CHRONOTROPIC INCOMPETENCE IN PATIENTS WITH HEART FAILURE
AND PRESERVED EJECTION FRACTION:
PREVALENCE AND IMPACT ON EXERCISE TOLERANCE

By

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DEDICATION

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TABLE OF CONTENTS

DEDICATION ................................................................................................................... ii

ACKNOWLEDGMENTS .................................................................................................... iii

ABSTRACT ....................................................................................................................... 1

INTRODUCTION AND REVIEW OF LITERATURE .................................................. 3
  Introduction/Epidemiology of Heart Failure ............................................................... 3
  Pathophysiology of Heart Failure .............................................................................. 5
  Acute Exercise Responses of Heart Failure Patients .................................................. 9
  Heart Rate Response to Exercise .............................................................................. 10
  Chronotropic Incompetence ..................................................................................... 11
  Diagnosis and Classification of Heart Failure ............................................................ 17
  Medical Management of Heart Failure ...................................................................... 19
  Benefit of Physical Activity/Exercise in Heart Failure .............................................. 25

PURPOSE ..................................................................................................................... 29

METHODS ................................................................................................................... 30
  Subjects ...................................................................................................................... 30
  Exercise Testing Protocol .......................................................................................... 30
  Chronotropic Incompetence Criteria ......................................................................... 32
  Interventions ............................................................................................................ 32
  Pharmacologic Intervention ....................................................................................... 34

STATISTICAL ANALYSES ......................................................................................... 36

RESULTS ...................................................................................................................... 37
  Patient Demographics .............................................................................................. 37
  Baseline Cardiopulmonary Exercise Test .................................................................. 40
  The Effect of Exercise Training and Pharmacology Intervention on Prevalence of Chronotropic Incompetence ................................................................. 46

DISCUSSION ............................................................................................................... 48
  Patient Demographics .............................................................................................. 49
  Baseline Cardiopulmonary Exercise Test .................................................................. 51
  Aerobic and Pharmacologic Effect on Prevalence of Chronotropic Incompetence ......................................................................................................................... 56
  Conclusion ................................................................................................................. 57

APPENDIX A ............................................................................................................... 58

APPENDIX B ............................................................................................................... 59
LIST OF TABLES AND FIGURES

TABLES
Table 1: Descriptive Characteristics of Study Participants
Table 2: Baseline CPET Resting and Peak Exercise Values from PARIS II, PIE I, and PIE II Groups

FIGURES
Figure 1: Pathophysiologic Syndrome of Heart Failure
Figure 2: Wilkoff Chronotropic Index
Figure 3: Prevalence of Chronotropic Incompetence (CI) at Baseline CPET
Figure 4: Peak VO₂ (VO₂peak) of Subjects with Chronotropic Incompetence (CI) and without Chronotropic Incompetence (Non-CI) at Baseline CPET
Figure 5: Comparisons of Heart Rate at Rest and Peak Exercise between Beta Blocked and Non-Beta Blocked Subjects
Figure 6: Prevalence of Chronotropic Incompetence (CI) in Beta Blocked versus Non Beta Blocked HFpEF Subjects
Figure 7: Heart Rate Reserve (HRR) Versus Peak Oxygen Consumption Reserve (VO₂ Reserve) at Baseline Testing
Figure 8: Peak Heart Rate Versus Peak Oxygen Consumption (VO₂peak) at Baseline Testing
Figure 9: Number of Patients Meeting Criteria for Chronotropic Incompetence (CI) for the Intervention Groups at Baseline and Prevalence of CI after Four Months of Respective Interventions
ABSTRACT

Cemal Ozemek

CHRONOTROPIC INCOMPETENCE IN PATIENTS WITH HEART FAILURE AND A PRESERVED EJECTION FRACTION: PREVALENCE AND IMPACT ON EXERCISE TOLERANCE

Thesis under the direction of Peter H. Brubaker, Ph.D., Department of Health and Exercise Science

BACKGROUND: An appropriate heart rate (HR) response to exercise is important, as it represents a key determinant of oxygen consumption (VO₂). Furthermore, the inability of HR to increase sufficiently, chronotropic incompetence (CI), has important functional and prognostic implications in heart failure (HF). While there have been several studies that have evaluated the prevalence and impact of CI in the HFrEF population, only one small study has examined this in HFpEF subjects. Furthermore, there are no published studies that have evaluated the effects of a pharmacologic or exercise intervention on the prevalence of CI in the HFpEF population.

OBJECTIVE: The primary objective of this study was to determine the prevalence of CI in a large group of HFpEF patients. The secondary objective was to evaluate the effect of beta blockers on the prevalence of CI in an HFpEF population. The final objective of this study was to evaluate the effects of a four month aerobic intervention, as well as an enalapril and a spironolactone intervention on the prevalence of CI in HFrEF patients.

METHODS: Prevalence and impact of CI on exercise tolerance was evaluated in 207 HFpEF subjects from three previously conducted studies (PARIS II, PIE I, PIE II). Symptom limited graded exercise tests with expired gas analyses were conducted on 207 HFpEF subjects using a bicycle ergometer protocol that started at 12 watts and progressed to 25 watts after 2 minutes.

RESULTS: Determination of chronotropic incompetence (CI) indicated that 58 participants out of the total 207 HFpEF subjects evaluated had CI (28%). Prevalence rates of CI in PARIS II, PIE I and PIE II were 27.9% (19/68), 15.5% (11/71) and 41.8% (28/67) respectively. Further analysis of VO₂peak in CI and non-CI participants revealed a
significantly higher VO$_{2peak}$ in individuals without CI (14.5 ± 3.2 ml·kg$^{-1}$·min$^{-1}$) compared to participants with CI (12.3 ± 2.3 ml·kg$^{-1}$·min$^{-1}$). There was no significant difference in the prevalence of CI in beta blocked patients (36.5%, 23/65) as compared to non beta blocked patients (24.3%, 35/144). The change in HR from rest to peak exercise, HR reserve, was significantly (p<.001) correlated (r = 0.48) with VO$_2$ reserve during baseline CPET. Moreover, these findings indicate that the increase in HR during exercise accounts for nearly one quarter ($R^2 = 23.4\%$) of the observed difference in VO$_2$ reserve in these HFpEF subjects. Furthermore, peak HR was also significantly (p<.001) correlated (r = .42) with VO$_{2peak}$. This relationship indicates that 18.4% of the observed difference in VO$_2$peak can be explained by peak HR. In both PARIS II (exercise) and PIE II (spironolactone) trials, there was a significant reduction (p<.05, p = .03 respectively) in the number of patients that meet criteria for CI after the intervention. Additionally, there were no changes in number of patients with CI from baseline to follow up in PIE I (enalapril) study.

CONCLUSION: The present study was the first to examine the prevalence and effect of CI on exercise tolerance in a larger sample of HFpEF patients. It was determined that the prevalence of CI (28%) in the HFpEF population was similar to that seen in several studies of HFrEF patients. Moreover, significantly lower VO$_{2peak}$ values in these older HFpEF patients with CI suggest there is a need to develop therapies to improve chronotropic function in HF patients. In fact, one pacemaker manufacturer has initiated a randomized controlled trial to test the effectiveness of rate-responsive pacing in older HFpEF patients. Other potential therapies, including medications, to improve chronotropic function in HFpEF patients should be explored.
INTRODUCTION AND REVIEW OF LITERATURE

Introduction/Epidemiology of Heart Failure

Heart failure (HF) has become a major public health problem in the United States where it is estimated that in 2006 approximately 5.7 million individuals had HF. This represents a staggering increase from 5.0 million in 2003. Even more sobering, HF is the only cardiac disorder that is on the rise and the prevalence rate is forecasted to reach 10 million people in the United States by the year 2030. The average age in the HF population is approximately 74 years with 750,000 new cases being diagnosed each year. Data collected in the Framingham Heart Study suggests the incidence of HF approaches 10 per 1000 after 65 years of age. The increased prevalence of HF in the elderly is due to the overall “aging” of the population and improved survival from cardiac events. The increased prevalence of this condition is also evident with a documented rise in hospital visits for HF from 877,000 in 1996 to 1,106,000 in 2006. Moreover, in 2006, 3,390,000 visits to the hospital occurred due to HF related conditions making it the leading cause of hospitalization in the elderly. Heart failure is a very expensive disorder to treat, with direct and indirect estimated costs reaching 37.2 billion dollars in 2009. Furthermore, HF a major cause of morbidity and mortality resulting in 292,214 deaths in the US in 2005 and carries a five year survival rate of 46%. It has been shown than men and women who had a cardiac event by the age of 40, had a life time risk of one in five of developing HF. However, those who were 40 years old and had no history of a prior myocardial infarction (MI), had a life time risk of just one in nine for men and one in six for women.
There are many risk factors associated with the development of HF, including hypertension and diabetes. High blood pressure is a major risk factor in the development of HF and it is estimated that 74% of patients with HF have high blood pressure. Levy et al. demonstrated hypertension (systolic $\geq$ 140mmHg, diastolic $\geq$ 90mmHg or taking prescribed hypertensive medications) was the most prevalent risk factor for the development of HF. By observing individuals in the Framingham Heart Study and Framingham Offspring Study, Levy et al. found that of the 392 individuals with HF, 357 (91%) participants were hypertensive prior to HF diagnosis. Furthermore, medical records of Olmsted County, Minnesota between the years 1979-2002 were utilized to observe the prevalence of risk factors (coronary disease, hypertension, diabetes, obesity and smoking) from the age of 18 to the year of incident HF. Hypertension was found to be the most prevalent risk factor (66%) in the development of HF and smoking was second (51%). Given the strong relationship between hypertension and HF, it is not surprising that treating hypertension can delay ventricular remodeling and reduce the development of HF by 50%.

Diabetes and obesity have also been associated with an increased risk of developing HF. A study observed 2,763 postmenopausal women from 1993-2006 and found that diabetic women with no additional risk factors for coronary disease had a three percent incidence of HF, whereas women with three or more risk factors had a 8.2% incidence of HF. Although obesity has been linked to the development of cardiomyopathy in previous studies, the independent relationship between body mass index (BMI) and HF incidence has only recently been established. The Physicians’ Health Study examined 21,094 men (average age 53 years) without known coronary
disease. After adjusting for hypertension, diabetes mellitus and hypercholesterolemia, the relative risk for developing HF in obese men was 2.8 compared to a relative risk of 1.49 for lean men. A likely pathway to developing HF is that risk factors lead to myocardial dysfunction directly or by causing myocardial ischemia/infarction through the development of coronary artery disease.\textsuperscript{18}

**Pathophysiology of Heart Failure**

Heart failure is most simply defined as the inability of the heart to deliver adequate blood flow to the body and is often the final pathway of all cardiac diseases.\textsuperscript{19} It is often described as a “syndrome” that begins with damage to the heart that ultimately leads to peripheral abnormalities (see figure 1). A variety of structural changes to the myocardium can occur that initiates the process of this debilitating syndrome. One problem, impaired myocardial contractility, is a consequence of left ventricle (LV) remodeling that occurs through the destruction of cardiac myocytes, abnormal myocyte function, or myocardial fibrosis.\textsuperscript{20, 21} Common events that may impair LV contractility include; myocardial infarction, myocardial ischemia, mitral regurgitation, aortic regurgitation and/or dilated cardiomyopathy. Myocardial infarction leads to tissue necrosis that creates areas of the ventricle that are no longer functional during active contraction. Furthermore, abnormal loading conditions such as hypertrophy, results in adaptive structural changes that lead to dilation of the ventricle.\textsuperscript{22} Moreover, conditions that reduce the LV’s ability to relax during diastole are generally due to LV hypertrophy, hypertrophic cardiomyopathy and restrictive cardiomyopathy. The obstruction of left ventricular filling can be brought on by mitral stenosis and pericardial constriction or
tamponade. Long term exposure to the increased afterload results in LV wall thickening and chronic stiffening \(^{23}\).

It is important to recognize that the HF syndrome can be initiated into two different types of left ventricular dysfunction; heart failure with a reduced ejection fraction (HFrEF) or heart failure with a preserved ejection fraction (HFpEF). The prevalence of these two disorders are relatively similar with HFpEF present in 44% of HF patients compared to 46% with HFrEF \(^{24}\). As the names of these two types of HF suggest, ejection fraction (EF) is a critical variable in the categorization of the syndrome. Ejection fraction is determined by dividing the volume of blood ejected from the heart with one beat (stroke volume) by the volume of blood in the LV at the end of the filling phase in the cardiac cycle (end diastolic volume). A normal EF value is typically considered to be greater or equal to 50\% \(^{24-26}\). The HFrEF condition causes the heart to have an increased end diastolic volume (EDV), while the impaired myocardial contractility causes an increase in the end systolic volume (ESV) or the volume of blood in the LV at the end of the contractile phase. Consequently, SV is reduced, thereby reducing the EF. Unlike HFrEF patients, the LV of HFpEF patients has a reduced LV distensibility or ability to relax during the diastolic phase (left ventricular filling) of the cardiac cycle. However, these patients do have a reduced SV as a result of a decreased EDV. Because HFpEF patients have a compromised EDV, the ratio between the reduced SV and EDV results in a normal EF.
Each form of LV systolic and diastolic dysfunction can occur independently or together, but both result in similar peripheral abnormalities that originate from LV dysfunction. It is clear that the two forms of HF present different phenotypic characteristics, yet each has a similar diminished cardiac output (CO), which is the volume of blood pumped by the heart each minute (ml blood/min). Both HFrEF and HFpEF reduce SV and therefore reduce CO. The diminished CO seen in both forms of HF results in similar peripheral abnormalities (figure 1). In HF, dyspnea is caused by a mismatching between pulmonary ventilation and pulmonary perfusion. While the lungs are adequately ventilated, the reduced CO to the lungs causes an increase in physiological dead space and inefficient ventilation.

In order to compensate for reductions in CO, HF patients have increased neurohormonal activity. The renin-aldosterone system is one pathway in which compensation may occur. The reduced CO observed in HF patients reduces the renal
arterial perfusion pressure, causing a decrease in salt delivery to the macula densa of the kidney, leading to direct stimulation of juxtaglomerular β-1-receptors by the activated adrenergic nervous system. Consequently, renin is secreted from the juxtaglomerular cells of the kidney in order to cleave circulating angiotensinogen to form angiotensin I, which is then cleaved by angiotensin converting enzyme (ACE) to form an effective vasoconstrictor, angiotensin II. The primary objective of these elevated neurohormones is to elevate and maintain the reduced blood pressure in addition to stimulate the release of aldosterone to promote sodium reabsorption. While the intent of the neurohormones is to increase blood volume to augment left ventricular preload and fully utilize the Frank-Starling mechanism, a variety of pathophysiological consequences occur.

The aforementioned neurohormonal responses increase arterial vasoconstriction which in turn reduces the volume of blood directed to skeletal muscle. The inability of the skeletal muscles to receive adequate perfusion results in a variety of peripheral abnormalities. Skeletal muscles not receiving a sufficient amount of oxygen to satisfy oxygen demand causes an increase in lactic acid production, further contributing to the reduction in exercise tolerance via muscular fatigue. An increase in arterial vasoconstriction also leads to an increase in afterload so that the LV must generate more pressure to overcome pressure in the aorta and eject blood from the ventricle. As a result, the LV myocardium must expend most of its energy on opening the aortic valve and thus the remaining energy levels may not be sufficient to fully empty the LV, which limits CO. Collectively, these compensatory mechanisms contribute to the symptoms these patients experience, particularly fatigue and dyspnea upon exertion or even at rest.
Acute Exercise Responses of Heart Failure Patients

As mentioned earlier, one of the hallmark symptoms of HF patients is exercise intolerance associated with exercise fatigue as well as dyspnea on exertion. The evaluation of exercise capacity is best quantified through the measurement of oxygen consumption (VO$_2$). The components of VO$_2$ can be evaluated through the Fick equation which states that $VO_2 = CO \cdot$ arteriovenous oxygen difference (a-vO$_2$). The arteriovenous oxygen difference is the difference in oxygen content between arterial and venous blood and is expressed in milliliters of oxygen per 100ml of blood. During periods of increased metabolic demand, such as physical exertion, the heart and peripheral organs facilitate an increase in VO$_2$ by increasing the central (HR · SV = CO) as well as the peripheral components (a-vO$_2$) of the Fick Equation. In normal adults VO$_2$ can be increased 7.7 times from rest to maximal exertion, due to a 3.2 fold increase in CO and a 2.5 fold increase in a-vO$_2$ $^{28}$. Generally the increase in CO during exercise is achieved through a two to four fold increase in HR and a 20% to 50% increase in SV $^{29}$. In healthy individuals resting a-vO$_2$ values are roughly 5.6 ml of O$_2$/100ml of blood, but at maximal exercise, where greater volumes of oxygen are required to satisfy metabolic demands, values can reach near maximal levels 16-18 ml of O$_2$/100 ml $^{30}$.

Numerous studies have shown that VO$_2$ at peak exercise (VO$_2$max) in HF patients is 15-40% lower than healthy individuals $^{19,25}$. This can be explained by examining the components of the Fick equation. There are many factors that lower VO$_2$max compared to the normal population and contribute to exercise intolerance in HF patients $^{25}$. A major component of the reduced VO$_2$ is the HF patient’s inability to significantly increase SV during exercise. Healthy individuals are able to increase SV from resting values of 50-70
ml/beat to 110-130ml/beat at maximal exertion, where as SV at rest and peak exercise produced by HF patients are similar at 50 to 65ml/beat\textsuperscript{29,31}. Despite significant increases in LV EDV, the HFrEF patient cannot increase SV due to reduced contractility. In contrast, the HFpEF patient has normal contractile function of the LV, however is unable to increase SV due to the inability to increase EDV. Additional abnormalities in the peripheral vascular structure and function, such as endothelial dysfunction and elevated neurohormonal responses, contribute to the skeletal muscle’s limited ability to extract oxygen from the blood, further limit VO\textsubscript{2peak}. Wilson et al. demonstrated that the reduced maximal exercise capacity in HFrEF patients was attributed to reduced perfusion of the exercising leg, creating high levels of lactic acid build up and severe leg fatigue\textsuperscript{32}. While many studies\textsuperscript{32,33} have examined the effects of SV and a-vO\textsubscript{2} difference on VO\textsubscript{2} in HF patients, very few studies have evaluated the HR response in HF patients and it’s subsequent effect on VO\textsubscript{2}. Since HR is a major component to the Fick equation, further studies are warranted in order to evaluate this important exercise measure in the HF population.

**Heart Rate Response to Exercise**

Many “central” factors including CO, SV and “peripheral” factors which limit the utilization of oxygen, contribute to the limited exercise capacity (VO\textsubscript{2}) in both HFrEF and HFpEF patients. In addition, an adequate HR response is critical to increase CO, and subsequently VO\textsubscript{2} during exercise. As exercise intensity increases, HR should respond by increasing in a linear fashion until it begins to plateau as VO\textsubscript{2peak} is reached. Heart rate at maximal levels of exertion (age prediced maximal HR = APMHR) is determined largely
by age and can be predicted with reasonable accuracy by subtracting age from 220 beats/min. While it is not well understood why there is age related decline of HRmax, some have speculated that it could be due to a decline in the intrinsic chronotropic function of the heart (the heart’s ability to maintain its own rhythm) \(^\text{34}\). Individual variations in HRmax are common as some individuals exceed or fail to reach APMHR. An inadequate HR response to exercise is often referred to as chronotropic incompetence (CI).

**Chronotropic Incompetence**

Chronotropic incompetence, the inability to generate an appropriate HR response to exercise, has prognostic significance in healthy populations \(^\text{35}\). One of the earliest description of CI was broad in that it simply described as an “attenuated” heart rate response to dynamic exercise \(^\text{36}\). More recent studies have defined CI as the inability to reach 80\% \(^\text{37}\) or 85\% \(^\text{38, 39}\) of APMHR. This condition has attracted attention as several studies have associated it to an increased mortality rate in healthy subjects \(^\text{35, 40-43}\). Lauer and colleagues \(^\text{35}\) evaluated a group of 2,953 patients that were referred for a symptom limited exercise treadmill stress test with thallium imagining. Using a CI criteria of <85\% of APMHR, 316 out of the 2953 subjects (11\%) had CI. Analysis of their data after adjustment for age, sex, thallium perfusion defects and other confounders, determined that those with CI had an increased risk of death (relative risk of 1.84). Dressing et al. \(^\text{44}\) made similar observations in healthy adults (mean age of 58 years) that were referred for symptom limited exercise treadmill testing at the Cleveland Clinic Foundation. Based on exercise test responses, 61 out of 384 these subjects (16\%) were classified as having CI.
During the six year follow up period, those subjects diagnosed with CI had an increased relative risk of death (RR = 1.85).

In order to evaluate for CI the subject must reach maximal exertion. A healthy adult subject is considered to reach maximal exertion when achieving a respiratory exchange ratio (RER) of 1.1 or greater. Heart Failure patients may have additional co-morbidities that can influence the ability to tolerate high levels of exercise, an RER of 1.05 or greater has been accepted as an appropriate value representing maximal effort. To reduce the dependence on maximal effort, the Wilkoff mathematical model was developed \(^{45}\) and has been employed in many studies \(^{38,39,44,46}\). This model is based on the linear relationship between %HR reserve and %metabolic reserve. Components of this model include APMHR, resting HR, MET level at a selected stage of an exercise test as well as the peak MET value. When entering these variables into the model, shown in Figure 2, an estimated HR (EHR\textsubscript{stage}) at the selected stage is determined. In order to determine if CI is present, the actual HR at the selected stage of the exercise test is divided by the estimated HR. If this value is less than .8, the individual is considered to have chronotropic incompetence. This model is widely applicable since it considers age and functional capacity (METS).

\[
EHR_{\text{stage}} = \frac{(220 - \text{age} - HR_{\text{rest}}) \cdot (\text{MET}_{\text{stage}} - 1)}{(\text{MET}_{\text{peak}} - 1)} + HR_{\text{rest}}
\]

Numerous studies have addressed the prevalence of CI in various populations with and without HF. Brubaker et al. \(^{39}\) examined older (>60) adults with and without HF and found a 26% prevalence rate of CI in HFrEF and a 19.6% prevalence rate of CI in
HFpEF patients. Where as only 7% of the healthy age matched subjects demonstrated CI criteria. Clark et al. found similar prevalence rates in HFrEF (28%) as the previous study using <80% of APMHR as the CI criteria. In contrast, Roche et al. 47 found a 66% prevalence rate (14 of 21) in a study conducted in HFrEF patients using the same <80% criteria. In addition, separate criteria 45 for beta blockers have been created because of their impact on heart rate. Witte et al. 48 determined prevalence of CI in 237 HFrEF patients with a portion of the group on beta blocker blocker therapy. Using the <80% APMHR criteria 32% of patients not on beta blockers and 49% of patients on β-blocker therapy presented with CI. Since a high percentage of patients on beta blockers were classified as having CI, an alternate HR criterion was proposed. Thus, Khan et al. suggested using 62% of APMHR for patients on beta blockers 49.

There have been several studies 37, 39, 50, 51 that have evaluated the impact of CI in HF patients, but these have mainly focused on HFrEF patients. The inability of HR to increase appropriately in a substantial (~30%) group of HF patients has obvious consequences to VO2peak in the context of the Fick Equation. Failure of HR to increase during exercise contributes to the decreased CO and reduced a-vO2 difference and further limits VO2. Brubaker et al. have shown that HR response to exercise explains approximately 15% of the variance in VO2peak in older HFrEF and HFpEF patients 39.

A study conducted by Clark and Coats 37 examined the effect of CI in 57 HFrEF patients. Maximal exercise testing revealed reduced VO2peak and reduced exercise time for those HFrEF subjects with CI. A later study conducted by Brubaker et al. 39 compared 59 HFrEF, 60 HFpEF patients and 28 healthy participants all over the age of 60. Results from maximal exercise stress tests revealed that healthy subjects were able to achieve a
higher peak workload (W), peak HR and VO\textsubscript{2peak} than HFrEF and HFpEF patients. Further evaluation of HF patients revealed that those with CI had significantly lower VO\textsubscript{2peak} values compared to HF patients without CI. The average peak work load, HR, and VO\textsubscript{2peak} achieved were 40.9 ± 5.0 vs. 61.3 ± 2.7 W, 107.8 ± 2.9 vs. 140.1 ± 1.5 beats/min, and 12.4 ± .8 vs. 14.6 ± .4 ml·kg\textsuperscript{-1}·min\textsuperscript{-1} respectively for individuals with CI and without CI.

Currently it is hypothesized that CI is due to the increased levels of circulating catecholamines in HF patients which results in desensitization and down regulation of the beta adrenergic receptors. A peak heart rate is generated by the increase in sympathetic drive to the heart in addition to beta adrenergic receptors response to circulating catecholamines\textsuperscript{52}. Work performed by Colucci and colleagues\textsuperscript{52} provides valuable insight in this area of research. Subjects in this study were 59 patients with HFrEF and 46 healthy subjects with no history of cardiac disease, hypertension, myocardial infarction, myocardial ischemia, valvular heart disease. Every three minutes during progressive overload of exercise intensity, plasma norepinephrine (NE) levels were measured. Results showed that at any given VO\textsubscript{2}, NE levels were higher in patients and at any given NE level, HR was lower in HFrEF patients compared to healthy subjects.

Bristow et al.\textsuperscript{53} further added to this area by examining the beta adrenergic receptor density, adenylate cyclase and creatine kinase activities in failing hearts compared to normal hearts obtained from cardiac transplant recipients and prospective donors. To evaluate beta adrenergic receptor density, the hearts were minced and then homogenized, followed by a period of centrifugation leaving the supernatant and combining it with a dihydroalprenolol solution which binds to the receptors. The failing
hearts demonstrated a 50 to 56% reduction in beta adrenergic receptor density compared to the normal hearts. To assess contractile properties of the two groups, adenylate cyclase activity was stimulated via isoproterenol administration and the activity of this reaction was documented. The failing hearts had a 45% reduction in maximal isoproterenol-mediated adenylate cyclase stimulation. Furthermore, a 54 to 73% reduction in maximal isoproterenol stimulated muscle contraction was observed. Further analyses revealed no significant differences between cytoplasmic creatine kinase activity or actin or myosin levels between the two groups. This observation suggests that there was no difference in the amount of functioning cardiac tissue in the failing heart compared to the healthy heart. Furthermore, results indicate that the decrease in maximal isoproterenol stimulation of adenylate cyclase was similar in scale to the reduction in receptor density, suggesting no difference in the coupling of receptor and agonist. While this study did not directly prove that there is beta adrenergic receptor down regulation in HF, it did provide valuable information on potential causes of CI in this population.

While no study has been able to reverse CI, there has been promising data collected demonstrating slight increases in HR and improvements in exercise capacity with endurance exercise training. Keteyian et al. 38, studied a group of 51 men diagnosed with HFrEF and randomized them into an exercise training (n=26) and no exercise (n=25) group. Each patient performed a maximal exercise test on a stationary cycle ergometer at baseline and at week 24. Chronotropic incompetence was diagnosed by subjects reaching less than 85% of age predicted maximal heart rate. Exercise training sessions were held three times per week for 33 minutes. Participants distributed their exercise time on three different pieces of equipment (motor driven treadmill, stationary
cycle, and arm ergometer) for 11 minutes each. Exercise training levels were based on the individuals HR reserve and set at 50% HR reserve for the first two weeks and then increased, as tolerated, to 80% for the remainder of the study. After the exercise intervention, there was an average 12 beat per minute increase in peak HR in the 14 individuals diagnosed with CI, whereas individuals in the non-exercise control group with CI only increased peak HR by 1 beat per minute after the study. Furthermore, the changes in peak HR and HR reserve secondary to exercise training were significantly (P<.001) related to the changes observed in VO2peak. These authors suggest an exercise training intervention may improve HR by up regulating beta receptors.

In contrast, a more direct approach in the effort of reducing the effects of CI is through rate adaptive pacing. Tse et al. 54 enrolled 20 patients (14 men; mean age 65 ± 3 years) with NYHA class III (n =11) or IV (n = 9) randomly into three different rate adaptive pace settings. All devices had an accelerometer based rate adaptive sensor with a lower rate limit of 50 and an higher end limit of 140 beats/min. Cardiopulmonary exercise tests were performed 4 weeks before the study was initiated using the off mode to familiarize them with the equipment and all patients exhibited chronotropic incompetence. Testing was repeated with the rate adaptive feature turned on. With the pacing on, patients achieved higher peak HR as well as a longer exercise time. However, there were no significant differences in VO2peak with the pacemaker on or off. Of note, patients that had severe CI and were unable to achieve 70% of APMHR during the initial exercise test demonstrated the greatest increases in peak exercise HR, exercise time and VO2peak compared to those with less severe CI. This study concluded that rate adaptive pacing is most beneficial for those that have severe chronotropic incompetence. Further
studies need to be conducted in order to fully understand the benefits of this therapeutic modality.

To date, there have been no studies that have specifically examined the effects of a pharmacologic intervention on the prevalence of CI in the HF population. However, medications such as enalapril, an ACE inhibitor (ACEI) and spironolactone (an aldosterone antagonist) may potentially play a role in improving HR response to exercise, by decreasing circulating levels of sympathetic hormones and making the beta receptors more responsive.

**Diagnosis and Classification of Heart Failure**

As described earlier, the most common symptoms experienced by HF patients are a decreased tolerance to exercise associated with fatigue or dyspnea. Additionally, retention of fluid in the limbs and/or lung creates further alarm and reason for further evaluation of HF. Evaluating the presence of HF should begin with an assessment of the patient’s medical history to rule out other conditions that may produce symptoms similar to HF.

Initial medical evaluation of HF usually begins with a 12-lead electrocardiogram (ECG) to identifying the presence of left ventricular hypertrophy, MI, or arrhythmias. However since the sensitivity of diagnosing HF through the ECG alone is low, the next step is generally to perform myocardial imaging techniques that will allow for a clearer understanding of the etiology of the HF syndrome. Imagining techniques provide the most effective data for evaluating the structural and functional integrity of the heart. The use of chest radiography gives information concerning the degree of cardiac enlargement.
and pulmonary congestion and/or to detect the presence of pulmonary disease. While this is a valuable tool, there are imaging techniques that can provide greater and more valuable information for the HF diagnosis process. A very valuable HF diagnostic test is a comprehensive two dimensional echocardiogram coupled with Doppler flow. Measures that can be accurately quantified through echocardiogram are the EF, ventricular dimensions and/or volumes, wall thickness and regional wall motion. These measures can help determine the specific cardiac abnormalities that may be the cause of the HF syndrome.

A more recent method of HF diagnosis involves the measurement of neurohormone levels in patients experiencing dyspnea and exertional fatigue. B-type natriuretic peptide (BNP) is frequently utilized to differentiate between HF and pulmonary disease. This neurohormone is secreted in response to the heart ventricles being subjected to volume expansion and pressure overload. A study conducted by Dao and colleagues investigated the utility of using BNP as a diagnostic measure of HF in an urgent care setting. Results indicated that BNP was both sensitive and specific for the identification of HF, with a diagnostic accuracy of 80%.

Outcomes of these diagnostic tests help place patients into a four stage classification scale; A, B, C or D. Patients in Stage A are those who are at high risk for HF but do not yet have structural heart disease or symptoms of HF. These individuals tend to present with hypertension, atherosclerotic disease, diabetes, obesity or the metabolic syndrome. Individuals in the next category, Stage B, have structural heart disease but do not demonstrate signs or symptoms of HF. In addition, the patients most likely share similar risk factors as those in Stage A, but may have had an MI, left
ventricular hypertrophy, a low EF or asymptomatic valvular disease. Patients in Stage C include those with structural heart disease with prior or current symptoms of HF including shortness of breath and fatigue or reduced exercise tolerance. The last and most severe stage, Stage D, are patients who have marked symptoms at rest despite maximal medical therapy are frequently hospitalized. Based on the determined stage, specific therapies/treatments are recommended (AHA).

Another common system of classification was created by the New York Heart Association (NYHA) 60. Similar to the previous classification scale, there are four separate classes, however this system is different in that the patients functional state is addressed with no reference to structural characteristics of the heart. Patients in Class I have no limitation of activities and they do not suffer any symptoms from ordinary activities. Those that are comfortable with rest or mild exertion and have mild limitations of activity are placed in Class II. Physical limitations become more evident in patients that are grouped into Class III. Class IV is the most severe stage and at this point patients are confined to a bed or chair while any physical activity elicits discomfort and symptoms can be experienced at rest. In most exercise studies, patients in phase IV are excluded due to severe symptoms.

**Medical Management of Heart Failure**

Similar to many cardiovascular disorders, appropriate steps can be taken in reducing the risk of developing HF. Moreover, there are a variety of surgical, pharmacologic and lifestyle options to effectively manage HFrEF once it is present. Individuals at risk for HF, who are classified as Stage A on the AHA/ACC heart failure
classification, can take appropriate steps in reducing existing risk factors (blood pressure, diabetes, obesity) to prevent undesirable LV remodeling. As previously mentioned, a major cause of LV dysfunction, particularly HFrEF, is coronary artery disease (CAD). Thus surgical and catheter based interventions designed to revascularize ischemic myocardium can potentially improve LV function and increase EF. In much more severe cases, particularly for those in Category D, cardiac transplantation or LV reduction surgery may be a viable option. Unfortunately, cardiac transplants can only be performed on approximately 3,000 patients/year due to limited donors. Moreover, surgical morbidity is high in this high risk population. Left ventricle reduction surgery, where a section of the dilated LV wall is removed to reduce the size of the heart, has also become a potential surgical option for patients with end stage HF. A recent study has shown that survival rates for cardiac transplant and LV reduction surgeries were similar at six months. However further analysis indicated that only 25% of patient’s HF condition improved following the LV reduction surgery.

Currently there is no therapy that can completely reverse the cardiac abnormalities associated with the HF syndrome. Consequently, the main objectives of most therapies are to improve survival, slow the progression of disease, alleviate symptoms, and minimize risk factors. Patients in all stages are recommended to make life style changes as well as begin pharmacologic therapies. There are several classes of medication that have become standard pharmacology in HFrEF. These are described in the AHA treatment algorithm. Digitalis, one of the oldest cardiac medications commonly used in HFrEF is utilized to improve the contractile ability of the myocardium, thereby increasing CO and LVEF. It also decreases the activation of the renin-angiotensin system.
and slows conduction through the sino-atrial node, thus making it useful for controlling arrhythmias such as atrial fibrillation \(^{64}\). The Digitalis Investigators Group (DIG) study found that HFrEF patients on digitalis compared to patients on a placebo had reduced heart failure related deaths and hospitalization rate but no reduction in overall mortality. For patients with a LVEF <45%, there was a 39% incidence of mortality or HF related hospitalization in patients taking Digitalis vs. control \(^{65}\).

Beta blockers are another pharmacologic option that has become standard therapy for HFrEF patients. Beta blockers used to mitigate harmful effects of increased sympathetic nervous system activation. One of the first studies to examine the effects of the beta blocker metoprolol on symptomatic HF patients was the Metoprolol in Dilated Cardiomyopathy (MDC) trial \(^{66}\). Many favorable outcomes were documented after a 12 month period of HFrEF patients on metoprolol including a significant reduction of all cause mortality (34%), improved LV function, improved quality of life (QOL), reduced incidence of hospitalizations and improved exercise tolerance. A much larger study, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) \(^{67}\), consisting of 3,991 HFrEF patients observed similar findings to the MDC trial. The MERIT-HF subjects were between the ages of 40 and 80 with an average age of 63 and were diagnosed as NYHA function class II-IV for three months prior to randomization. After a one year follow up, subjects on metoprolol had a significantly lower mortality rate (145 vs. 217 deaths in treatment vs. control).

Similar findings were seen with the beta blocker carvedilol in the Multicenter Oral Carvedilol in Heart Failure Assessment (MOCHA) trial \(^{68}\). This multicenter study randomly assigned 345 patients with mild to moderate HFrEF to a placebo or carvedilol
group. In addition to effectively reducing mortality risk by 73% compared to the control group and being well tolerated, the MOCHA study demonstrated greater improvements in LV function with increased doses of carvedilol. A similar study focused on the effect of carvedilol on a higher risk HFrEF population (moderate to severe HF) \(^69\). The PRECISE (Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise) trial randomized 278 patients into a placebo (n = 145) or carvedilol group (n = 133) for 6 months. Findings suggest that those taking carvedilol showed symptomatic improvements, lower risk of clinical deterioration, as well as a significant increase in EF as well as a reduction in the combined risk of morbidity and mortality. However, no significant difference was observed between the groups for exercise tolerance or QOL.

Another particular class of medications called angiotensin converting enzyme inhibitors (ACEI) has become widely used in HF patients. Most studies have observed improvements in survival, the rate of hospitalization, symptoms, cardiac function, and neurohormonal levels in HF patients taking an ACEI \(^70\). The Cooperative North Scandinavian Enalapril Survival Study (CONSESUS) study \(^71\) examined the effects of the ACEI enalapril on long term mortality in individuals with HF. Results indicated that individuals in the enalapril group had lower mortality rates compared to those that were in the placebo control group, strongly suggesting that enalapril protects the failing myocardium. Further evidence of the mortality benefit of enalapril is provided by the Studies of Left Ventricular Dysfunction (SOLVD) trial. This large study randomly assigned patients into an enalapril group (n = 2111) or a placebo group (n = 2117) with an average follow up period of 37.4 months. Fewer deaths (313 vs. 334) were observed in the enalapril vs. control groups resulting in an 8% reduction in risk. When combining the
incidence of heart failure and the total number of deaths, those in the enalapril treatment
group had a significantly lower incidence than the control group (630 vs. 818
respectively). These outcomes suggest that enalapril significantly reduced the incidence
of HF and mortality among patients with HFrEF. Furthermore, this study indicated that
individuals prescribed enalapril had a decreased progression of LV dilation as well as an
improvement in ESV. The authors of this study suggest that these outcomes could be the
result of altered remodeling and/or reduction in preload and afterload.

Another class of drugs that are prescribed to combat the negative effects of the
renin-angiotensin-aldosterone system in HFrEF patients are the aldosterone antagonists.
These medications are frequently prescribed in combination with ACEI because the later
medication does not always completely suppress negative effects of the renin-
angiotensin-aldosterone system. It has been shown that aldosterone can be produced
through angiotensin II independent mechanisms which contribute to aldosterone “escape”
Cicoira et al. demonstrated many beneficial aspects associated with long term use of
the aldosterone antagonist spironolactone. HFrEF patients, already taking ACEI (n =
106) were randomly assigned to receive spironolactone (n = 54) or a placebo (n = 52) for
12 months. Patients in the spironolactone treatment group increased their EF from 33 ±
7% to 36 ± 9% on average where as the control group did not demonstrate any changes in
EF. Furthermore, exercise tolerance improved in patients on the highest dose of
spironolactone.

While numerous pharmacotherapeutic approaches have been developed and used
effectively in managing HFrEF patients, there has been comparatively little progress in
strategies to manage HFpEF patients. Consequently most pharmacologic therapies used
in HFrEF have been used in HFpEF patients. Wu et al. 77, studied the survival rate of HFpEF patients on an ACEI (n = 85) compared to similar patients not on ACEI (n = 85) for a period of ten years. The subsequent analyses revealed that 18% of HFpEF patients on ACEI versus 33% not taking ACEI died from all causes. Similar benefits of the aldosterone antagonist spironolactone in HFpEF patients has been observed in a recent study by Daniel and colleagues 78. After four months of taking 25mg of spironolactone or placebo, those in the spironolactone group demonstrated a significant 8.3% increase in peak VO2 and a trend towards significance in the reduction of left ventricular posterior wall thickness (p = .076). These findings are important as they provide support for the safety and potential efficacy of spironolactone use in the HFpEF. More clinical trials to test different pharmacologic interventions in HFpEF patients are clearly needed.

In addition to adhering to prescribed medications, it is crucial for HF patients adopt appropriate lifestyle habits as well. Congestive symptoms due to fluid retention, limits many HF patients and consequently moderate restriction of sodium is highly recommended. Body weight and degree of fluid retention can be easily monitored so that appropriate changes to diet, patients sodium and fluid intake can be made55. Although physical activity for stable, well managed HFrEF patients is recommended by several professional organizations, (specifically American College of Cardiology, European Society of Cardiology), the American Heart Association treatment algorithm does not specifically include physical activity when describing important lifestyle changes for these types of patients. Furthermore, there are no professional organizations that presently recommend physical activity/exercise for HFpEF patients as adequate research in this area is lacking.
**Benefit of Physical Activity/Exercise in Heart Failure**

Prior to the late 1980’s it was common practice to discourage HF patients from participating in exercise and/or physical exertion. There was a widespread belief that placing additional stress on an already weak and damaged heart would have had deleterious effects and ultimately shorten the lifespan of these patients. However, numerous investigations have subsequently demonstrated that exercise is a safe lifestyle intervention in HF patients as exercise capacity, quality of life (QOL) and ability to perform activities of daily living are all generally improved. The improvements seen in VO$_{2peak}$ are mostly due to peripheral adaptations, as there are modest, if any changes in cardiac hemodynamic variables such as CO and SV. Many of the peripheral changes responsible for the increase in VO$_{2peak}$ include improvements in skeletal muscle metabolism, as well as vascular function.

The effect of exercise training has been well studied in the HFrEF population. A large scale, multicenter, randomized controlled study, HF-ACTION, evaluated the efficacy and safety of exercise training among 2,331 medically stable outpatients with HFrEF. Individuals that were eligible for this study had an EF of 35% or less, were NYHA class II to IV symptoms, had not been exercising regularly (not more than once a week) and had not experienced a major cardiovascular event 6 weeks prior to study recruitment. Subjects were then randomly assigned to a usual care plus exercise training group (n = 1159) or a usual care group (n = 1172). Supervised aerobic exercise training consisted of walking on a treadmill or riding a stationary bike for 36 sessions at 60 to 70% of heart rate reserve three times per week. This was followed by home based training at the same intensity five times per week for one to three years, depending on
date of entry to the study\textsuperscript{79}. Whellan and colleagues evaluated the effects of exercise training on health status among patients with HF in this study\textsuperscript{82}. At baseline, all characteristics between the two groups were similar. The Kansas City Cardiomyopathy Questionnaire (KCCQ) was utilized to measure health status. All participants had the greatest improvement of health status within the first three months of the study, with the exercise training individuals having the greatest improvement. In addition improvement in the overall scale, improvements were also noted in the sub scales of physical limitations, symptoms, QOL and social limitations. However, after three months, no further improvements were observed in these measures. Potential explanations for these findings include poor home based exercise compliance or a lack of social support. This study effectively demonstrated the benefits and importance of exercise training on self reported health status in HFrEF patients.

While health status may provide a glimpse of the patients overall well being; improvements in physiologic measurements such as VO\textsubscript{2peak} may provide information about the patients prognosis. Belardinelli and colleagues\textsuperscript{83} randomized 99 patients with stable HFrEF into an exercise intervention group or a non-exercise control group. The exercise training group (n = 50) performed 40 minutes of exercise at 60\% of VO\textsubscript{2peak} on an electronically braked cycle ergometer, three days a week for 8 weeks. After successful completion of this phase, participants continued to exercise for an additional 12 months at the same intensity and duration two days per week. At the end of the study, those in the exercise training group demonstrated an 18\% increase in VO\textsubscript{2peak} compared to controls as well as a 24\% increase in thallium activity score after two months of the intervention. These findings suggest that exercise training increases myocardial blood flow in HFrEF
patients. Furthermore, the exercise training group demonstrated improved QOL scores. Additionally, there were significantly fewer deaths (relative risk = .37) in the exercise training group (n = 9) than for the controls (n = 20).

Aerobic exercise training performed in a continuous fashion (i.e. single bout of 30–40 minutes) has been widely prescribed and studied in the HFrEF population. However, several studies have suggested that high intensity aerobic interval training may be more effective in HFrEF patients. Wisloff et al. 84 randomized 27 HFrEF patients to either a moderate continuous training group (70% of peak HR) or an aerobic interval training group (95% of peak HR). Both groups exercised three times per week for 12 weeks whereas the continuous training group exercised for 30-40 minutes continuously, the interval training group walked at 4 minute intervals at 90% to 95% of peak HR with 3 minute active pauses at 50% to 70% of peak HR. After 12 weeks, the interval training group increased VO$_{2peak}$ by 46% compared to just a 14% increase in the continuous training group. Greater improvements in cardiac hemodynamics were observed in the interval training group as EDV and ESV declined by 18% and 25% respectively. Furthermore, LVEF increased 35% and BNP levels decreased by 40% in the high intensity interval group. There were also greater improvements in endothelial function, mitochondrial activity as well as QOL in the interval training group. This study has important implications for exercise prescription in rehabilitation programs, however further studies are needed to evaluate safety and compliance of this approach in HFrEF patients.

Although numerous studies have demonstrated that EDV and SV fail to increase after exercise training in HFrEF patients, few studies have examined the effect of
exercise training on two other important determinants of CO, and subsequently VO\textsubscript{2peak}, HR. Keteyian evaluated 26 HFrEF patients before and after a 24 week exercise training program. Exercise training was conducted at 80\% of HRR for 33 minutes, three days a week. In addition to a 14.3\% increase in VO\textsubscript{2peak}, there was a 7\% increase in peak HR in these HFrEF patients after the exercise training period. This one study suggests that exercise training may improve HR response of HFrEF patients potentially through improvement in beta receptor activity.

While exercise training has been widely studied in HFrEF patients, very few studies to date have examined the effects of exercise training in the HFpEF population. Smart and colleagues compared the effects of an exercise training intervention in an HFrEF group (n = 24) and a HFpEF group (n = 18). Both groups exercised for 16 weeks on a cycle ergometer at intensity 60 \% to 70\% of VO\textsubscript{2peak} for one hour sessions, three times per week. Similar improvements were seen in QOL scores as well as functional capacity in both HFrEF and HFpEF groups. Peak oxygen consumption increased by 24\% in the HFrEF population and 30\% in the HFpEF population with no significant difference between the groups \textsuperscript{85}. The improvement in VO\textsubscript{2peak} observed in HFpEF is similar to those reported in previously described studies of HFrEF and appears to be due mainly to changes in peripheral physiology as there was little impact in cardiac hemodynamics in these HFpEF patients. Furthermore, no studies performed to date have examined the effects of exercise training on HR response or prevalence of CI in HFpEF patients.
PURPOSE

An appropriate heart rate (HR) response to exercise is important, as it represents a key determinant of oxygen consumption (VO$_2$). Furthermore the inability of HR to increase sufficiently, chronotropic incompetence (CI), has important functional and prognostic implications in heart failure (HF). While there have been several studies that have evaluated the prevalence and impact of CI in the HFrEF population, only one small study has examined this in HFP EF subjects. Therefore, the primary aim of this study was to determine the prevalence of CI in a large group of HFP EF patients. Beta blockers are a commonly prescribed medication in HF patients and are known to attenuate HR in healthy subjects through beta adrenergic receptor blockade. However, the influence of this drug on HR response and prevalence of CI in the HFP EF population has not been studied. Therefore, the secondary aim was to evaluate the effect of beta blockers on the prevalence of CI in an HFP EF population. Additionally, HR is an important determinant of VO$_{2peak}$, consequently the tertiary aim of this investigation was to evaluate the impact CI has on exercise tolerance (VO$_{2peak}$) compared to non-CI subjects in the HFP EF population. Furthermore, there are no published studies that have evaluated the effects of a pharmacologic or exercise intervention on the prevalence of CI in the HFP EF population. Therefore, the final aim of this study was to evaluate the effects of a four month aerobic intervention, as well as an enalapril and a spironolactone intervention on the prevalence of CI in HFrEF patients.
METHODS

Subjects

In order to address these objectives, data collected from three previously completed randomized controlled trials (RCTs) studies were analyzed. These RCTs include; Prospective Aerobic Reconditioning Intervention Study II (PARIS II), Pharmacological Intervention in the Elderly I (PIE I) and Pharmacological Intervention in the Elderly II (PIE II). Although this thesis analyzed subjects from three studies conducted at three different time points; the primary study personal, recruitment methods and testing methodologies were identical across the three studies. All subjects enrolled in these trials had isolated HFpEF which was defined by history, symptoms, and signs of heart failure, a preserved LV ejection fraction (≥ 50%), and no evidence of significant coronary artery disease, valvular, pulmonary disease, or any other medical condition that could mimic heart failure symptoms, such as anemia or thyroid dysfunction. Subjects with coronary artery disease were excluded in all subjects as determined by history, medical records, electrocardiogram, and rest and exercise echocardiogram. The diagnosis of heart failure was based on clinical criteria as previously described that included a heart failure clinical score from the National Health and Nutrition Examination Survey-I of ≥3 and verified by a board certified cardiologist.

Exercise Testing Protocol

The study protocol was approved by the Wake Forest University Baptist Medical Center Institution Review Board. Written informed consent was obtained from all patients. Each participant was familiarized with the testing environment and procedures
during the screening visit. Baseline measures of exercise capacity, left ventricular function, neuroendocrine function, and health-related quality of life were obtained and have been previously reported. However, for the purpose of this thesis, only data from the cardiopulmonary exercise test (CPET) was examined. The CPET was performed in the morning and participants had not ingested caffeine or eaten food for more than 4 hours. Testing was conducted and results were analyzed by individuals blinded to subject group and other clinical information.

Cardiopulmonary exercise tests in all three studies were performed on an upright position on an electronically braked cycle ergometer (Medical Graphics, Minneapolis, MN). After the collection of supine and seated resting measures, the initial stage of exercise was performed at 12 watts for two minutes, and then increased to 25 watts with each subsequent stage thereafter being increased by 25 watts every three minutes. During the exercise test subjects were encouraged by a blinded exercise physiologist to reach the point of maximal fatigue. Continuous expired gas analysis was collected using Medical Graphics CPX System that was calibrated before each test using known volumes and concentrations of gasses. In addition, continuous 12-lead electrocardiographic monitoring was performed and 30 second strips at the end of each stage were utilized for heart rate. Blood pressures were taken with an arm cuff manually during each exercise stage. The exercise test was terminated because of severe fatigue, exhaustion, or dyspnea. Immediately after the test, subjects were transferred onto a gurney in the supine position for acquisition of immediate recovery data.
**Chronotropic Incompetence Criteria**

To evaluate the prevalence of CI in heart failure with a preserved ejection fraction (HFpEF) patients, data obtained from each participant’s study folder was retrospectively assessed. The data extracted included; age predicted maximal heart rate (APMHR), resting HR, metabolic equivalent (MET) value at stage two, peak MET value, respiratory exchange ratio (RER) and the presence of beta blocker therapy. If subjects achieved a peak RER value greater than or equal to 1.05 during the cardiopulmonary exercise test, their peak HR value was divided by their APMHR. A peak HR/APMHR ratio less than .8 would indicate the presence of CI. In contrast, if the peak RER during the exercise test was less than 1.05, the Wilkoff mathematical model (seen below) was employed to estimate the HR at stage two (all subjects were able to advance to this stage of the exercise test, therefore values from this stage were analyzed).

\[
EHR_{stage} = \frac{(220 - \text{age} - \text{HR}_{rest}) \cdot (\text{MET}_{stage} - 1)}{(\text{MET}_{peak} - 1)} + \text{HR}_{rest}
\]

The actual HR at stage two was then divided by the predicted HR at stage two and a ratio less than .8 was indicative of CI. Subjects taking beta blockers were diagnosed using this approach and were also assessed using a cut off ratio of .62 as previously recommended by Khan et al.

**Interventions**

Participants for the three trials were recruited using the same screening process such that it included review of patient charts and clinical notes. Furthermore, there were 17 subjects that had participated in more than one of the three trials. Only the data
collected during the subject’s first study participation was utilized for analyses. In PARIS II, 68 subjects met inclusion criteria and were randomly assigned into either an exercise intervention group (n= 32) or a control group (n = 36). In PIE I, 164 patients were scheduled for a screening clinic visit. From these a total of 71 patients were enrolled in the trial, with 35 patients randomized to receive enalapril and 36 randomized to receive placebo. Of the 142 patients completing a clinical screening visit for PIE II, 67 were enrolled in the trial with 36 patients randomized to receive spironolactone and 31 patients randomized to receive placebo.

Participants were randomized to the exercise training group in the PARIS II study met at the Wake Forest Cardiac Rehabilitation Center on the Wake Forest University Reynolda campus from 7:45 to 9:00 a.m. on Monday, Wednesday, and Friday for 16 weeks. Before each session the subjects had HR and blood pressure (BP) measured and recorded. Each exercise session lasted one hour and consisted of a warm-up, a stimulus phase and a recovery period. During warm-up, subjects were led by an exercise physiologist through a series of stretching and light exercises designed to gradually increase physiologic responses in preparation for the more strenuous phase of the program. Based on data (HR, VO₂, and rating of perceived exertion) obtained from initial CPET tests, an individualized exercise prescription was developed for each subject. The intensity of the exercise sessions began at a low level (approximately 40-50% of maximal capacity) and was gradually increased to where the subject was able to maintain 70% HR reserve (HRR) for at least 20 minutes cycling and 20 minutes walking. The exercise prescription was adjusted as needed based on medical considerations and clinical responses. During the training period, exercise training intensity was reevaluated at least
every four weeks by assessment of HR response during submaximal bicycle exercise. Exercise training logs were used to collect HR, workload data. Adherence to the exercise program was determined from these logs. Any missed exercise sessions had to be made-up, thus all participants completed 48 sessions.

Patients randomized to the control group in PARIS II were contacted by phone at pre-arranged times and dates approximately every 2 weeks by the same person primarily responsible for the exercise training intervention. These conversations were leisurely and involved inquiry regarding overall well-being of the subject, and any changes in health status. A log was kept of all telephone contact encounters. Patients in the control group were asked not to change their physical activity level/pattern while in the 16 week trial.

**Pharmacologic Intervention**

Subjects enrolled in PIE I and PIE II pharmacologic intervention were randomized, using a computer program, to either a placebo or active drug group for 16 weeks. Other than the research pharmacist that labeled the medicine, all investigators, staff, and patients were blinded to group assignment. Subjects in PIE I began taking their respective drug (enalapril) at 2.5mg twice a day, and was increased to 5 mg of drug twice a day by week 2. If tolerated, they were increased to 10 mg of drug twice a day by week 3 and maintained this dosage for the remainder of the study. Those patients unable to tolerate 20 mg per day they were reduced to 10 mg per day. Those subjects in PIE II were gradually increased to take 25mg per day of spironolactone or placebo and dosages were adjusted for those unable to tolerate the 25mg per day. Compliance to the study protocol was evaluated through pill counts while tolerability and safety was assessed at each visit,
by measuring blood pressure and heart rate, as well as a focused interview and physical exam. Safety labs, including serum chemistry panel with creatinine were drawn at baseline, 2 weeks, 6 weeks, and every 6 weeks thereafter. Formal symptom assessments and quality of life-surveys (Minnesota Living with Heart Failure) were also performed at baseline and 6 and 12 months.
STATISTICAL ANALYSES

Descriptive statistics were used to determine distributions, means, and standard deviations. A chi-square analysis was used to evaluate the prevalence of CI within beta blocked and non beta blocked subjects. An independent t-test was used to compare mean VO$_{2\text{peak}}$ values between subjects with CI and those without CI. To evaluate the relationship between peak HR and VO$_{2\text{peak}}$ as well as between HRR and VO$_2$ reserve, a linear regression model was employed. Lastly, a chi-square analysis compared differences in CI prevalence from baseline to follow up between subjects with CI in the intervention groups (exercise, enalapril or spironolactone), before and after respective interventions. For all analyses, the level of significance was set at p<0.05.
RESULTS

As mentioned previously, there were three objectives of this investigation. The first was to determine the prevalence of CI in a sample of patients with heart failure and a preserved ejection fraction (HFpEF). The second objective was to examine the effect of beta blockers on the prevalence of CI in HFpEF. The final objective of this study was to evaluate the effect of three different interventions; four months of aerobic exercise training in the Prospective Aerobic Reconditioning Intervention Study II (PARIS II), four months of treatment with the angiotensin converting enzyme inhibitor enalapril in the Pharmacologic Intervention in the Elderly (PIE I), four months of the aldosterone antagonist spironolactone (PIE II) on the prevalence of CI in HFpEF patients.

Patient Demographics

Descriptive characteristics of all participants are shown in Table 1. There were no significant differences in mean age among the subjects in the three studies. It is worth noting that mean age of all three groups was 70.1 ± 7.1 years, which is somewhat older than most of the previous studies conducted in the heart failure (HF) population \(^{47, 50, 86}\). There were no significant differences in gender distribution between the three studies. The majority of the HFpEF patients were women, which is commonly observed, especially at older ages (≥70 years) \(^{61, 87}\). The total mean body mass index (BMI) was 31.3 ± 6.0 and the total average weight was 84.5 ± 18.5 kg. Consequently, many patients were categorized as obese, a known risk factor for the development of HF and a common characteristic in HFpEF patients. Differences in average weight (kg) and BMI was observed between PARIS II and PIE I participants. The average body weight in PARIS II
and PIE I groups were 87.6 ± 19.4 and 80.1 ± 15.4 respectively. Mean BMI values between PARIS II (32.2 ± 6.6) and PIE I (30.1 ± 4.7) were significantly different, however both would still be categorized as obese.

The majority of the participants in PIE I (n = 58) and PIE II (n = 51) were in the New York Heart Association (NYHA) class II and the remainder of the subjects (14 and 16 respectively) were NYHA class III. However, in PARIS II there was a more even distribution of subjects between class II (n = 33) and class III (n = 34) and one subject in class I. There was a high prevalence (82.6%) of hypertension in the three groups, which was expected as this is an established risk factor for HFpEF. Participants in PARIS II and PIE II had a significantly greater prevalence (88%) of hypertension compared to the PIE I (72%). More than 16% of participants in the three studies were diabetic but there were no significant difference between the groups. Current medications at the time of the study are also listed in Table 1 and are representative of medication regularly prescribed to HFpEF patients.
Table 1. Descriptive Characteristics of Study Participants

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<th>Characteristics</th>
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<th>PARIS II</th>
<th>PIE I</th>
<th>PIE II</th>
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<td>(n = 68)</td>
<td>(n = 72)</td>
<td>(n = 67)</td>
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<td>Age, years</td>
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<td>64 (88.9)**‡</td>
<td>49 (73.1)‡</td>
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<td>80.1 ± 15.4*</td>
<td>85.9 ± 19.9</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>31.3 ± 6.0</td>
<td>32.2 ± 6.6*</td>
<td>30.1 ± 4.7*</td>
<td>31.7 ± 6.6</td>
</tr>
<tr>
<td>NYHA class, No. (%)</td>
<td>1 (.1)</td>
<td>1 (.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I</td>
<td>142 (68.6)</td>
<td>33 (48.5)</td>
<td>58 (80.1)</td>
<td>51 (76.1)</td>
</tr>
<tr>
<td>II</td>
<td>64 (30.9)</td>
<td>34 (50)</td>
<td>14 (19.4)</td>
<td>16 (28.1)</td>
</tr>
<tr>
<td>III</td>
<td>171 (82.6)</td>
<td>60 (88.2)*</td>
<td>52 (72.2)**‡</td>
<td>59 (88.1)‡</td>
</tr>
<tr>
<td>History of hypertension No. (%)</td>
<td>34 (16.4)</td>
<td>13 (19.1)</td>
<td>8 (11.1)</td>
<td>13 (19.4)</td>
</tr>
<tr>
<td>Diabetes mellitus No. (%)</td>
<td>40 (19.3)</td>
<td>22 (32.4)</td>
<td>0</td>
<td>18 (26.9)</td>
</tr>
<tr>
<td>Current medications, No.</td>
<td>8 (3.9)</td>
<td>5 (7.4)</td>
<td>2 (2.8)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>64 (30.9)</td>
<td>16 (23.5)</td>
<td>25 (34.7)</td>
<td>23 (34.3)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>63 (30.4)</td>
<td>22 (32.4)</td>
<td>19 (26.4)</td>
<td>22 (32.8)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>24 (11.5)</td>
<td>10 (14.8)</td>
<td>7 (9.7)</td>
<td>7 (10.4)</td>
</tr>
</tbody>
</table>

Data presented are mean ± SD, unless otherwise noted
No. (%) equals number of patients in these studies that have that characteristic and % equals the number of that characteristic divided by total number of participants in that study.
Participants on ACE inhibitors in PIE I before baseline CPET discontinued ACE inhibitor treatment for the remainder of the study
* Significantly different (p < 0.05) between PARIS II and PIE I
† Significantly different (p < 0.05) between PARIS II and PIE II
‡ Significantly different (p < 0.05) between PIE I and PIE II
**Baseline Cardiopulmonary Exercise Test**

Cardiopulmonary exercise test (CPET) responses at baseline for all three studies are shown in Table 2. There were no significant differences observed in measures obtained at rest prior to the CPET including HR and blood pressure.

At peak exercise the average peak oxygen consumption ($\text{VO}_{2\text{peak}}$) of the three studies was $13.9 \pm 3.2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; a value expected of HFpEF, particularly when considering age and gender of most participants. The average peak heart rate (HR) of all participants was $127.4 \pm 19.5$ beats/min. There was significant differences observed in peak HR between PIE I and PIE II ($132.7 \pm 17.7$ and $121.5 \pm 20.4$ beats/min respectively) participants. Furthermore, subjects in the three studies had on average heart rate reserve (HRR) of $58.8 \pm 17.2$ beats/min. Significant differences in HRR were observed between PARIS II ($57.2 \pm 17.5$ beats/min) and PIE I ($64.4 \pm 16.2$ beats/min) as well as between PIE I and PIE II ($54.4 \pm 16.5$ beats/min) groups. Moreover, significant differences were observed in peak systolic blood pressure (SBP) and peak diastolic blood pressure (DBP) measures between PIE I and PIE II groups in addition to a significant differences in peak DBP measures between PARIS II and PIE II participants. While the blood pressure differences were statistically significant, none of these differences were considered “clinically meaningful”.
Table 2. Baseline CPET Resting and Peak Exercise Values from of PARIS II, PIE I, and PIE II Groups

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>PARIS II</th>
<th>PIE I</th>
<th>PIE II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO₂, ml·kg⁻¹·min⁻¹</td>
<td>3.3 ± 0.6</td>
<td>3.3 ± 0.7</td>
<td>3.4 ± 0.6</td>
<td>3.3 ± 0.7</td>
</tr>
<tr>
<td>RER</td>
<td>0.84 ± 0.01</td>
<td>0.85 ± 0.01</td>
<td>0.82 ± 0.01</td>
<td>0.84 ± 0.01</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>144.1 ± 17.9</td>
<td>146.2 ± 18.3</td>
<td>144.1 ± 16.8</td>
<td>141.8 ± 18.5</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>81.6 ± 9.9</td>
<td>82.1 ± 10.6</td>
<td>83.1 ± 9.0</td>
<td>79.4 ± 10.1</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>68.5 ± 11.1</td>
<td>70.1 ± 10.6</td>
<td>68.3 ± 11.5</td>
<td>67.1 ± 10.9</td>
</tr>
<tr>
<td><strong>Peak Exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO₂, ml·kg⁻¹·min⁻¹</td>
<td>13.9 ± 3.2</td>
<td>13.7 ± 2.9</td>
<td>14.6 ± 3.5</td>
<td>13.4 ± 2.9</td>
</tr>
<tr>
<td>RER</td>
<td>1.12 ± 0.01</td>
<td>1.11 ± 0.01</td>
<td>1.11 ± 0.01</td>
<td>1.13 ± 0.01</td>
</tr>
<tr>
<td>HR, beats/minute</td>
<td>127.4 ± 19.5</td>
<td>127.6 ± 19.1</td>
<td>132.7 ± 17.7 ‡</td>
<td>121.5 ± 20.4‡</td>
</tr>
<tr>
<td>HRR, beats/minute</td>
<td>58.8 ± 17.2</td>
<td>57.2 ± 17.5*</td>
<td>64.4 ± 16.2 *‡</td>
<td>54.4 ± 16.5‡</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>191.6 ± 24.3</td>
<td>192.0 ± 24.3</td>
<td>197.9 ± 24.3 ‡</td>
<td>182.3 ± 21.9‡</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>87.7 ± 11.7</td>
<td>91.2 ± 13.1†</td>
<td>88.2 ± 9.9 ‡</td>
<td>81.5 ± 8.9 †‡</td>
</tr>
<tr>
<td>Workload (Watts)</td>
<td>65.9 ± 26.8</td>
<td>66.5 ± 28.9</td>
<td>70.4 ± 24.9</td>
<td>60.2 ± 25.9</td>
</tr>
</tbody>
</table>

Data represented as mean ± standard deviation
VO₂: volume of oxygen consumption; RER: respiratory exchange ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; HRR: heart rate reserve;
Workload is highest workload achieved on bicycle during CPET

* Significantly different (p < 0.05) between PARIS II and PIE I
† Significantly different (p < 0.05) between PARIS II and PIE II
‡ Significantly different (p < 0.05) between PIE I and PIE II
Determination of chronotropic incompetence (CI) according to criteria described in the Methods section, indicated that 58 participants out of the total 207 HFpEF subjects evaluated had CI (28%) (Figure 3). This prevalence rate observed in these HFpEF patients is in the range of CI prevalence previously reported in HFrEF patients \(^{37, 39}\). Prevalence rates of CI in PARIS II, PIE I and PIE II were 27.9% (19/68), 15.5% (11/71) and 41.8% (28/67) respectively.

Further analysis of VO\(_{2}\)\(_{\text{peak}}\) in CI and non-CI participants (Figure 4) revealed a significantly higher VO\(_{2}\)\(_{\text{peak}}\) in individuals without CI (14.5 ± 3.2 ml·kg\(^{-1}\)·min\(^{-1}\)) compared to participants with CI (12.3 ± 2.3 ml·kg\(^{-1}\)·min\(^{-1}\)). This significant difference was still present when controlling for age, gender and weight when expressed in liters per minute.

The effect of beta blocker therapy on heart rate response as well as its effect on CI prevalence was also investigated. Beta blocker therapy did not have a significant effect on resting and peak HR (figure 5) as no significant differences were observed between beta-blocked and non beta-blocked subjects. In total there were 63 out of 207 participants (30.4%) on this medication and 144 (69.6%) not on this medication. As seen in Figure 6, there was no significant difference in the prevalence of CI in beta blocked patients (36.5%, 23/65) as compared to non beta blocked patients (24.3%, 35/144).
Figure 3. Prevalence of Chronotropic Incompetence (CI) at Baseline CPET

Figure 4. Peak VO₂ (VO₂peak) of Subjects with Chronotropic Incompetence (CI) and without Chronotropic Incompetence (Non-CI) at Baseline CPET
* Indicates Non-CI VO₂peak was significantly higher (p<0.05) than CI VO₂peak
○ = individual, ● = mean for group
Figure 5. Comparisons of Heart Rate at Rest and Peak Exercise between Beta Blocked and Non-Beta Blocked Subjects

![Heart Rate Comparison](image)

Figure 6. Prevalence of Chronotropic Incompetence (CI) in Beta Blocked versus Non Beta Blocked HFpEF Subjects

![Prevalence of CI](image)
Heart rate reserve plotted against VO₂ reserve and peak HR plotted against VO₂peak are important relationships in determining the contribution of HR to exercise capacity. As seen in Figure 7, HRR (the change in HR from rest to peak exercise) was significantly (p<.001) correlated (r = 0.48) with VO₂ reserve during baseline CPET. The relationship can be predicted with a regression line of \( y = 0.0856x + 5.5243 \) where \( y = \text{VO}_2 \) and \( x = \text{HR} \). Moreover, these findings indicate that the increase in HR during exercise accounts for nearly one quarter \( (R^2 = 23.4\%) \) of the observed difference in VO₂ reserve in these HFpEF subjects. Furthermore, peak HR was also significantly (p<.001) correlated \( (r = .42) \) with VO₂peak with a regression line of \( y = 0.0691x + 5.0989 \). This relationship indicates that 18.4% of the observed difference in VO₂peak can be explained by peak HR.

Figure 7. Heart Rate Reserve (HRR) Versus Peak Oxygen Consumption Reserve (VO₂ Reserve) at Baseline Testing
The Effect of Exercise Training and Pharmacology Intervention on Prevalence of Chronotropic Incompetence

Of the 68 patients who participated in PARIS II, 32 were randomized into the exercise intervention. Of the 72 patients that participated in PIE 1, 35 were randomized to the active drug treatment (enalapril) group. Of the 67 patients that participated in the PIE II study, 36 were all randomized into the spironolactone treatment group. The number, expressed as %, of those classified with CI before and after the interventions are presented in Figure 9. In both PARIS II (exercise) and PIE II (spironolactone) trials, there was a significant reduction (p<.05, p = .03 respectively) in the number of patients that meet criteria for CI after the intervention. Additionally, there were no changes in number of patients with CI from baseline to follow up in PIE I (enalapril) study.
Figure 9. Number of Patients Meeting Criteria for Chronotropic Incompetence (CI) for the Intervention Groups at Baseline and Prevalence of CI after Four Months of Respective Interventions
DISCUSSION

While there were several objectives of this thesis, a primary interest was to determine the prevalence of chronotropic incompetence (CI) in a group of heart failure with a preserved ejection fraction (HFpEF) patients and to determine if beta blockers influence the prevalence of CI in this population. Our results indicate that in an older HFpEF patient population, 28% of the participants met the criteria (<80% of APMHR) for CI. Furthermore, use of beta blockers did not appear to significantly increase to the prevalence of CI in HFpEF patients.

Since heart rate (HR) is an important determinant of peak oxygen consumption (VO₂peak), the secondary aim of this thesis was to examine the effect CI had on VO₂peak. We found that HFpEF subjects with CI had a significantly lower VO₂peak relative to HFpEF without CI (12.3 ± 2.3 versus 14.5 ± 3.2 ml·kg⁻¹·min⁻¹ respectively). This finding has significant implications as a previous investigation demonstrated significant changes in function when VO₂peak changes by 2 ml·kg⁻¹·min⁻¹ in HF patients.

The final aim of this study was to evaluate the effects of a four month aerobic intervention (PARIS II), as well as an enalapril (PIE I) and a spironolactone (PIE II) intervention on the prevalence of CI in HFpEF patients. While the numbers used in these analyses were small, it appeared that there were fewer PARIS II and PIE II meeting CI criteria following the intervention. Heart rate response to exercise may have improved due to an “up-regulation” of beta adrenergic receptor activity from the exercise training or the pharmacologic intervention with spironolactone.
**Patient Demographics**

A unique aspect of this investigation was the older age of subjects enrolled in the Prospective Aerobic Reconditioning Intervention Study II (PARIS II), Pharmacologic Intervention in the Elderly (PIE I) and PIE II studies. The mean age (70.1 ± 7.1 years) of participants in the three studies is older than most previously conducted trials, where subjects are typically less than 70 years of age. Furthermore, research has shown that HFpEF normally presents itself in elderly patients and more commonly in women. Thus the large percentage of women (78.7%) with HFpEF in the present investigation was expected. Although of interest, there are insufficient data in this study to compare and contrast male versus female HFpEF patients.

Common risk factors in the development of HF, such as obesity, hypertension and diabetes are well represented in the subjects of the present investigation. The average participant in the present investigation had a body mass index over 30, placing them in the obese category. Furthermore, the HFpEF is often the consequence of long-standing, untreated hypertension and thus it was not surprising that 82.6% of the subjects in this investigation had hypertension. There was a significantly greater prevalence of hypertension in subjects enrolled in PARIS II (88.2%) and PIE II (88.1) compared to PIE I (72.2) and higher than previously reported. Owan and colleagues extracted electronic data on 2,167 HFpEF patients at the Mayo Clinic and found that patients at Mayo were on average 74.4 ± 14.4 years of age and had an average BMI of 29.7 ± 7.8. In contrast to our investigation, only 62.7% of the patients at Mayo were hypertensive. A much larger population from the Acute Decompensated Heart Failure National Registry (ADHERE) database revealed that 77% of 26,322 HFpEF patients were hypertension.
Medications used by subjects in the present investigation are generally consistent with pharmacotherapy typically prescribed for HFpEF patients. The use of specific medications varied slightly between studies due to the requirements of the intervention as well as the time period in which the study was conducted. Angiotensin converting enzyme inhibitors (ACEI) are a common medication prescribed to both heart failure with a reduced ejection fraction (HFrEF) and HFpEF patients. Angiotensin converting enzyme inhibitors have been demonstrated to decrease long term mortality and cardiovascular events in HF patients 77. While more than 50% of HF patients are now prescribed this medication, only 32% and 27% of subjects in PARIS II and PIE II, respectively, were prescribed ACEI. Inclusion criteria for PIE I required that subjects could not been on ACEI at baseline of the study, as enalapril is an ACEI, thus the reason for 0% on this medication at baseline.

While the benefits of beta blocker therapy in HFrEF patients have been demonstrated in numerous investigations 68, 69, 91 the benefit of this medication in HFpEF is less clear. Recent data from the Acute Decompensated Heart Failure National Registry indicates that 52.2% of HFpEF patients and 62.6% of HFrEF patients were on beta blockers at hospital discharge 92. In contrast to these previous findings, there was a much lower prevalence of beta blocker use in the three studies; PARIS II (23.5%), PIE I (34.7%) and PIE II (34.3%) examined for this investigation. The low number could be due to the initiation dates of these studies, particularly PARIS II which began in 1997, when potential benefits of beta blocker therapy in HFpEF was less clear. Furthermore, Digoxin is commonly prescribed to HFrEF patients in order to improve myocardial contractility, but since EF% is not reduced in HFpEF patients, fewer receive Digoxin.
Thus as expected, only a small percentage (3.9%) of HFpEF subjects in the current investigation were prescribed Digoxin.

**Baseline Cardiopulmonary Exercise Test**

Expired gas measures obtained during the cardiopulmonary exercise test (CPET), particularly VO$_{2\text{peak}}$, are often the primary outcome measure in research and clinical settings. Moreover, a primary symptom of HFpEF and HFrEF patients is a severely reduced exercise tolerance, due in large part to a reduced VO$_{2\text{peak}}$. Furthermore, VO$_{2\text{peak}}$ has been established as a powerful predictor of mortality in HF patients $^{93, 94}$, and specifically, a VO$_{2\text{peak}}$ of $\leq$14 ml·kg$^{-1}$·min$^{-1}$ is an important criteria for determining need and timing of cardiac transplantation. The average VO$_{2\text{peak}}$ of the three studies in the current investigation was 13.9 ± 3.2 ml·kg$^{-1}$·min$^{-1}$. While this value is very low, it may not have as much prognostic significance as the VO$_{2\text{peak}}$ levels in the present study were effected by; 1) the advanced age of the subjects 2) most subjects being female 3) the mode of testing was bicycle ergometry where VO$_{2\text{peak}}$ is reduced 5-25% compared to treadmill exercise $^{95}$.

Additional values collected during CPET, such as respiratory exchange ratio (RER) and peak heart rate (HR$_{\text{peak}}$) were used to determine the prevalence of CI in this investigation. At peak exercise effort, HFpEF subjects in this investigation were only able to achieve a work load of 65.9 ± 26.8 watts, a value much lower than reported in an earlier publication of similar HFpEF patients (83.1 ± 4.4 watts) $^{39}$. The average RER value at peak exercise for the three trials used in this investigation was 1.12 ± .01, which suggests that a majority of subjects were able to exceed a ratio of 1.05, a level thought to
reflect maximal exertion in this population\textsuperscript{45}. Age predicted maximal heart rate (APMHR) for an average age of 70 year is 150 beats/min. On average subjects in the present investigation only reached a HR\textsubscript{peak} of 127 beats/min, much lower than age predicted maximal heart rate (APMHR) of 150 beats/min. However it is worth noting that on average, the overall mean peak HR of 127 was higher than the 80% of APMHR (120 beats/min) criteria used to decide CI. An additional value of importance is heart rate reserve (HRR) or the difference between HR\textsubscript{peak} and resting HR. This value decreases as age increases, primarily due to a reduction in HR\textsubscript{peak}. Subjects in this investigation had a HRR of 58.8 ± 17.2 beats/min which is considered to be typical of this age group\textsuperscript{96}. The average resting systolic blood pressure (144 mmHg) was considered to be in the hypertensive category and is common in older people while the diastolic blood pressure (81 mmHg) was in the normal range. Further indications of good levels of exertion during CPET were supported by an increase of blood pressure to high (systolic blood pressure: 191.6 ± 24.3 mmHg, diastolic blood pressure: 87.7 ± 11.7 mmHg), appropriate levels at peak exercise.

Using valid and commonly accepted methods of determining CI, 28% of the total 207 subjects used in the present investigation were found to have CI. Analysis of each individual study revealed that 27.9% (19/68) of subjects in PARIS II, 15.5% (11/71) of subjects in PIEI and 41.8% (28/67) of subjects in PIE II met CI criteria. Significant differences in prevalence rates were found between PIE I and PIE II (p = .001), total prevalence and PIE I (p = .04) as well as between total prevalence and PIE II (p = .04). There has been wide range (19-66%) of reported prevalence rates of CI in HFrEF patients. This variability could be due to differences in CI criteria used in different studies (<80%
or <85% of APMHR) as well as patient characteristics (age, disease, type/dose of medications). Clark and Coats reported a 28% prevalence of CI (<80% of APMHR) in non-beta blocked HFrEF patients. In contrast, Roche et al. found the greatest prevalence of CI (66%) in 22 non-beta blocked HFrEF patients. One of the few studies that has examined prevalence of CI in the HFpEF population was conducted by Brubaker and colleagues. Chronotropic incompetence was observed in 19.6% (11/56) of the HFpEF patients they examined. While the prevalence of CI in the PIE I (15.5%) study was significantly less than PIE II and the total study population, it is similar to what was observed in the formerly mentioned study (19.6%). Further more, the prevalence of CI in PIE II was higher compared to the PARIS II, PIE I and the total study cohort. This may potentially be due to differences in the dose of rate affecting medications, such as digoxin and/or beta blockers. Findings of CI in the total study cohort in the present investigation are consistent with these observations of both HFrEF and HFpEF. These current findings add to the existing literature since this prevalence rate was observed in a much larger sample of HFpEF patients.

As mentioned in earlier chapters, the Fick Equation \( \text{VO}_2 = (HR \cdot SV) \cdot a-v\text{O}_2 \) describes the important central and peripheral components of \( \text{VO}_2\text{peak} \). While HF patients are known to have an impaired SV response to exercise, HR response to exercise in this population has not been well studied. Brubaker and colleagues found that HFrEF and HFpEF patients with CI had a 2.2 ml·kg\(^{-1}\)·min\(^{-1}\) reduction in \( \text{VO}_2\text{peak} \) compared to HF patients without CI. Similarly, in the current investigation HFpEF patients with CI had a significantly lower \( \text{VO}_2\text{peak} \) (12.3 ± 2.3 ml·kg\(^{-1}\)·min\(^{-1}\)) than HFpEF subjects without CI (14.5 ± 3.2 ml·kg\(^{-1}\)·min\(^{-1}\)). While the difference of 2.2 ± .9 ml·kg\(^{-1}\)·min\(^{-1}\) may seem
insignificant, it reflects a difference of ~20% of $\text{VO}_2\text{peak}$ in this population. This difference of 2 ml·kg$^{-1}$·min$^{-1}$ could result in a significant difference in physical function and/or quality of life. While it is clear that HR plays an important role in determining $\text{VO}_2\text{peak}$ in HFpEF patients, as seen in figure 4, there is still significant “overlap” in $\text{VO}_2\text{peak}$ in those with and without CI. This observation suggests that other “central” and/or “peripheral” factors can also contribute to the reduced $\text{VO}_2\text{peak}$ seen in HFpEF patients.

The relationship between HRR and VO$_2$ reserve as well as peak HR and VO$_2$peak helps to evaluate the contribution of heart rate to VO$_2$peak. Figure 7 shows a significant positive correlation between HRR and VO$_2$ reserve with the increase in HR during exercise accounting for nearly one quarter (23.5%) of the observed difference in VO$_2$ reserve in these older HFpEF patients. This level is slightly greater than reported (15-17%) in a smaller study of HFpEF subjects. Additionally, there was a significant positive relationship between peak HR and VO$_2$peak (Figure 8), with peak HR accounting for 18.4% of the observed difference in VO$_2$peak. Therefore, it appears that heart rate response to exercise is an important contributor to the exercise intolerance commonly observed in an older HF population.

Beta blockers commonly attenuate resting, as well as peak HR in non-HF patients by inhibiting Beta-1 adrenergic receptors. Thus it is expected that the prevalence of CI would be greater in subjects that were on beta blockers than those not on a beta blocker. However there were no statistically or clinically significant differences between beta blocked and non-beta blocked subjects in resting ($65.3 \pm 12.5$ vs. $69.9 \pm 10.1$ beats/min) and peak HR ($122.3 \pm 19.9$ vs. $129.6 \pm 19.0$ beats/min) (Figure 5). Furthermore, both beta
blocked and non-beta blocked groups reached an average peak HR that was >80% of APMHR (120 beats/min). Of the 63 subjects taking beta blockers in this investigation (36%), 23 met CI criteria (<80% of APMHR) where as 35 subjects (24.3%) of the 144 subjects not on beta blockers still had CI. The difference in prevalence rates was not significantly different and suggests that the use of beta blockers do not significantly increase the prevalence of CI in HFpEF patients. This finding is important in light of the separate CI criteria (<62% of APMHR) has been recommended for patients on beta blockers 49. Although, subjects with HF were excluded from this previous investigation, the use of this criterion has been applied to HF patients on beta blockers. Use of the HR < 62% of APMHR criteria would categorize just 7.9% of the subjects on beta blockers in the present investigation as having CI. Such a low prevalence rate would be considerably less than what has been reported in every other study.

Data from the current investigation suggests that there may be a “beta blocker paradox” in HFpEF patients. This paradox may be due to the unique neurohormonal responses and beta receptor activity in HF patients. Heart failure is a syndrome that results in increased activity of the sympathetic nervous system and elevated catecholamine levels. The chronic increase in catecholamine levels may result in a “down-regulation” and/or decreased beta receptor sensitivity 53. Since beta blockers prevent the binding of norepinepherine and epinephrine to beta adrenergic receptors, it is hypothesized that patients taking beta blockers will have increased beta adrenergic receptor sensitivity to norepinepherine and epinephrine 98. While the present study did not examine specific mechanisms, or if a beta blocker paradox exists in HFpEF. The data
from the current study does suggest that HR response to exercise is similar in HFpEF patients either taking or not taking beta blockers.

**Aerobic and Pharmacologic Effect on Prevalence of Chronotropic Incompetence**

A novel element of this current investigation was evaluating the effect of an exercise (PARIS II), enalapril (PIE I) or spironolactone (PIE II) interventions on the presence of CI. There were very few subjects with CI at baseline who were randomized to an intervention group (PARIS II = 6 subjects; PIE I = 7 subjects; PIE II = 13 subjects). After four months of respective interventions, significantly fewer subjects enrolled in PARIS II (exercise) (p<.05) and PIE II (spironolactone) (p = .03) met criteria for CI.

The mechanism by which subjects who no longer met CI criteria after the PARIS II and PIE II post intervention can not be determined definitively from this investigation. Potential mechanisms associated with exercise training include a reduction in neurohormonal levels and or an increase in beta adrenergic receptor sensitivity, thereby improving inotropic and chronotropic responses\(^99\). Furthermore, subjects in the exercise training group were likely to have an increase in exercise capacity and thus an increase in time and workload on the CPET. This additional work/time may have stimulated a greater increase in HR, thereby reducing the prevalence of CI. In addition spironolactone therapy reduces aldosterone levels and consequently decreases the reabsorption of sodium and water in the renal tubules and decreases blood volume. The reduced blood volume initially helps alleviate symptoms of congestion in the lungs but could also reduce the activity of the renin-angiotensin system and release of sympathetic...
neurohormones. This could potentially improve beta adrenergic receptor sensitivity and improve HR response to exercise.

There were several important limitations of the present study. The three separate interventions were conducted at different time points and employed different interventions. However, these studies were conducted in sequence from 1997-2009 and other than slight changes in personnel; the procedures and specific testing methodologies remained essentially the same throughout all three trials. Furthermore, evaluating the effect of exercise and pharmacologic interventions was limited by a small sample size of patients with CI. Obviously a randomized controlled trial of just CI patients would be the best way to evaluate the effects of these therapies.

**Conclusion**

The present study was the first to examine the prevalence and effect of CI on exercise tolerance in a larger sample of HFpEF patients. It was determined that the prevalence of CI (28%) in the HFpEF population was similar to that seen in several studies of HFrEF patients. This finding adds to the evidence that these unique forms of HF (HFpEF versus HFrEF) share many pathophysiologic similarities. Moreover, significantly lower VO\(_{2}\)\text{peak} values in these older HFpEF patients with CI suggest there is a need to develop therapies to improve chronotropic function in HF patients. In fact, one pacemaker manufacturer has initiated a randomized controlled trial to test the effectiveness of rate-responsive pacing in older HFpEF patients. Other potential therapies, including medications, to improve chronotropic function in HFpEF patients should be explored.
New York Heart Association Functional Classification

Class I: Symptoms exacerbated at levels that would limit normal individuals

Class II: Symptoms occur at levels of ordinary exertion

Class III: Symptoms occur on levels at less than ordinary exertion

Class IV: Symptoms occur at rest
APPENDIX B

American Heart Association and American College of Cardiology Heart Failure Classification System

Stage A: Patient who has no structural disorder of the heart but is at high risk for developing heart failure

Stage B: Patient with a structural disorder of the heart but has yet to develop heart failure symptoms

Stage C: Patient with underlying structural heart disease that is associated with past or current symptoms of heart failure

Stage D: Patient with end-stage heart failure that requires specialized treatment strategies such as mechanical circulatory support, cardiac transplantation, continuous inotropic infusions, or hospice care
### APPENDIX C

Heart Failure Clinical Score (>3 required)

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>Score</th>
</tr>
</thead>
</table>

#### Dyspnea/difficulty breathing
- Trouble with breathing (shortness of breath) 1
- Hurrying on the level or up slight hill 1
- At ordinary pace on the level? 2
- Do you stop for breath when walking at own pace? 2
- Do you stop for breath after 100 yards on the level? 2

#### Physical examination
- Heart rate (beats/min)
  - 91 to 110 1
  - 111+ 2

#### Rales/crackles
- Either lower lung field 1
- Either lower and either upper lung field 2

#### Jugulovenous distention
- Alone 1
- Plus edema 2
- Plus hepatomegaly 2

#### Chest x-ray film
- Cephalization of pulmonary vessels 1
- Interstitial edema 2
- Alveolar fluid plus pleural fluid 3
- Interstitial edema plus pleural fluid 3
APENDIX D

Exclusionary criteria for isolated HFpEF patients

- Medical
  - A. Valvular heart disease as the primary etiology of CHF
  - Significant change in cardiac medication <4 weeks
  - Uncontrolled hypertension (controlled blood pressure is defined according to current JNC guidelines)
  - recent or debilitating stroke
  - B. Cancer or other noncardiovascular conditions with life expectancy less than 2 years
  - C. Anemia (<11 gms Hgb)
  - D. Serum postassium > 5.1 mEq/L
  - E. Renal insufficiency (creatinine >2.4 mg/dl)
  - F. Psychiatric disease- uncontrolled major psychoses, depressions, dementia, or personality disorder
  - G. Allergy to spironolactone
  - H. Current taking spironolactone or any aldosterone antagonist

- Other
  - A. Plans to leave area within 1 year
  - B. Refuses informed consent

- Mini-mental exam score <24

- Screening pulmonary function test: FEV1 or FVC < 80th percentile for age and gender

- Screening Echocardiogram
  - A. Left ventricular ejection fraction < 50%
  - B. Segmental wall motion abnormality
  - C. Significant valvular heart disease

- Familiarization/Screening Exercise Test
  - D. Evidence of significant ischemia
    - ECG: 1mm flat ST depression (confirm with echocardiogram wall motion)
    - Echo: Wall motion abnormality or decrease in global contractility
  - E. Stopped exercising due to chest or leg pain or any reason other than exhaustion/fatigue/dyspnea
  - F. Exercise SBP > 240 mmHg, DBP > 110 mmHg
  - G. Unstable hemodynamics or rhythm
  - H. Unwilling or unable to complete adequate test

- Magnetic resonance imaging
  - I. Indwelling metal-containing prosthesis (orthopedic, valvular, other)
  - J. Pacemaker or defibrillator
  - K. History of welding occupation (ocular metal debris)
  - L. Uncontrollable claustrophobia
  - M. Any other contra-indication to MRI
REFERENCE LIST


SCHOLASTIC VITA

CEMAL OZEMEK

PERSONAL INFORMATION

Birthplace:       San Jose, California
Birth date:        May 16, 1986

UNDERGRADUATE STUDY

2004-2008  University of California, Davis
           Davis, California
           B.S. Exercise Biology
           Concentration in Applied Exercise Physiology

GRADUATE STUDY

2008-2010  Wake Forest University
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           M.S. Health and Exercise Science
           Advisor: Peter H. Brubaker, Ph.D.
           Thesis: “Chronotropic incompetence in patients with heart failure
and a preserved ejection fraction: prevalence and impact on
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PROFESSIONAL EXPERIENCE

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2008-2010  Research Assistant
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           Winston-Salem, NC

2009-2010  Exercise Specialist
           Action Health: Physical Activity, Lifestyle and Nutrition (PLAN) Program
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2006  Physical Therapy Summer Intern
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PUBLICATIONS AND PRESENTATIONS

Peter H. Brubaker; Cemal Ozemek. Exercise therapy for the failing heart: Harmful or helpful? ACSM Health and Fitness Journal. March 2010

Peter H. Brubaker; Alimer Gonzales; Cemal Ozemek; Underwater and traditional treadmill exercise may produce similar cardiorespiratory responses in collegiate athletes. Journal of Sports Rehabilitation.

May 2010, ACSM Annual Meeting
Cemal Ozemek BS; Peter H. Brubaker PhD FACSM; Dalane W. Kitzman MD. Impact of Beta Blockers on Chronotropic Incompetence in Heart Failure with Preserved Ejection Fraction

May 2009, ACSM Annual Meeting
Cemal Ozemek BS; Peter H. Brubaker PhD FACSM; Alimer Gonzales BS; S. Wiley MS, PT, ATC; G. Collins MS, ATC. Cardiorespiratory responses to aquatic vs. traditional treadmill exercise: Implications for exercise prescription
MEMBERSHIPS

2008-2010   American College of Sports Medicine
2004-2008   Tau Kappa Epsilon Fraternity

CERTIFICATIONS

2009-2010   ACSM Certified Clinical Exercise Specialist
2008-2010   Adult CPR/AED