothelial progenitor cells to restore the damaged endothelium.

Several pharmacological strategies have been shown to be effective at ameliorating the endothelial dysfunction that is observed in the setting of CHF, such as, the use of angiotensin converting enzyme inhibitors, endothelin antagonism, antioxidants and mineralocortioid receptor blockers (Bauersachs & Schafer, 2004). Aerobic exercise is a low-cost modality that can be utilized to improve/normalize endothelial function in patients with CHF that has been attracting interest in recent years (Erbs et al., 2010; Wisloff et al., 2007).

There is compelling evidence to show that aerobic exercise can result in significant improvements in conduit vessel and resistance artery endothelial function. An improvement in endothelial function in conduit vessels appears to be primarily a result of several events (Hambrecht et al., 2003) - At a cellular level,

exercise induced shear stress results in shear stress induced Akt –dependent increase in phosphorylation of Ser^{1177} in endothelial cells. This in turn, increases the endothelial expression of eNOS resulting in increased activity and enhanced NO production. The correlation coefficient(r) between eNOS expression and Akt expression is 0.8. The correlation between peak arterial flow and eNOS expression is 0.6.

Hambrecht et al (Hambrecht et al., 2003) demonstrated significant improvements in internal mammary artery (IMA) endothelium dependent function. The investigators invasively assessed IMA endothelial function before and after 4 weeks of exercise training. IMA endothelium dependent vasodilation as measured by acetylcholine infusions improved by ~100%. Adenosine mediated flow dependent dilation improved by 150%. The research group also examined IMA tissue that was excised during coronary artery bypass grafting for changes in eNOS expression and found that it was 96% higher as compared to the control group.

Wisloff et al (Wisloff et al., 2007) demonstrated similar findings with regard to improvements in endothelial function in subjects with CHF. Thirty subjects were randomized into control, traditional moderate intensity exercise or high intensity interval training groups (n=10 per group). The group with the high intensity interval training demonstrated the greatest improvements in endothelial function followed by the moderate intensity training group as compared to control. The greater improvements in the high intensity interval training group

may be a consequence of exposure to greater exercise induced shear stress in those patients.

Another novel pathway through which exercise may induce improved endothelial function may be due to enhanced recruitment of endothelial progenitor cells as well as improved activity of the same. Erbs et al (Erbs et al., 2010) demonstrated that a 12 week moderate intensity exercise program in patients with CHF enhanced CD34+ endothelial progenitor cell recruitment by ~40%. These cells also demonstrated an improvement in migratory capacity (in vitro) that could be considered a direct measure of their capacity to home in on damaged and/or ischemic tissue and repair it. The exercise training program also appeared to reduce oxidative stress as evidenced by reductions in lipid peroxides and tumor necrosis factor – α. A complete normalization of radial artery flow mediated dilation was observed in the intervention group was observed.

In summation, exercise training appears to improve peripheral vasomotion (a potent marker of cardiovascular risk in patients with CHF) by –

1. Improving flow mediated dilation through exercise induced shear stress that improves endothelial cell eNOS expression.
2. Reducing oxidative stress which in turn may enhance production and function of endothelial progenitor cells that repair the damaged endothelial lining.

It is important to note that a majority of research with regard to exercise and endothelial function in patients with heart failure appears to utilize moderate intensity exercise (~60% VO_2peak). Recently however, Wisloff et al (Wisloff et

al., 2007) demonstrated the utility of a high intensity exercise program in improving endothelial function in patients with CHF. The long-term, safety and efficacy of high intensity exercise training programs in patients with CHF however remains to be demonstrated.

An important question that needs to be addressed by future research in this field is the minimum dose (time and intensity) of exercise that can elicit the maximum improvements in endothelial function without jeopardizing the safety of this clinically "fragile" demographic. A large, clinical outcome (utilizing hard clinical end-points such as death, stroke, and urgent cardiovascular transplantation) based trial that examines the safety and effectiveness of the exercise dose-response relationship in these patients would be ideally placed to address this concern.

VO_2peak: An important predictor of disease risk and potential target of therapy in heart failure

Cardiorespiratory fitness as quantified by peak oxygen uptake (VO_2peak) is a strong predictor of cardiovascular morbidity and mortality in patients with congestive heart failure (CHF). It is also important to note that patients that improve VO_2peak following exercise training appear to have better outcomes as compared to patients that fail to improve VO_2peak (Tabet et al., 2008).

Tabet and colleagues tested the effectiveness of exercise training in 155 patients with heart failure and reduced ejection fraction (Tabet et al., 2008). All subjects underwent 20 exercise training sessions and were followed-up for 16$\pm$6

months. Multivariate analysis revealed that delta VO_2peak along with baseline BNP levels were the only predictors of adverse cardiovascular events, namely, sudden cardiac death, cardiac transplantation or hospitalization for acute heart failure. The authors concluded that amongst patients with heart failure a lack of improvement in exercise capacity following an exercise training program was a strong prognostic factor that predicted adverse outcomes.

Improvements in VO_2peak following exercise training largely appear to be driven by training intensity (Helgerud et al., 2007; Kemi et al., 2005; Warburton et al., 2005; Wenger & Bell, 1986; Wisloff et al., 2007). Helgerud and colleagues (Helgerud et al., 2007)conducted a randomized controlled trial to examine the differential effects of training intensity on VO_2peak and stroke volume. They demonstrated that a high intensity aerobic interval training program of 4 x 4 minutes of interval running consisting of 4 minutes of running at 90-95% heart rate max (as determined by a graded peak exercise test) followed by 3 minutes of active recovery at 70% heart rate max resulted in greater improvements in VO_2peak and stroke volume.

Warburton et al examined the effects of high intensity interval training in 14 men with stable coronary artery disease. (Warburton et al., 2005) They compared the effects of traditional moderate intensity exercise (65% heart rate reserve/VO_2 reserve) to high intensity interval training [90% heart rate reserve/VO_2reserve (2 minutes on/off)] carried out for 30 min/day, 2 days/week. VO_2peak improved significantly in both groups and improvements in treadmill

time were greater in the interval training group as compared to the moderate intensity group.

Wisloff et al examined the effects of high intensity interval training in patients with heart failure and reduced ejection fraction (Wisloff et al., 2007). The training intensities used were similar to those used by Helgerud and colleagues (of 4 x 4 minutes of interval running consisting of 4 minutes of walking at 90-95% heart rate max followed by 3 minutes of active recovery at 70% heart rate max. VO_2peak improved by 46% versus 14% in the interval training group as compared to the moderate intensity training group. Left ventricular ejection fraction improved by 35% and pro-brain natriuretic peptide decreased 40%. Significant favorable left ventricular modeling occurred and diastolic function improved significantly as well. Since several authors (De Keulenaer & Brutsaert, 2011) have suggested that systolic and diastolic heart failure are overlapping phenotypes within the heart failure spectrum, it is plausible that an interval training strategy may be beneficial for patients with symptomatic heart failure with a preserved ejection fraction i.e. diastolic heart failure.

Although aerobic exercise has historically been shunned in the setting of CHF there is now a robust body of evidence that attests to its safety, efficacy and low-cost per quality adjusted life-year gained. Georgiou et al (Georgiou et al., 2001) demonstrated that exercise training in the setting of heart failure resulted in an increase in life-expectancy by 2.16 years at the low cost-effectiveness ratio of $1494 per life-year saved. Not only that but in a study by Belardinelli et al (Belardinelli, Georgiou, Cianci, & Purcaro, 1999) patients with CHF who

underwent supervised exercise training showed a 63% reduction in cardiac mortality and a 71% reduction in heart failures hospitalizations. An independent predictor of survival in these patients, the post-training thallium activity score index, showed that this appeared to be a result of improved coronary perfusion which appeared to be independent of the severity and number of stenosis of the epicardial coronary arteries.

Pathophysiology of ventilatory abnormalities in congestive heart failure

As mentioned in the previous section, the cardiopulmonary exercise test (CPET) has considerable prognostic importance in the management of congestive heart failure. Other than oxygen uptake (VO_2) several other ventilatory components are measured during a CPET such as carbon dioxide production (VCO_2) and minute ventilation (VE).

The VE/VCO_2 relationship has been shown to be of prognostic importance in patients with CHF as well (Arena, Myers, Aslam, Varughese, & Peberdy, 2004; Koike et al., 2002). The rise in VE and VCO_2 with increasing exercise intensity is coupled to increased carbon dioxide levels that are the result of increased metabolic rate as well as buffering. During a typical CPET the VE/VCO_2 slope is linear until a non-linear break point called the anerobic threshold is reached. Larger increases in the slope are associated with a worse prognosis in patients with CHF. Slope ranges from 17 – 69 have been reported in patients with heart failure (Arena, Myers, Aslam, Varughese, & Peberdy, 2003).

There are several potential causes behind the elevated VE/VCO_2 slope that is observed in patients with congestive heart failure, viz., ventilation perfusion abnormalities, declining cardiac output, increased right sided vascular pressures that contribute to ventilation perfusion abnormalities, depressed nitric oxide production in the pulmonary vascular tree and heightened activation of central / peripheral chemoreceptors as well as skeletal muscle ergoreceptors (Adachi et al., 1997; Banning, Lewis, Northridge, Elborn, & Hendersen, 1995; Chua, Clark, Amadi, & Coats, 1996; Lewis et al., 1996; M. Piepoli et al., 1996; Ponikowski et al., 2001; Reindl et al., 1998; Uren et al., 1993; Wada et al., 1993).

The prognostic value of the VE/VCO_2 slope has been extensively studied in patients with heart failure and reduced ejection fraction. Interestingly, in patients with heart failure and preserved ejection fraction Guazzi and colleagues demonstrated that the VE/VCO_2 slope was superior to VO_2peak (Guazzi, Myers, & Arena, 2005). A slope threshold of 34 units has been used to differentiate between high and low-risk patients in several studies while other authors have used multiple cut-points (<28, 28-35, 35-42 and >42). The prognosis is less favorable with an increase in the slope (Arena et al., 2004; Chua et al., 1997; Corra et al., 2002; Francis et al., 2000).

Exercise training has been shown to improve the VE/VCO_2 slope. Myers et al demonstrated that a two month long aerobic exercise program lowered the VE/VCO_2 slope by ~6 units in patients with post myocardial infarction systolic dysfunction (Myers, Dziekan, Goebbels, & Dubach, 1999). Guazzi *et al* reported a ~5 unit reduction in the VE/VCO_2 slope following two months of exercise

training in patients with CHF (Guazzi, Reina, Tumminello, & Guazzi, 2004). Guazzi et al also demonstrated significant improvements in lung diffusion (25%), alveolar-capilarry conductance (15%), pulmonary capillary blood volume (10%), VO_2peak (13%) and brachial artery flow mediated dilation (71%).

At this point however, no long term study has examined the effects of changes in ventilatory parameters and survival in patients with CHF. The effects of high intensity interval training on ventilation abnormalities in patients with HFPEF are unknown.

Health related quality of life and depression in the setting of congestive heart failure

Health related quality of life (HRQOL) may be a useful outcome especially in the setting of chronic disease (Jenkinson et al., 1997). Congestive heart failure can be significantly detrimental to health related quality of life (Bennett et al., 2001; Riedinger, Dracup, & Brecht, 2002; Westlake et al., 2002). This is largely a qualitative measure which is typically evaluated using questionnaires. Several questionnaires have been used in the setting of cardiac disease (Franzen, Blomqvist, & Saveman, 2006). However, given that patients often have limited time and resources, short questionnaires that can provide a meaningful measure of change in health status are valuable (Jenkinson et al., 1997).

To that end, the Short Form – 12 (SF-12) questionnaire has been previously validated in the setting of heart failure. The SF-12 appears to perform

as well as the longer Short Form – 36 scale (SF-36) with regard to physical and mental health status and is largely similar in detecting changes in health status with minimal differences observed in detected effect size (Jenkinson et al., 1997). The scale also appears to correlate well with the Minnesota living with heart failure questionnaire (r = 0.6) and the MacNew Heart disease scale (r = 0.74 and r = 0.68 for the physical and mental component respectively) and consists of only 12 items (Franzen et al., 2006; Sansgiry, Chien, Jayawant, & Raju, 2008). High intensity aerobic interval training has been shown to improve HRQOL (Wisloff et al., 2007) as measured by the MacNew quality of life questionnaire. The effects of high intensity interval aerobic exercise on changes in HRQOL as measured by the SF-12 are as yet unknown.

Another mental health issue in patients with congestive heart failure is depression and it may be an important predictor of heart failure mortality (hazard ratio – 2.2) (Friedmann et al., 2006). Depression as defined by American Psychiatric Association criteria has been associated with increased neurohormonal activation, hypercoaguablity, autonomic dysfunction and cytokine activation that may result in increased mortality and ventricular arrhythmias (Brown, Varghese, & McEwen, 2004; Joynt, Whellan, & O'Connor C, 2004; Thomas et al., 2008).

The prevalence of depression in patients with heart failure is fairly substantial and ranges from 13% - 77.5%. The wide range is reflective of the wide variety of assessment tools that have been deployed in the setting of heart failure (Thomas et al., 2008). The Beck Depression Inventory is a fairly effective tool that can be used to detect depression with a sensitivity and specificity of 0.9 and

0.87 respectively and has been linked to the increased risk of mortality and rehospitalization in patients with congestive heart failure (Jiang et al., 2001).

The inventory consists of 21 items to assess the intensity of depression which are graded n a scale of 0, 1, 2, 3 each. The scores range from 0 = least severe depression to 63 = most severe depression. Scores greater than 14 – 15 indicate the presence of major depression.

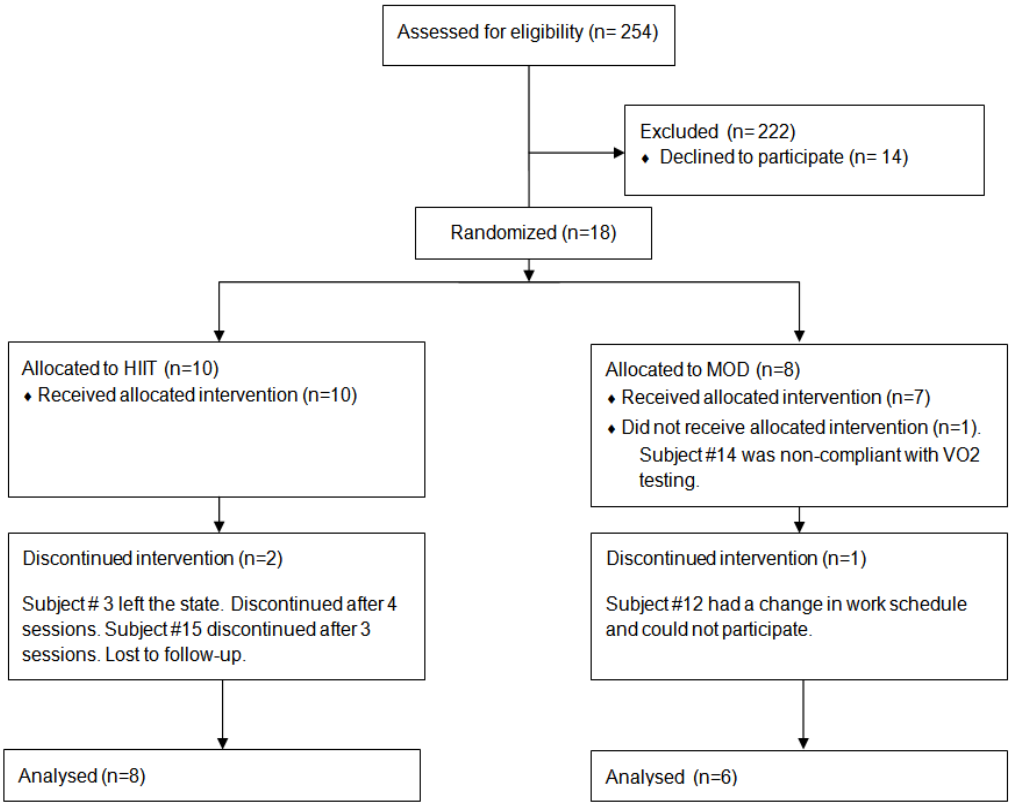
Exercise has been shown to be a fairly effective treatment modality for the management of depression. In a meta-regression analysis conducted by Lawlor and colleagues, aerobic exercise when compared to no treatment reduced symptoms of depression and reduced scores on the Beck depression inventory by 7.3 points (Lawlor & Hopker, 2001). When compared to cognitive behavioral therapy, aerobic exercise was similar in its effects. At present the effects of high intensity interval training on depressive symptoms in patients with heart failure with preserved ejection fraction are unknown.

Chapter 3

METHODS AND MATERIALS

The study was approved by the Mayo Clinic and Arizona State University Institutional review boards. All procedures were carried out as per the declaration of Helsinki. Subjects were screened using a combination of Mayo Clinic echocardiography lab records and other medical records. Subjects living within a 40-mile radius of the Mayo Clinic campus in Scottsdale, AZ were typically approached to enroll in the study. I enrolled a total of 18 patients with HFPEF (New York Heart Association heart failure Class II-III) from 40-80 years of age. Subjects were screened and excluded if they had unstable angina, myocardial infarction in the past 4 weeks, uncompensated heart failure, New York Heart Association class IV symptoms, complex ventricular arrhythmias, medical / orthopedic conditions precluding treadmill walking, symptomatic severe aortic stenosis, acute pulmonary embolus, acute myocarditis, and non-use of ß-blockers or ace-inhibitors. Four subjects dropped out of the study because of non-compliance due to factors such as change in employment status, other non-cardiovascular illnesses or non-compliance with test procedures. Medication use was recorded and kept constant while the patients were enrolled in the study. The CONSORT diagram for this trial is depicted in Figure 2.

Figure 1: CONSORT Diagram



Measurements (before and after 4 weeks of training)

All testing procedures were carried out following an overnight fast. Testing time was kept constant to reduce the impact of diurnal variations in the clinical variables measured. Post-testing was typically carried out within 72-96 hours following the last exercise training session.

Peak oxygen uptake (VO_2peak) was evaluated by using a 12-lead EKG monitored continuous treadmill ramp protocol (modified Bruce protocol) with increasing grade and speed until volitional fatigue or test termination criteria were met . The decision to terminate the test was taken if the subject meets previously defined American College of Cardiology/ American Heart Association criteria from the guidelines for exercise testing (Gibbons et al., 1997).

Gas exchange during exercise was continuously monitored and recorded using a Medigraphics Ultima Cardioperfect (St. Paul, MN) metabolic cart. The metabolic cart was calibrated prior to every test. The VO2peak test was deemed to be of good quality if patients achieved a respiratory exchange ratio (RER) $\geq$ 1.05 or showed evidence of plateau in heart rate and/or oxygen uptake. All subjects that completed the study managed to meet the aforementioned end-points with the majority achieving RER > 1.15 before they requested to have the test terminated due to fatigue.

Examination of vascular function

Subjects were asked to omit caffeine beverages and alcohol for at least 12 hours before the assessment. All measurements were taken in the supine position

in a quiet, temperature-controlled room after 15 minutes of rest and 2 sequential arterial blood pressure measurements that established hemodynamic stability. All vascular measurements were made at the same time during the day to minimize the effects of circadian variation.

Endothelium-dependent dilation of the brachial artery was measured by B-mode ultrasound (Terason t3000+^{TM}, Burlington MA) using guidelines set forth by the Brachial Artery Reactivity Task Force (Corretti et al., 2002). Participants were asked to lie quietly for 15 minutes on the ultrasound table before baseline images were obtained for 30 seconds from the participant's non-dominant arm. Simultaneous ultrasound images (B-mode) and doppler waveforms were always recorded.

Subsequently, an appropriately sized blood pressure cuff was wrapped around the patient's forearm. After the baseline images were acquired, the blood pressure cuff was inflated on the participants forearm to 250mmHg for 5 minutes to completely occlude the arteries in the forearm. 30 seconds prior to cuff release imaging of the artery was commenced. At 5 following cuff inflation, the cuff was rapidly deflated and arterial images were recorded for up to 5 minutes. Images that were obtained were analyzed by a blinded researcher using a previously validated, brachial artery edge-detection software (Tinken, Thijssen, Black, Cable, & Green, 2008).

Determination of aortic pulse wave velocity and central vascular compliance was carried out using Sphymocor^{TM} (AtCor Medical, Itasca, IL) using validated methodology (Pauca, O'Rourke, & Kon, 2001). Briefly, an

ascending aortic pressure waveform derived from the radial artery waveforms was recorded at the wrist, using applanation tonometry with a high-fidelity micromanometer. After 20 sequential waveforms were acquired, a validated generalized transfer function was used to generate the corresponding central aortic pressure waveform. The augmentation index (AIx) was calculated as the difference between the first and second systolic peaks of the ascending aortic waveform expressed as a percentage of the central pulse pressure (the difference between central systolic and diastolic pressure). In addition, because AIx is influenced by heart rate, an index normalized for heart rate of 75 bpm (AIx at 75) was used. Only high-quality recordings, defined as an in-device quality index ≥80% (derived from an algorithm including average pulse height, pulse height variation, diastolic variation, and the maximum rate of rise of the peripheral waveform) and acceptable curves on visual inspection were included in the analysis.

Echocardiography

Left ventricular diastolic function was assessed using transmitral pulsed Doppler recordings. The sample volume was placed in the mitral valve orifice by the mitral leaflets. Peak E and A (peak early transmitral filling velocity and preak transmitral atrial filling velocity during late diastole respectively), E/A ratio and e' (myocardial early diastolic velocity by tissue Doppler) were calculated. The E/e' was calculated as well. Deceleration time (DT) was calculated in milliseconds as the time elapsed between the peak E velocity and the point where the deceleration slope crossed the baseline. The isovolumetric relaxation time was

calculated as the time elapsed between aortic valve closure and mitral valve opening. Pseudonormalized filling patterns were unmasked by asking the patients to carry out a Valsalva maneuver which results in a reduction in LV filling pressures.

Exercise Training

Following baseline testing, patients were randomized to either the high-intensity aerobic interval exercise group, or to the continuous, moderate-intensity exercise group. Randomization was carried out using a simple software generated randomization table. Because significant improvements in VO_2peak and FMD can be observed after just 4 weeks of training, a 4-week training program was deemed to be sufficient for this pilot project (Moholdt et al., 2009; Tinken et al., 2008). Patients in each group were required to complete a total of 12 training sessions over a period of 4 weeks (3 days / week). Patients carried out exercise training at a phase II cardiac rehabilitation facility. All exercise training was carried out using real-time wireless EKG telemetry monitoring.

Patients in the moderate-intensity group began with 15 min of continuous exercise at 60% of peak heart rate (PHR), gradually increasing to 30 min of continuous exercise at 70% PHR by the 4th week (within limits of tolerance). Patients in the high-intensity aerobic interval exercise group started with intervals of 2 min duration at 80-85% of PHR, separated by 2 min of recovery at 50% of PHR to achieve a total "on-time" of 16 minutes of high intensity exercise. They were progressed to four, 4-min intervals at 85-90% PHR, separated by 4 min at 50% PHR (Wisloff et al., 2007). Each training session began with a 10-minute warm-up at 50% of PHR and end with a 5-min cool down at 50% PHR. Exercise progression was modified according to individual patient exercise tolerance.

Exercise sessions were terminated if the patient requested to stop, or if malignant ventricular arrhythmias or atrial fibrillation appeared during exercise. No significant adverse events were detected during the exercise training in both groups. Subjects were instructed to maintain usual levels of physical activity and usual diet during the study and not to make any modifications in the same.

Quality of Life and depression questionnaires

Quality of life was assessed using the short form 12 questionnaire. The questionnaire consists of 12 questions that assess scores in the physical and mental health domains (Franzen et al., 2006). The Beck depression inventory was also administered at the same time (Jiang et al., 2001). The questionnaires were given to the subjects at the end of the test procedures at the start and at the end of the study. Subjects were instructed to mail-in the questionnaires when they completed them and given information and return mail envelopes for the same. Unfortunately, less than 50% of the subjects sent in complete questionnaires and the data were not analyzed.

Sample Size and Analysis

The primary outcome measure was FMD percent change assessed by B-mode ultrasound. The sample size was calculated to detect 5% difference (SD = 3.2%) of FMD scores between treatment and control groups with 4 weeks intervention, which was based on the previous publications of chronic heart failure patients (Berger et al., 2001). In addition, I anticipated a 15% dropout rate with 90% of power at a 0.05 alpha level of significance (two-sided). Based on these parameters, the recruitment goal was 20 patients (n=10 per group, Table 1). Even though I failed to recruit the projected amount of patients in the stipulated amount of time I met minimum guidelines that were delineated by the power analysis outlined below.

Table 1: Sample size estimation

Estimates of total sample size (2N) for HIIT and MOD groups with significance level (α) of 0.05 (two-sided).

	Power		
Detectable difference	80%	85%	90%
5 % (FMD)	15	17	20
6 % (FMD)	11	12	15
7 % (FMD)	8	9	10

Statistical Analysis

General linear models (GLM) were used to investigate the effects of high intensity training on BAFMD, aortic pulse wave velocity, Vo_2peak values, and systolic and diastolic functions compared with control group after adjustment for covariates. The Mann-Whitney or Kruskal-Wallis tests were used if the assumption of normality or homogeneity of variance was unjustified. Paired t-tests were used to examine within group differences and unpaired t-tests were used to examine the difference between the deltas between both exercise groups. Partial Pearson or Spearman rank-ordered correlations were used to examine the associations of BAFMD, aortic pulse wave velocity, VO_2peak and diastolic dysfunction grade values. All statistical procedures were performed by PASW software (IBM Inc., Armonk, NY).

Chapter 4

RESULTS

The descriptive characteristics of the subjects who participated in this study are presented in Table 2. There were no significant differences between patient characteristics at baseline in the high-intensity interval training and the moderate intensity exercise groups.

Within-group effects of exercise on diastolic, vascular and cardiopulmonary function in patients with HFPEF

Results of within-group differences are presented in Table 3. High intensity interval training had a significant beneficial effect on modifying the degree of diastolic dysfunction observed on two-dimensional echocardiography that was present in the patients with HFPEF. Training lowered diastolic dysfunction by approximately 1 grade (pre: 2.13 $\pm$ .354 vs. post: 1.25 + .707, p = 0.031). Early diastolic filling (E) was significantly reduced post-training as well (pre – 0.93 $\pm$ 0.28 m/s vs. post – 0.28 m/s, p = 0.033). Deceleration time increased significantly in the HIIT group as well (pre – 189.4 $\pm$ 56.9 ms vs. post – 222.9 $\pm$ 42 ms, p = 0.022). A trend was observed for reductions in the left atrial volume index at the end of training as well (pre – 36 $\pm$ 3.1 vs. post – 31.6 $\pm$ 7.2, p = 0.086). The medial E/e' ratio which is an important component of diastolic dysfunction grading also showed a trend towards improvement (pre – 14.8 $\pm$ 6 vs. 12.3 $\pm$ 4.8, p = 0.1).

Table 2: Baseline characteristics of subjects (means ± SD)

	HIIT (n = 8)	Mod (n = 6)
Age (yrs)	69 ± 6.5	71.5 ± 11.7
3Sex	7 m, 1 f	4 m, 2 f
Weight (kg)	86.8 ± 15.3	87.4 ± 12.1
BMI (kg/m^2)	28.4 ± 4.8	29.3 ± 2.8
SBP (mmHg)	131.2 ± 11.7	133.5 ± 24.4
DBP (mmHg)	82 ± 8	77.7 ± 7.3
VO_2peak (ml/kg/min)	18.6 ± 5.7	16.87 ± 3
Diastolic dysfunction grade	2 ± 0.5	2 ± 0.63

"m" and "f" denote male and female respectively.

No significant differences were detected at baseline between the high intensity interval and the moderate intensity training groups.

High intensity interval training did not result in significant improvements in VO_2peak at the end of the month long intervention ($p = 0.45$). However, the rate pressure product (RPP) at the ventilatory threshold (VT) and at VO_2peak showed trends that suggested an improvement in those parameters (Table 3). Total treadmill time also showed a trend towards improvement at the end of the 4-week long intervention.

Table 3: Within-group effects of high intensity interval training

	HIIT		p-value
	Pre	Post	
DD grade	2.13 ± 0.4	1.3 ± 0.7	0.031
LA volume index (ml/m^2)	36 ± 3.1	31.6 ± 7.2	0.086
E (m/s)	0.93 ± 0.3	0.76 ± 0.3	0.033
A (m/s)	0.74 ± 0.2	0.71 ± 0.2	0.649
E/A ratio	1.35 ± 0.6	1.18 ± 0.5	0.303
DT (ms)	189.3 ± 56.9	222.9 ± 41.9	0.022
e' (m/s)	0.06 ± 0.01	0.06 ± 0.01	0.598
E/e'	14.8 ± 6	12.3 ± 4.8	0.10
IVRT (ms)	91.3 ± 11.7	98 ± 23.6	0.651
BAFMD (%)	6.7 ± 4	7.7 ± 3.8	0.571
Aortic SBP (mmHg)	110.7 ± 10.2	113.4 ± 13.5	0.653
Aortic DBP (mmHg)	75.1 ± 7.4	74.3 ± 5.7	0.81
Augmentation index @ HR75	20.1 ± 15.2	22.4 ± 21.7	0.54
RPP at VT	14969 ± 3413	13624 ± 2317	0.1
RPP at VO2peak	20825 ± 4899	18741 ± 3544	0.12
Treadmill time (secs)	843.8 ± 155	900 ± 152	0.12

No significant improvements in endothelium-dependent flow-mediated dilation or vascular stiffness were observed. The moderate intensity exercise program appeared to have no significant effects on diastolic dysfunction, vascular function and cardiorespiratory exercise capacity. However, the moderate-intensity exercise program did result in slightly lowered systolic blood pressures (pre – 133.5 $\pm$ 24.42 mmHg vs. post – 122.2 $\pm$ 26.66 mmHg, $p = 0.062$).

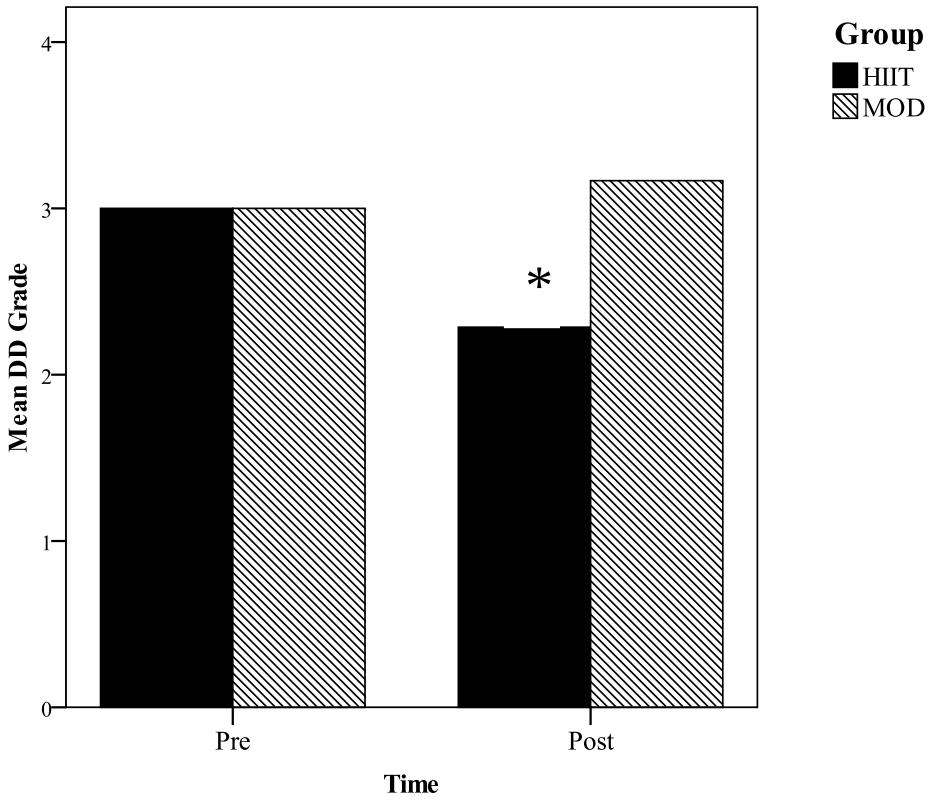
Table 4: Within-group effects of moderate intensity training

	MOD		p-value
	Pre	Post	
DD grade	2 ± 0.6	2.2 ± 0.8	0.317
LA volume index (ml/m^2)	40.5 ± 9.3	46.3 ± 18.1	0.241
E (m/s)	0.9 ± 0.2	0.8 ± 0.4	0.235
A (m/s)	0.8 ± 0.1	0.6 ± 0.5	0.38
E/A ratio	1.2 ± 0.6	1.6 ± 1.1	0.265
DT (ms)	199.2 ± 70.5	220.2 ± 42.6	0.421
e' (m/s)	0.05 ± 0.01	0.06 ± 0.01	0.259
E/e'	17.7 ± 6.3	16.7 ± 5.2	0.734
IVRT (ms)	92.8 ± 20.9	74.3 ± 49.7	0.465
BAFMD (%)	8.1 ± 4.2	3.4 ± 3.6	0.144
Aortic SBP (mmHg)	127.67 ± 16	118.3 ± 25.3	0.312
Aortic DBP (mmHg)	74.8 ± 7.3	71.2 ± 10.4	0.427
Augmentation index @ HR75	18.7 ± 10.4	22.5 ± 3.9	0.264
RPP at VT	13771 ± 4077	12118 ± 2870	0.377
RPP at VO2peak	20350 ± 4110	18816 ± 3616	0.371
Treadmill time (secs)	760 ± 241	778 ± 204	0.264

Between-group effects of exercise on diastolic, vascular and cardiopulmonary function in patients with HFPEF

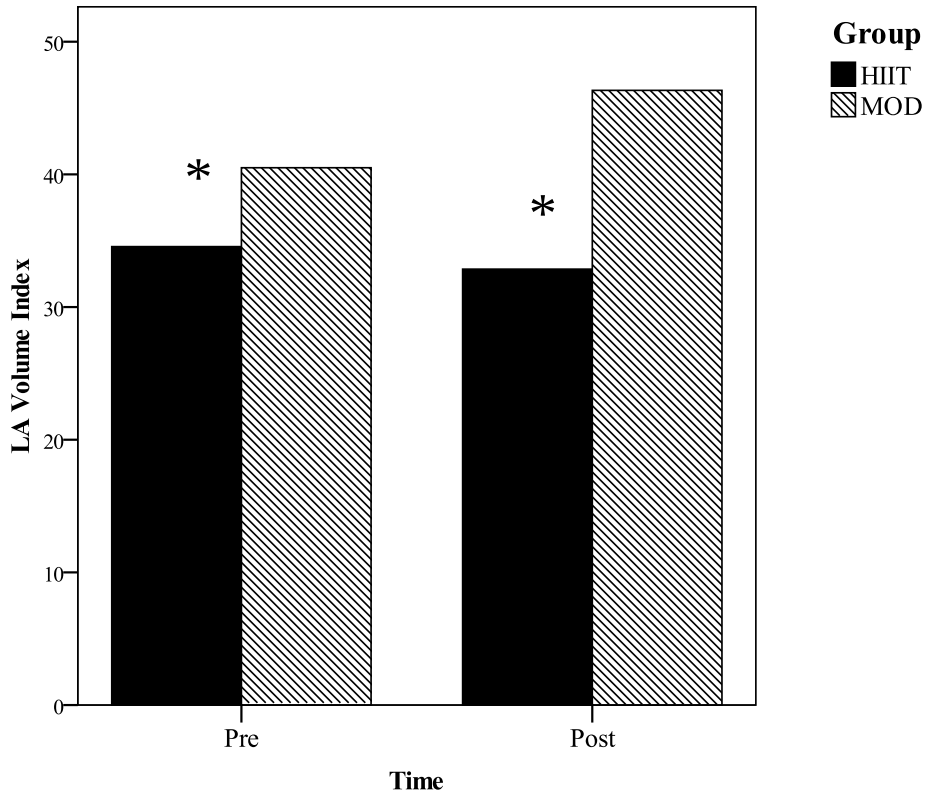
High-intensity interval training appeared to be superior to moderate intensity exercise with regard to improvements in diastolic function ($p = 0.003$; Figure 2). The left atrial volume index improved significantly in the high intensity exercise group as compared to the moderate intensity group ($p = 0.02$; Figure 3).

Figure 2: Changes in diastolic function in both groups



* p = 0.031 within-group

Figure 3: Changes in left atrial volume index (in ml/m^2) across both groups



* p = 0.02 between groups

Relationship between vascular function and left ventricular diastolic function

A two-way ANOVA revealed a trend towards a condition-by-time interaction that was observed for change in brachial artery flow-mediated dilation and change in diastolic function grade ($p = 0.06$). A significant inverse correlation was observed between BAFMD and change in diastolic dysfunction grade ($r = -0.585$, $p = 0.028$) was noted when all the data was pooled. Specifically, as BAFMD improved, diastolic function appeared to improve as well (Figure 5). No significant correlation was observed between change in vascular stiffness and change in diastolic function.

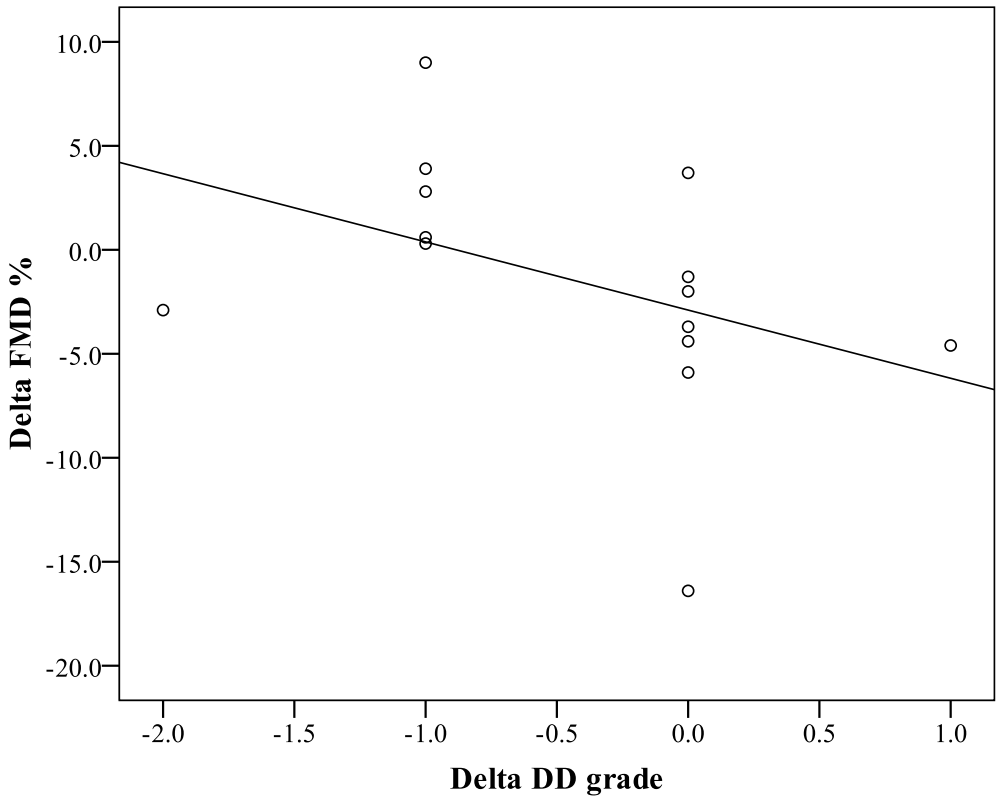
Quality of life

I met with very poor compliance on the return rates on the quality of life questionnaires. Only 50% of the subjects filled out complete SF-12 and Beck depression inventory forms. Since this greatly reduced sample size, I did not analyze the data.

Compliance

Compliance with exercise training was extremely good. Of the 14 subjects that completed the study each completed the allotted 12 sessions of exercise.

Figure 4: Relationship between change in BAFMD and change in diastolic function (N=14)



Chapter 5

DISCUSSION

This is the first randomized control trial to demonstrate the efficacy of a high-intensity interval training program with regard to improving diastolic dysfunction in patients with heart failure and preserved ejection fraction. Patients randomized to the month long high intensity exercise intervention improved their grade of diastolic function by ~ 1 grade and reduced their E/e' ratio ($p = 0.1$).

This may have important health implications for patients with heart failure and preserved ejection fraction because HFPEF is a disease without any established or proven evidence-based therapies that improve outcomes (Borlaug & Redfield, 2011a). High intensity interval training in patients with heart failure and reduced ejection fraction has been shown to improve markers of diastolic function (Wisloff et al., 2007). Similarly, moderate intensity exercise training has been shown to improve diastolic stiffness in patients with heart failure and reduced ejection fraction (Malfatto et al., 2009). This pilot study demonstrates a "proof of concept" that similar improvements may be possible in patients with heart failure and preserved ejection fraction. Given that these improvements were observed with just a month long training program, it suggests that high intensity interval training may be a time-efficient strategy to improve diastolic function in patients with heart failure and preserved ejection fraction.

Previously, several authors have demonstrated the effectiveness of long term (12- 24 week long) moderate intensity exercise training programs on

improving markers of diastolic function in patients suffering from heart failure with preserved ejection fraction (Alves et al., 2011; Edelmann et al., 2011). I did not observe any significant improvements in diastolic function in the moderate intensity exercise training group in the present study. This may in part be due to the length of the intervention and it is plausible that similar improvements would have been observed in the moderate intensity group if the length of the intervention were to be matched with previously published data.

No significant improvements in VO_2peak were observed in the present study in both the high intensity and moderate intensity exercise groups. However, trends for improvement were observed in total treadmill time, and rate pressure product at the ventilation threshold and VO_2peak in the HIIT group. Interestingly, reductions in E/e' was significantly correlated with reductions in the rate pressure product at the ventilation threshold ($r = 0.786$, $p = 0.021$) in the HIIT group. This finding would be associated with lower myocardial workload at submaximal exercise. These findings suggest possible improvements in cardiorespiratory function and the lack of significant results likely signifies a power issue. Previous 12-24 week long exercise trials that have utilized moderate intensity exercise in the treatment of heart failure and preserved ejection fraction have shown significant improvements in VO_2peak (Alves et al., 2011; Edelmann et al., 2011; Kitzman, Brubaker, Morgan, Stewart, & Little, 2010). One could speculate that the lack of improvements in VO_2peak in the present study may be a result of improvements in cardiorespiratory function lagging improvements in diastolic function.

Reductions in resting left atrial volume index have been previously reported following exercise training (Edelmann et al., 2011). The changes I observed in the left atrial volume index were in line with those reported by Edelmann and colleagues after 12 weeks of moderate intensity exercise and resistance training. It is encouraging to note that salutary cardiac remodeling can occur in a relatively short amount of time following the initiation of a high intensity interval training program.

A trend towards a condition by time interaction was observed for brachial artery flow mediated dilation and a significant association was observed between change in BAFMD and change in diastolic function across all subjects (Figure 4). Subject # 7 complained of an upper respiratory tract infection during the post-testing period (patient was afebrile and did not meet any exclusion criteria for VO_2peak testing) and the subject's BAFMD dropped from 15% in the pre-testing period to – 1%. However, even when this subjects' values were removed from the dataset the p-values for the correlation went from r = - 0.585 (p = 0.02) to r = - 0.561 (p = 0.046). It is unclear as to why the BAFMD in the moderate intensity group decreased in the post-testing period. Diastolic function appeared to improve in-line with improvements in BAFMD. This is likely because improvements in brachial artery flow mediated dilation have been observed to be positively correlated with improvements in coronary endothelial function (Teragawa et al., 2005). Coronary NO production has been linked to LV diastolic function (Paulus & Shah, 1999). It is plausible that these changes which are analogous to improved

nitric oxide bioavailability may have had salutary effects on LV diastolic function.

One possible limitation of the study was that I did not rigorously control for dietary intake. However, subjects were instructed to not deviate from their normal dietary habits but this was not confirmed via a food recall. However, it is important to note that subjects always reported for vascular testing after a $\geq$ 12 hour fast and thus, it's unlikely that meals affected their vascular function.

Adverse events

Subject # 1 complained of lightheadedness during a high intensity exercise session and was found to transiently be in a junctional rhythm. However, the patient was hemodynamically stable and after consultation with the treating cardiologist, the decision was made to continue with exercise training. He did not have any further episodes. Subject # 6 did have an emergency department admission during the study after 2 sessions of moderate intensity exercise due to suspected community acquired pneumonia. Upon discharge and recuperation he elected to re-enter the study. His treating cardiologist agreed to the same. He was then enrolled into the study again following repeat baseline testing. His initial exercise sessions were considered null and void and he carried out the full 12 sessions of moderate intensity exercise. No significant major adverse cardiac events were observed during the study and this serves to further underscore the safety of exercise training in patients with heart failure and preserved ejection fraction.

Chapter 6

CONCLUSION

In conclusion, the results show that significant improvements in diastolic function are possible after a month-long, high-intensity aerobic interval training program. These improvements in diastolic function were observed in conjunction with improvements in other echocardiographic variables such as left atrial volume index and E/e' ratio and are in line with previous findings in patients with heart failure and reduced ejection fraction that underwent high intensity interval training (Wisloff et al., 2007). These improvements in diastolic function may have important implications for health outcomes in patients with heart failure and preserved ejection fraction. Previous studies have demonstrated the utility of moderate intensity exercise on improving diastolic function in patients suffering from heart failure and preserved ejection fraction. However, the training volume in those studies ranged from 3 – 6 months. I have demonstrated that similar improvements may be possible with a substantially lower training volume. The broader question of how to best maintain these changes remains and, is the next logical avenue of inquiry.

REFERENCES

Abhayaratna, W. P., Seward, J. B., Appleton, C. P., Douglas, P. S., Oh, J. K., Tajik, A. J., et al. (2006). Left atrial size: physiologic determinants and clinical applications. *J Am Coll Cardiol, 47*(12), 2357-2363.

Adachi, H., Nguyen, P. H., Belardinelli, R., Hunter, D., Jung, T., & Wasserman, K. (1997). Nitric oxide production during exercise in chronic heart failure. *Am Heart J, 134*(2 Pt 1), 196-202.

Agnoletti, L., Curello, S., Bachetti, T., Malacarne, F., Gaia, G., Comini, L., et al. (1999). Serum from patients with severe heart failure downregulates eNOS and is proapoptotic: role of tumor necrosis factor-alpha. *Circulation, 100*(19), 1983-1991.

Ahmed, A., Aronow, W. S., & Fleg, J. L. (2006). Higher New York Heart Association classes and increased mortality and hospitalization in patients with heart failure and preserved left ventricular function. *Am Heart J, 151*(2), 444-450.

Alves, A. J., Ribeiro, F., Goldhammer, E., Rivlin, Y., Rosenschein, U., Viana, J. L., et al. (2011). Exercise Training Improves Diastolic Function in Heart Failure Patients. *Med Sci Sports Exerc*.

Arena, R., Myers, J., Aslam, S. S., Varughese, E. B., & Peberdy, M. A. (2003). Technical considerations related to the minute ventilation/carbon dioxide output slope in patients with heart failure. *Chest, 124*(2), 720-727.

Arena, R., Myers, J., Aslam, S. S., Varughese, E. B., & Peberdy, M. A. (2004). Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. *Am Heart J, 147*(2), 354-360.

Banning, A. P., Lewis, N. P., Northridge, D. B., Elborn, J. S., & Hendersen, A. H. (1995). Perfusion/ventilation mismatch during exercise in chronic heart failure: an investigation of circulatory determinants. *Br Heart J, 74*(1), 27-33.

Bauersachs, J., & Schafer, A. (2004). Endothelial dysfunction in heart failure: mechanisms and therapeutic approaches. *Curr Vasc Pharmacol, 2*(2), 115-124.

Belardinelli, R., Georgiou, D., Cianci, G., & Purcaro, A. (1999). Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation, 99*(9), 1173-1182.

Bennett, S. J., Perkins, S. M., Lane, K. A., Deer, M., Brater, D. C., & Murray, M. D. (2001). Social support and health-related quality of life in chronic heart failure patients. *Qual Life Res, 10*(8), 671-682.

Berger, R., Stanek, B., Hulsmann, M., Frey, B., Heher, S., Pacher, R., et al. (2001). Effects of Endothelin A Receptor Blockade on Endothelial Function in Patients With Chronic Heart Failure. *Circulation, 103*(7), 981-986.

Borlaug, B. A., & Kass, D. A. (2008). Ventricular-vascular interaction in heart failure. *Heart Fail Clin, 4*(1), 23-36.

Borlaug, B. A., Lam, C. S., Roger, V. L., Rodeheffer, R. J., & Redfield, M. M. (2009). Contractility and ventricular systolic stiffening in hypertensive heart disease insights into the pathogenesis of heart failure with preserved ejection fraction. *J Am Coll Cardiol, 54*(5), 410-418.

Borlaug, B. A., Melenovsky, V., Russell, S. D., Kessler, K., Pacak, K., Becker, L. C., et al. (2006). Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. *Circulation, 114*(20), 2138-2147.

Borlaug, B. A., Nishimura, R. A., Sorajja, P., Lam, C. S., & Redfield, M. M. (2010). Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail, 3*(5), 588-595.

Borlaug, B. A., Olson, T. P., Lam, C. S., Flood, K. S., Lerman, A., Johnson, B. D., et al. (2010). Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. *J Am Coll Cardiol, 56*(11), 845-854.

Borlaug, B. A., & Redfield, M. M. (2011a). Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. *Circulation, 123*(18), 2006-2013; discussion 2014.

Borlaug, B. A., & Redfield, M. M. (2011b). Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. *Circulation, 123*(18), 2006-2014.

Brown, E. S., Varghese, F. P., & McEwen, B. S. (2004). Association of depression with medical illness: does cortisol play a role? *Biol Psychiatry, 55*(1), 1-9.

Brubaker, P. H., Joo, K. C., Stewart, K. P., Fray, B., Moore, B., & Kitzman, D. W. (2006). Chronotropic incompetence and its contribution to exercise intolerance in older heart failure patients. *J Cardiopulm Rehabil, 26*(2), 86-89.

Bruch, C., Klem, I., Breithardt, G., Wichter, T., & Gradaus, R. (2007). Diagnostic usefulness and prognostic implications of the mitral E/E' ratio in patients with heart failure and severe secondary mitral regurgitation. *Am J Cardiol, 100*(5), 860-865.

Brutsaert, D. L., Sys, S. U., & Gillebert, T. C. (1993). Diastolic failure: pathophysiology and therapeutic implications. *J Am Coll Cardiol, 22*(1), 318-325.

Cameron, J. D., & Dart, A. M. (1994). Exercise training increases total systemic arterial compliance in humans. *The American journal of physiology, 266*(2 Pt 2), H693-701.

Chua, T. P., Clark, A. L., Amadi, A. A., & Coats, A. J. (1996). Relation between chemosensitivity and the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol, 27*(3), 650-657.

Chua, T. P., Ponikowski, P., Harrington, D., Anker, S. D., Webb-Peploe, K., Clark, A. L., et al. (1997). Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol, 29*(7), 1585-1590.

Corra, U., Mezzani, A., Bosimini, E., Scapellato, F., Imparato, A., & Giannuzzi, P. (2002). Ventilatory response to exercise improves risk stratification in patients with chronic heart failure and intermediate functional capacity. *Am Heart J, 143*(3), 418-426.

Corretti, M. C., Anderson, T. J., Benjamin, E. J., Celermajer, D., Charbonneau, F., Creager, M. A., et al. (2002). Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol, 39*(2), 257-265.

De Keulenaer, G. W., & Brutsaert, D. L. (2011). Systolic and diastolic heart failure are overlapping phenotypes within the heart failure spectrum. *Circulation, 123*(18), 1996-2005.

Dokainish, H., Zoghbi, W. A., Lakkis, N. M., Ambriz, E., Patel, R., Quinones, M. A., et al. (2005). Incremental predictive power of B-type natriuretic peptide and tissue Doppler echocardiography in the prognosis of patients with congestive heart failure. *J Am Coll Cardiol, 45*(8), 1223-1226.

Edelmann, F., Gelbrich, G., Dungen, H. D., Frohling, S., Wachter, R., Stahrenberg, R., et al. (2011). Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. *J Am Coll Cardiol, 58*(17), 1780-1791.

Erbs, S., Hollriegel, R., Linke, A., Beck, E. B., Adams, V., Gielen, S., et al. (2010). Exercise training in patients with advanced chronic heart failure (NYHA IIIb) promotes restoration of peripheral vasomotor function, induction of endogenous regeneration, and improvement of left ventricular function. *Circ Heart Fail, 3*(4), 486-494.

Francis, D. P., Shamim, W., Davies, L. C., Piepoli, M. F., Ponikowski, P., Anker, S. D., et al. (2000). Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO(2)slope and peak VO(2). *Eur Heart J, 21*(2), 154-161.

Franzen, K., Blomqvist, K., & Saveman, B. I. (2006). Impact of chronic heart failure on elderly persons' daily life: a validation study. *Eur J Cardiovasc Nurs, 5*(2), 137-145.

Friedmann, E., Thomas, S. A., Liu, F., Morton, P. G., Chapa, D., & Gottlieb, S. S. (2006). Relationship of depression, anxiety, and social isolation to chronic heart failure outpatient mortality. *Am Heart J, 152*(5), 940 e941-948.

Georgiou, D., Chen, Y., Appadoo, S., Belardinelli, R., Greene, R., Parides, M. K., et al. (2001). Cost-effectiveness analysis of long-term moderate exercise training in chronic heart failure. *Am J Cardiol, 87*(8), 984-988; A984.

Giannattasio, C., Failla, M., Stella, M. L., Mangoni, A. A., Carugo, S., Pozzi, M., et al. (1995). Alterations of radial artery compliance in patients with congestive heart failure. *The American journal of cardiology, 76*(5), 381-385.

Gibbons, R. J., Balady, G. J., Beasley, J. W., FAAFP, J. W., Bricker, J. T., Duvernoy, W. F. C., et al. (1997). ACC/AHA Guidelines for Exercise Testing: Executive Summary : A Report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *Circulation, 96*(1), 345-354.

Gottdiener, J. S., McClelland, R. L., Marshall, R., Shemanski, L., Furberg, C. D., Kitzman, D. W., et al. (2002). Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. *Ann Intern Med, 137*(8), 631-639.

Guazzi, M., Myers, J., & Arena, R. (2005). Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. *J Am Coll Cardiol, 46*(10), 1883-1890.

Guazzi, M., Reina, G., Tumminello, G., & Guazzi, M. D. (2004). Improvement of alveolar-capillary membrane diffusing capacity with exercise training in chronic heart failure. *J Appl Physiol, 97*(5), 1866-1873.

Guimaraes, G. V., Ciolac, E. G., Carvalho, V. O., D'Avila, V. M., Bortolotto, L. A., & Bocchi, E. A. (2010). Effects of continuous vs. interval exercise training on blood pressure and arterial stiffness in treated hypertension. *Hypertension research : official journal of the Japanese Society of Hypertension, 33*(6), 627-632.

Gure, T., Kabeto, M., Blaum, C., & Langa, K. (2008). Degree of Disability and Patterns of Caregiving among Older Americans with Congestive Heart Failure. *Journal of General Internal Medicine, 23*(1), 70-76.

Hambrecht, R., Adams, V., Erbs, S., Linke, A., Krankel, N., Shu, Y., et al. (2003). Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. *Circulation, 107*(25), 3152-3158.

Hambrecht, R., Gielen, S., Linke, A., Fiehn, E., Yu, J., Walther, C., et al. (2000). Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: A randomized trial. *JAMA, 283*(23), 3095-3101.

Helgerud, J., Hoydal, K., Wang, E., Karlsen, T., Berg, P., Bjerkaas, M., et al. (2007). Aerobic high-intensity intervals improve VO2max more than

moderate training. *Medicine and science in sports and exercise, 39*(4), 665-671.

Hillege, H. L., Nitsch, D., Pfeffer, M. A., Swedberg, K., McMurray, J. J., Yusuf, S., et al. (2006). Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation, 113*(5), 671-678.

Hillis, G. S., Moller, J. E., Pellikka, P. A., Gersh, B. J., Wright, R. S., Ommen, S. R., et al. (2004). Noninvasive estimation of left ventricular filling pressure by E/e' is a powerful predictor of survival after acute myocardial infarction. *J Am Coll Cardiol, 43*(3), 360-367.

Hurrell, D. G., Nishimura, R. A., Ilstrup, D. M., & Appleton, C. P. (1997). Utility of preload alteration in assessment of left ventricular filling pressure by Doppler echocardiography: a simultaneous catheterization and Doppler echocardiographic study. *J Am Coll Cardiol, 30*(2), 459-467.

Jenkinson, C., Layte, R., Jenkinson, D., Lawrence, K., Petersen, S., Paice, C., et al. (1997). A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? *J Public Health Med, 19*(2), 179-186.

Jiang, W., Alexander, J., Christopher, E., Kuchibhatla, M., Gaulden, L. H., Cuffe, M. S., et al. (2001). Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. *Arch Intern Med, 161*(15), 1849-1856.

Jones, R. C., Francis, G. S., & Lauer, M. S. (2004). Predictors of mortality in patients with heart failure and preserved systolic function in the Digitalis Investigation Group trial. *J Am Coll Cardiol, 44*(5), 1025-1029.

Joynt, K. E., Whellan, D. J., & O'Connor C, M. (2004). Why is depression bad for the failing heart? A review of the mechanistic relationship between depression and heart failure. *J Card Fail, 10*(3), 258-271.

Kass, D. A., & Kelly, R. P. (1992). Ventriculo-arterial coupling: concepts, assumptions, and applications. *Ann Biomed Eng, 20*(1), 41-62.

Katz, S. D., Hryniewicz, K., Hriljac, I., Balidemaj, K., Dimayuga, C., Hudaihed, A., et al. (2005). Vascular endothelial dysfunction and mortality risk in patients with chronic heart failure. *Circulation, 111*(3), 310-314.

Kavanagh, T., Mertens, D. J., Hamm, L. F., Beyene, J., Kennedy, J., Corey, P., et al. (2002). Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation, 106*(6), 666-671.

Kelly, R. P., Tunin, R., & Kass, D. A. (1992). Effect of reduced aortic compliance on cardiac efficiency and contractile function of in situ canine left ventricle. *Circulation research, 71*(3), 490-502.

Kemi, O. J., Haram, P. M., Loennechen, J. P., Osnes, J. B., Skomedal, T., Wisloff, U., et al. (2005). Moderate vs. high exercise intensity: differential effects on aerobic fitness, cardiomyocyte contractility, and endothelial function. *Cardiovascular research, 67*(1), 161-172.

Kitzman, D. W., Brubaker, P. H., Morgan, T. M., Stewart, K. P., & Little, W. C. (2010). Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *Circ Heart Fail, 3*(6), 659-667.

Koike, A., Itoh, H., Kato, M., Sawada, H., Aizawa, T., Fu, L. T., et al. (2002). Prognostic power of ventilatory responses during submaximal exercise in patients with chronic heart disease. *Chest, 121*(5), 1581-1588.

Lage, S. G., Kopel, L., Monachini, M. C., Medeiros, C. J., Pileggi, F., Polak, J. F., et al. (1994). Carotid arterial compliance in patients with congestive heart failure secondary to idiopathic dilated cardiomyopathy. *The American journal of cardiology, 74*(7), 691-695.

Lam, C. S., Roger, V. L., Rodeheffer, R. J., Bursi, F., Borlaug, B. A., Ommen, S. R., et al. (2007). Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. *Circulation, 115*(15), 1982-1990.

Lawlor, D. A., & Hopker, S. W. (2001). The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. *Bmj, 322*(7289), 763-767.

Leite-Moreira, A. F. (2006). Current perspectives in diastolic dysfunction and diastolic heart failure. *Heart, 92*(5), 712-718.

Levy, D., Larson, M. G., Vasan, R. S., Kannel, W. B., & Ho, K. K. (1996). The progression from hypertension to congestive heart failure. *Jama, 275*(20), 1557-1562.

Lewis, N. P., Banning, A. P., Cooper, J. P., Sundar, A. S., Facey, P. E., Evans, W. D., et al. (1996). Impaired matching of perfusion and ventilation in heart failure detected by 133xenon. *Basic Res Cardiol, 91 Suppl 1*, 45-49.

Li, M., Chiou, K. R., Bugayenko, A., Irani, K., & Kass, D. A. (2005). Reduced wall compliance suppresses Akt-dependent apoptosis protection stimulated by pulse perfusion. *Circ Res, 97*(6), 587-595.

Little, W. C., Zile, M. R., Klein, A., Appleton, C. P., Kitzman, D. W., & Wesley-Farrington, D. J. (2006). Effect of losartan and hydrochlorothiazide on exercise tolerance in exertional hypertension and left ventricular diastolic dysfunction. *Am J Cardiol, 98*(3), 383-385.

Lloyd-Jones, D., Adams, R., Carnethon, M., De Simone, G., Ferguson, T. B., Flegal, K., et al. (2009). Heart Disease and Stroke Statistics--2009 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation, 119*(3), e21-181.

Malfatto, G., Branzi, G., Osculati, G., Valli, P., Cuoccio, P., Ciambellotti, F., et al. (2009). Improvement in left ventricular diastolic stiffness induced by physical training in patients with dilated cardiomyopathy. *J Card Fail, 15*(4), 327-333.

Melenovsky, V., Borlaug, B. A., Rosen, B., Hay, I., Ferruci, L., Morell, C. H., et al. (2007). Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction. *J Am Coll Cardiol, 49*(2), 198-207.

Moholdt, T. T., Amundsen, B. H., Rustad, L. A., Wahba, A., Løvø, K. T., Gullikstad, L. R., et al. (2009). Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: A randomized study of cardiovascular effects and quality of life. *American heart journal, 158*(6), 1031-1037.

Myers, J., Dziekan, G., Goebbels, U., & Dubach, P. (1999). Influence of high-intensity exercise training on the ventilatory response to exercise in patients with reduced ventricular function. *Med Sci Sports Exerc, 31*(7), 929-937.

Nagueh, S. F., Appleton, C. P., Gillebert, T. C., Marino, P. N., Oh, J. K., Smiseth, O. A., et al. (2009). Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr, 22*(2), 107-133.

O'Connor, C. M., Gattis, W. A., Shaw, L., Cuffe, M. S., & Califf, R. M. (2000). Clinical characteristics and long-term outcomes of patients with heart failure and preserved systolic function. *Am J Cardiol, 86*(8), 863-867.

Okura, H., Takada, Y., Kubo, T., Iwata, K., Mizoguchi, S., Taguchi, H., et al. (2006). Tissue Doppler-derived index of left ventricular filling pressure, E/E', predicts survival of patients with non-valvular atrial fibrillation. *Heart, 92*(9), 1248-1252.

Parnell, M. M., Holst, D. P., & Kaye, D. M. (2002). Exercise training increases arterial compliance in patients with congestive heart failure. *Clinical science, 102*(1), 1-7.

Pauca, A. L., O'Rourke, M. F., & Kon, N. D. (2001). Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension, 38*(4), 932-937.

Paulus, W. J., & Shah, A. M. (1999). NO and cardiac diastolic function. *Cardiovasc Res, 43*(3), 595-606.

Paulus, W. J., Tschope, C., Sanderson, J. E., Rusconi, C., Flachskampf, F. A., Rademakers, F. E., et al. (2007). How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J, 28*(20), 2539-2550.

Persson, H., Lonn, E., Edner, M., Baruch, L., Lang, C. C., Morton, J. J., et al. (2007). Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence:results from the CHARM Echocardiographic Substudy-CHARMES. *J Am Coll Cardiol, 49*(6), 687-694.

Piepoli, M., Clark, A. L., Volterrani, M., Adamopoulos, S., Sleight, P., & Coats, A. J. (1996). Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure: effects of physical training. *Circulation, 93*(5), 940-952.

Piepoli, M. F., Davos, C., Francis, D. P., & Coats, A. J. (2004). Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ, 328*(7433), 189.

Pina, I. L., Apstein, C. S., Balady, G. J., Belardinelli, R., Chaitman, B. R., Duscha, B. D., et al. (2003). Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. *Circulation, 107*(8), 1210-1225.

Ponikowski, P., Francis, D. P., Piepoli, M. F., Davies, L. C., Chua, T. P., Davos, C. H., et al. (2001). Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. *Circulation, 103*(7), 967-972.

Rakobowchuk, M., Stuckey, M. I., Millar, P. J., Gurr, L., & Macdonald, M. J. (2009). Effect of acute sprint interval exercise on central and peripheral artery distensibility in young healthy males. *European journal of applied physiology, 105*(5), 787-795.

Rakobowchuk, M., Tanguay, S., Burgomaster, K. A., Howarth, K. R., Gibala, M. J., & MacDonald, M. J. (2008). Sprint interval and traditional endurance training induce similar improvements in peripheral arterial stiffness and flow-mediated dilation in healthy humans. *American journal of physiology. Regulatory, integrative and comparative physiology, 295*(1), R236-242.

Redfield, M. M., Jacobsen, S. J., Burnett, J. C., Jr., Mahoney, D. W., Bailey, K. R., & Rodeheffer, R. J. (2003). Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *Jama, 289*(2), 194-202.

Reindl, I., Wernecke, K. D., Opitz, C., Wensel, R., Konig, D., Dengler, T., et al. (1998). Impaired ventilatory efficiency in chronic heart failure: possible role of pulmonary vasoconstriction. *Am Heart J, 136*(5), 778-785.

Riedinger, M. S., Dracup, K. A., & Brecht, M. L. (2002). Quality of life in women with heart failure, normative groups, and patients with other chronic conditions. *Am J Crit Care, 11*(3), 211-219.

Sansgiry, S. S., Chien, C., Jayawant, S. S., & Raju, A. (2008). Comparison of the Short-Form Survey 12 and the MacNew Heart Disease Health-Related Quality of Life Survey among patients with cardiac disease. *Ann Pharmacother, 42*(2), 200-206.

Senni, M., Tribouilloy, C. M., Rodeheffer, R. J., Jacobsen, S. J., Evans, J. M., Bailey, K. R., et al. (1998). Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation, 98*(21), 2282-2289.

Sharma, R., Pellerin, D., Gaze, D. C., Mehta, R. L., Gregson, H., Streather, C. P., et al. (2006). Mitral peak Doppler E-wave to peak mitral annulus velocity ratio is an accurate estimate of left ventricular filling pressure and predicts mortality in end-stage renal disease. *J Am Soc Echocardiogr, 19*(3), 266-273.

Sunagawa, K., Maughan, W. L., Burkhoff, D., & Sagawa, K. (1983). Left ventricular interaction with arterial load studied in isolated canine ventricle. *Am J Physiol, 245*(5 Pt 1), H773-780.

Sunagawa, K., Maughan, W. L., & Sagawa, K. (1985). Optimal arterial resistance for the maximal stroke work studied in isolated canine left ventricle. *Circ Res, 56*(4), 586-595.

Tabet, J. Y., Meurin, P., Beauvais, F., Weber, H., Renaud, N., Thabut, G., et al. (2008). Absence of exercise capacity improvement after exercise training program: a strong prognostic factor in patients with chronic heart failure. *Circ Heart Fail, 1*(4), 220-226.

Tabet, J. Y., Meurin, P., Driss, A. B., Weber, H., Renaud, N., Grosdemouge, A., et al. (2009). Benefits of exercise training in chronic heart failure. *Arch Cardiovasc Dis, 102*(10), 721-730.

Teragawa, H., Ueda, K., Matsuda, K., Kimura, M., Higashi, Y., Oshima, T., et al. (2005). Relationship between endothelial function in the coronary and brachial arteries. *Clin Cardiol, 28*(10), 460-466.

Thomas, S. A., Chapa, D. W., Friedmann, E., Durden, C., Ross, A., Lee, M. C., et al. (2008). Depression in patients with heart failure: prevalence, pathophysiological mechanisms, and treatment. *Crit Care Nurse, 28*(2), 40-55.

Tinken, T. M., Thijssen, D. H. J., Black, M. A., Cable, N. T., & Green, D. J. (2008). Time course of change in vasodilator function and capacity in response to exercise training in humans. *The Journal of Physiology, 586*(20), 5003-5012.

Troughton, R. W., Prior, D. L., Frampton, C. M., Nash, P. J., Pereira, J. J., Martin, M., et al. (2005). Usefulness of tissue doppler and color M-mode indexes of left ventricular diastolic function in predicting outcomes in systolic left ventricular heart failure (from the ADEPT study). *Am J Cardiol, 96*(2), 257-262.

Uren, N. G., Davies, S. W., Agnew, J. E., Irwin, A. G., Jordan, S. L., Hilson, A. J., et al. (1993). Reduction of mismatch of global ventilation and perfusion on exercise is related to exercise capacity in chronic heart failure. *Br Heart J, 70*(3), 241-246.

Valgimigli, M., Agnoletti, L., Curello, S., Comini, L., Francolini, G., Mastrorilli, F., et al. (2003). Serum from patients with acute coronary syndromes displays a proapoptotic effect on human endothelial cells: a possible link to pan-coronary syndromes. *Circulation, 107*(2), 264-270.

Vasan, R. S., Benjamin, E. J., & Levy, D. (1995). Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. *J Am Coll Cardiol, 26*(7), 1565-1574.

Wada, O., Asanoi, H., Miyagi, K., Ishizaka, S., Kameyama, T., Seto, H., et al. (1993). Importance of abnormal lung perfusion in excessive exercise ventilation in chronic heart failure. *Am Heart J, 125*(3), 790-798.

Wagner, J. A., Hu, K., Bauersachs, J., Karcher, J., Wiesler, M., Goparaju, S. K., et al. (2001). Endogenous cannabinoids mediate hypotension after experimental myocardial infarction. *J Am Coll Cardiol, 38*(7), 2048-2054.

Wang, M., Yip, G., Yu, C. M., Zhang, Q., Zhang, Y., Tse, D., et al. (2005). Independent and incremental prognostic value of early mitral annulus velocity in patients with impaired left ventricular systolic function. *J Am Coll Cardiol, 45*(2), 272-277.

Wang, M., Yip, G. W., Wang, A. Y., Zhang, Y., Ho, P. Y., Tse, M. K., et al. (2003). Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value. *J Am Coll Cardiol, 41*(5), 820-826.

Wang, M., Yip, G. W., Wang, A. Y., Zhang, Y., Ho, P. Y., Tse, M. K., et al. (2005). Tissue Doppler imaging provides incremental prognostic value in patients with systemic hypertension and left ventricular hypertrophy. *J Hypertens, 23*(1), 183-191.

Warburton, D. E., McKenzie, D. C., Haykowsky, M. J., Taylor, A., Shoemaker, P., Ignaszewski, A. P., et al. (2005). Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *The American journal of cardiology, 95*(9), 1080-1084.

Warner, J. G., Jr., Metzger, D. C., Kitzman, D. W., Wesley, D. J., & Little, W. C. (1999). Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. *J Am Coll Cardiol, 33*(6), 1567-1572.

Wenger, H. A., & Bell, G. J. (1986). The interactions of intensity, frequency and duration of exercise training in altering cardiorespiratory fitness. *Sports medicine, 3*(5), 346-356.

Westlake, C., Dracup, K., Creaser, J., Livingston, N., Heywood, J. T., Huiskes, B. L., et al. (2002). Correlates of health-related quality of life in patients with heart failure. *Heart Lung, 31*(2), 85-93.

Wisloff, Stoylen, A., Loennechen, J. P., Bruvold, M., Rognmo, O., Haram, P. M., et al. (2007). Superior Cardiovascular Effect of Aerobic Interval Training Versus Moderate Continuous Training in Heart Failure Patients: A Randomized Study. *Circulation, 115*(24), 3086-3094.

Wisloff, U., Ellingsen, O., & Kemi, O. J. (2009). High-intensity interval training to maximize cardiac benefits of exercise training? *Exerc Sport Sci Rev, 37*(3), 139-146.

Yamamoto, T., Oki, T., Yamada, H., Tanaka, H., Ishimoto, T., Wakatsuki, T., et al. (2003). Prognostic value of the atrial systolic mitral annular motion velocity in patients with left ventricular systolic dysfunction. *J Am Soc Echocardiogr, 16*(4), 333-339.

APPENDIX A

SHORT FORM – 12 QUALITY OF LIFE QUESTIONNAIRE

The SF-12v2™ Health Survey

Instructions for Completing the Questionnaire

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
b) Climbing several flights of stairs	○	○	○

3. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Accomplished less than you would like	○	○	○	○	○
b) Were limited in the kind of work or other activities	○	○	○	○	○

SF-12v2™ © 1999 QualityMetric, Inc. All Rights Reserved.

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Accomplished less than you would like	○	○	○	○	○
b) Did work or other activities less carefully than usual	○	○	○	○	○

5. During the *past 4 weeks*, how much did *pain* interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) have you felt calm and peaceful?	○	○	○	○	○
b) did you have a lot of energy?	○	○	○	○	○
c) have you felt downhearted and depressed?	○	○	○	○	○

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
○	○	○	○	○

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE!

SF-12v2™ © 1999 QualityMetric, Inc. All Rights Reserved.

APPENDIX B

BECK DEPRESSION INVENTORY

BDI®-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today.** Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness
- 0 I do not feel sad.
- 1 I feel sad much of the time.
- 2 I am sad all the time.
- 3 I am so sad or unhappy that I can't stand it.

2. Pessimism
- 0 I am not discouraged about my future.
- 1 I feel more discouraged about my future than I used to be.
- 2 I do not expect things to work out for me.
- 3 I feel my future is hopeless and will only get worse.

3. Past Failure
- 0 I do not feel like a failure.
- 1 I have failed more than I should have.
- 2 As I look back, I see a lot of failures.
- 3 I feel I am a total failure as a person.

4. Loss of Pleasure
- 0 I get as much pleasure as I ever did from the things I enjoy.
- 1 I don't enjoy things as much as I used to.
- 2 I get very little pleasure from the things I used to enjoy.
- 3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
- 0 I don't feel particularly guilty.
- 1 I feel guilty over many things I have done or should have done.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6. Punishment Feelings
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7. Self-Dislike
- 0 I feel the same about myself as ever.
- 1 I have lost confidence in myself.
- 2 I am disappointed in myself.
- 3 I dislike myself.

8. Self-Criticalness
- 0 I don't criticize or blame myself more than usual.
- 1 I am more critical of myself than I used to be.
- 2 I criticize myself for all of my faults.
- 3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10. Crying
- 0 I don't cry any more than I used to.
- 1 I cry more than I used to.
- 2 I cry over every little thing.
- 3 I feel like crying, but I can't.

Subtotal Page 1

Continued on Back

PEARSON

Copyright © 1996 Aaron T. Beck. All rights reserved.
Printed in the United States of America.

PsychCorp

26 27 28 29 30 A B C D E 281283-1 32

Product Number 0154018392

11. Agitation

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than before.
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

Subtotal Page 2

Subtotal Page 1

Total Score

NOTICE: This form is printed with blue and black ink. If your copy does not appear this way, it has been photocopied in violation of copyright laws.

APPENDIX C

ARIZONA STATE UNIVERSITY INSTITUTIONAL REVIEW BOARD APPROVAL

ASU Knowledge Enterprise Development

Office of Research Integrity and Assurance

To:	Glenn Gaesser
From:	Carol Johnston, Chair CJ Biosci IRB
Date:	07/09/2010
Committee Action:	**Expedited Approval**
Approval Date:	07/09/2010
Review Type:	Expedited F2 F4
IRB Protocol #:	1004005096
Study Title:	Effects of a novel, high-intensity aerobic interval training program on endothelial function, vascular compliance, and peak cardiorespiratory capacity in patients with heart failure with preserved ejection fraction.
Expiration Date:	07/08/2011

The above-referenced protocol was approved following expedited review by the Institutional Review Board.

It is the Principal Investigator's responsibility to obtain review and continued approval before the expiration date. You may not continue any research activity beyond the expiration date without approval by the Institutional Review Board.

Adverse Reactions: If any untoward incidents or severe reactions should develop as a result of this study, you are required to notify the Biosci IRB immediately. If necessary a member of the IRB will be assigned to look into the matter. If the problem is serious, approval may be withdrawn pending IRB review.

Amendments: If you wish to change any aspect of this study, such as the procedures, the consent forms, or the investigators, please communicate your requested changes to the Biosci IRB. The new procedure is not to be initiated until the IRB approval has been given.

Please retain a copy of this letter with your approved protocol.