IMPACT OF EXERCISE TRAINING AND/OR CALORIC RESTRICTION ON HEART RATE RESPONSE IN PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION

BY

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DEDICATION

I would like to dedicate this thesis to my family and my sweet boyfriend. You all supported me during one of the hardest times of my life so far. Words and deeds cannot express how grateful I am to you all, so for now I will dedicate this thesis to you.

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TABLE OF CONTENTS

LIST OF TABLES & FIGURES V

LIST OF ABBREVIATIONS VI

ABSTRACT VII

REVIEW OF LITERATURE 1

Overview 1

Epidemiology 2

Heart Failure Phenotypes 4

Pathophysiology of Heart Failure 6

Exercise Intolerance and The Fick Equation 12

Chronotropic Incompetence 15

Management of CI 21

METHODS 28

RESULTS 34

DISCUSSION 50

REFERENCES 59

CURRICULUM VITAE 74

LIST OF TABLES & FIGURES

Table 1. Baseline Characteristics of Study Participants……35

Figure 1a-f. Unadjusted means (±SE) HR Responses at Baseline & 20-Weeks in the Intervention Groups……...36

1a. HR_{rest}

1b. $HR_{submaximal}$

1c. HR_{peak}

1d. $HR_{reserve}$

1e. $HR_{recovery1}$

1f. $HR_{recovery}$

Figure 2. Relationship Between Change in Relative VO_{2peak} & $HR_{reserve}$……..41

Figure 3. Relationship Between Change in Absolute VO_{2peak} & $HR_{reserve}$…….43

Figure 4. Relationship Between Change in Body Weight & $HR_{reserve}$……...45

Table 2. Pearson Correlation Analyses……..46

Figure 5. Chronotropic Incompetence Prevalence at Baseline & 20-weeks……..…48

Table 3. Fisher- Freeman- Halton Results for CI Prevalence……49

LIST OF ABBREVIATIONS

APHRM	Age-Predicted Heart Rate Max
APHRR	Adjusted Percent Heart Rate Reserve
a-v$O_{2difference}$	Arteriovenous Oxygen Difference
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
CI	Chronotropic Incompetence
CO	Cardiac Output
CON	Attention Control Group
CPET	Cardiopulmonary Exercise Test
CR	Caloric Restriction/Calorically Restricted Diet
EDV	End Diastolic Volume
EF	Ejection Fraction
ET	(Aerobic) Exercise Training
HF	Heart Failure
HFpEF	Heart Failure with A Preserved Ejection Fraction
HFrEF	Heart Failure with A Reduced Ejection Fraction
HR	Heart Rate
LV	Left Ventricle/Left Ventricular
MCR	Metabolic Chronotropic Relationship (Also Known as the “Wilkoff Approach” Or “Chronotropic Index”)
MET	Metabolic Equivalent
MLWHF	Minnesota Living with Heart Failure Questionnaire
NT-proBNP	N-terminal prohormone of Brain Natriuretic Peptide
RER	Respiratory Exchange Ratio
RPE	Rating Of Perceived Exertion
SECRET I	Study Examining Caloric Restriction and Exercise Training
SNS	Sympathetic Nervous System
SV	Stroke Volume
VO_2	Volume Of Oxygen Consumption
VO_2peak	Peak Volume of Oxygen Consumption

ABSTRACT

Exercise intolerance is considered the hallmark symptom of heart failure with preserved ejection fraction (HFpEF). One factor that possibly contributes to exercise intolerance is an inadequate heart rate response, also known as chronotropic incompetence (CI). Chronotropic incompetence is potentially manageable with medications, rate-adaptive pacing, and lifestyle interventions such as aerobic exercise training (ET) and/or caloric restriction (CR). The purpose of this thesis was to determine the prevalence of CI in a HFpEF population and examine the effects of a 20-week ET, CR diet, or their combination, to manage CI and improve HR responses in HFpEF patients. Data from the Study Examining Caloric Restriction and Exercise Training (SECRET I Trial) was used for this analysis. It was hypothesized that the prevalence of CI in the SECRET I participants will not be significantly different from the estimates of CI in the HFpEF population. It was also hypothesized that ET, CR, or ET + CR will improve HR responses. Participants had typical clinical features of HFpEF: 67 $\pm$ 5 years, 81% female, and obese BMI. The prevalence of CI in SECRET I was 41%. There was a significant main effect from baseline to 20-weeks for HR_{rest}, $HR_{submaximal}$, and $HR_{recovery}$. There was a significant correlation between the change in $HR_{reserve}$ and change in relative VO_{2peak} (r= 0.400, p-0.001), change in $HR_{reserve}$ and change in absolute VO_{2peak} (r = 0.374, p-0.001), and the change in body weight to change in $HR_{reserve}$ (r= -0.288, p-0.016). Caloric restriction and ET together produced a larger, albeit non-significant, decrease in the prevalence of CI. This study suggests that ET and/or CR can improve the HR response of older, obese, patients with HFpEF but appears to have limited impact on reversing CI in these patients

REVIEW OF LITERATURE

Overview

It is estimated that approximately 26 million people world-wide have heart failure (HF) (1). Heart failure is a disorder that affects the left ventricle's structure and function (2). There are two main phenotypes of heart failure, systolic and diastolic, named for their impact on the structure and resulting function of the left ventricle (3). Systolic HF (impaired left ventricular contraction) is also known as HF with reduced ejection fraction (HFrEF), while diastolic HF (impaired left ventricular relaxation and filling) is known as HF with preserved ejection fraction (HFpEF) (3). The signs and symptoms of both types of HF are a result of inadequate cardiac output from the structurally and functionally impaired left ventricle and consequently, inadequate venous return (3). Common signs and symptoms in both phenotypes of HF are relatively non-specific to the condition, but include fatigue, dyspnea, cough, edema in the lower extremities, and palpitations (3, 4). Although there are numerous compensatory mechanisms that can compensate for impaired left ventricular function and the associated signs and symptoms, these often result in maladaptations that result in a further deterioration of cardiac function (3). Of the two phenotypes, HFpEF is currently the fastest growing form of HF (5) and commonly affects older adults, predominantly women (6). Heart failure with preserved ejection fraction is sometimes referred to as a "systemic syndrome" as it is commonly seen in older adults with numerous co-morbidities such as hypertension, diabetes mellitus, metabolic syndrome, anemia, chronic kidney disease, atrial fibrillation, and sedentary life-style (4, 7–11). Despite HFpEF's rapid growth and high prevalence, less is known about HFpEF treatment and pathophysiology when compared to HFrEF (6).

Epidemiology

The burden of HF on the healthcare system is growing as HF accounts for >1 million hospitalizations a year. Hospitalization of patients with HFpEF are increasing steadily with a current prevalence estimated to be 6 million people in the United States of America (U.S.A) alone (1, 4, 12, 13). It's been estimated that the HF prevalence could reach up to 9 million people by 2030 (12, 14). Two main factors that drive the increasing prevalence of HF are the aging population and increased presence of risk factors including diabetes and obesity with aging (4, 14). Another increasingly concern is that HF disproportionately affects racial and ethnic minorities as well as the elderly population (4, 12). What is striking about these data is that HF has ~50% mortality rate after 5 years (12, 15, 16). Unlike HFrEF whose prognosis is more influenced by cardiovascular factors, the prognostic relevance of non-cardiac co-morbidities such as respiratory disease, kidney disease, cancer, carries a worst prognostic value for patients with HFpEF (4, 17). Commonly seen HFpEF risk factors such as the metabolic syndrome, physical inactivity, deconditioning, and obesity are less common in HFrEF (4). As a result, it is important to target HFpEF interventions by addressing these underlying co-morbidities (4, 17).

Incidence of HF increases with age in both Caucasian and racial/ethnically diverse populations (14). For example, the HF incidence in Caucasian men is 9.2 HF events per 1000 person-years (in Caucasian men 64-75 y/o), 22.3 HF events per 1000 person-years (in Caucasian men 75-84 y/o), and 43.0 HF events per 1000 person-years in Caucasian men who are $\geq$ 85 y/o (14). Similarly, this trend is also found in Caucasian women: 4.7 HF events per 1000 person-years (64-75 y/o), 14.8 HF events per 1000

person-years (75-84 y/o), and 30.7 HF events per 1000 person-years ($\geq$ 85 y/o) (14). HF incidence rates in racial and ethnically diverse populations are 4.6 HF events per 1000 person-years for African Americans, 3.5 HF events per 1000 person-years for Hispanic Americans, and 1.0 HF events per 1000 person years for Chinese Americans (14). The increasing incidence rates, regardless of sex or race-ethnicity, is largely due to the aging population (18, 19). Consequently, it is very likely that HF will continue to represent an epidemiologic burden (19) around the globe.

In a study examining the risk factors for HFrEF and HFpEF in post-menopausal women (a population disproportionally affected by HF), researchers found risk factors for both HF phenotypes were: old age, hypertension, diabetes mellitus, smoking, coronary heart disease, and cancer (13). In addition, anemia and obesity were also found to increase risk in women with HFpEF. Moreover, risk factors for hospitalization in women with HFpEF included obesity, coronary heart disease - other than myocardial infarction, atrial fibrillation, more than one co-morbidity, and lastly, hysterectomy with partial oophorectomy. In contrast, the primary risk factors for HFrEF were a history of myocardial infarction and elevated heart rate (13). This same study also examined the population attributable risk (PAR%), which describes the incidence of disease in the population that is due to an exposure. In all 3 racial-ethnically diverse groups of post-menopausal women with HFpEF, 2/3 of the PAR% had hypertension and obesity, with diabetes mellitus and coronary heart disease being present in 25% of PAR%. More specifically, in African American and Hispanic post-menopausal women, hypertension and obesity made up >90% PAR% and 72% PAR%, respectively. In post-menopausal women with HFrEF, hypertension was the strongest PAR% in Caucasian, African

American, and Hispanic women. It is important to further appreciate the risk factors, treatment, and management of both types of HF as the epidemiologic burden of HF is estimated to increase in the near future.

Heart Failure Phenotypes

As mentioned previously, there are primary phenotypes for HF, HFrEF and HFpEF. Although 50% of HF cases are HFpEF (4–6), majority of the research on the management has been in patients with HFrEF. Characteristics of HFrEF include decreased myocardial contractility from ischemia and cardiomyopathy of any etiology (e.g. viral, idiopathic, post-partum) (4). Survival of HFrEF has consistently improved with medical treatments, but has remained unchanged in HFpEF (4). Furthermore, there are no widely accepted pharmacologic treatments specifically for the management of HFpEF (4, 12, 20–22). It is essential to understand treatments for both phenotypes of HF as the elderly population of the US is expected to double and will likely coincide with an increased HF burden, particularly in women as they will likely outnumber men in the expanding population (12).

Some researchers have even gone so far to question if HFpEF is actually considered "true" HF (7, 20). Patients with HFpEF show non-specific signs and symptoms that could also be the result of co-morbidities common in the aging population and the cardiovascular decline that coincides with increasing age. Kitzman and colleagues have been able to confirm HFpEF as "true HF" (4, 7), as both phenotypes also have decreased exercise capacity, neuroendocrine activation, and decreased quality of life (7). Pagel et al. described signs and symptoms from both types of HF as a "well-known constellation" that includes fatigue, tachypnea, dyspnea at rest and exertion, peripheral

edema, and reduced tissue perfusion (4). It is important to discern which type of HF one has as it is important to correspond their treatment and management to their specific HF phenotype (19).

It is well known that pharmacotherapy treatments (e.g. inhibitors of the renin angiotensin aldosterone system, β-blockers, nitrates) and cardiac devices work well to treat HFrEF (4, 19). In addition to medical management, exercise is also established as a treatment for HFrEF as exercise training improves HFrEF at both the central and peripheral levels (12). Contrary to HFrEF, which has different etiologies but results in similar pathophysiological adaptions, HFpEF does not respond as well to pharmacotherapy and other medical managements because HFpEF is the result of pathophysiology of multiple co-morbidities (19, 20, 22–29). To date, there is increasingly more research being done in HFpEF to better understand the complexities of the "systemic syndrome" (20). Medications (i.e. β-adrenergic blockers, calcium channel blockers, inhibitors of the renin- angiotensin aldosterone system, digoxin) have minimal impact on exercise tolerance and quality of life in patients with HFpEF, likely a result of the heterogeneity of the syndrome (4, 20, 22, 30, 31). Currently, HFpEF treatments are focused on lifestyle modifications including exercise and weight loss to manage symptoms (4). A meta-analysis has demonstrated that the physical activity guidelines of 500 MET_{min}/week was associated with 10% lower risk of HF with additive benefits when the general physical activity guidelines were exceeded (32, 33). After a pooled analysis from three cohort studies, investigators concluded that there was a strong, dose-dependent relationship between high leisure time physical activity and lower risk of HFpEF, a relationship that was not consistent in patients with HFrEF (32, 34). Two meta-

analyses and a systematic review examined randomized controlled trials of the use of exercise in HFpEF treatment and concluded that exercise training improves both cardiorespiratory fitness and health related quality of life (11, 35, 36).

Morbidity and mortality between the two HF phenotypes have been reported to be fairly similar (5, 17, 22, 37). A study from Gerber et al. identified a 20% mortality rate one-year after a HF diagnosis that increased to 52% five years after diagnosis (15). More significantly, Gerber also found that mortality rates increased at both the one year and five-year mark after diagnosis in both the 60-year-old group (7.4% and 24.4% respectively) and 80-year-old group (19.5% and 54.4%, respectively). Furthermore, a sub-study of the Framingham Heart Study, also concluded that age-adjusted mortality rates for men and women (65-74 years old) in 1990-1999, were 28% at one-year and 59% at five-years for men, and 24% at one year and 45% at 5 years for women (16). The risk of death from cardiovascular etiologies is actually lower in HFpEF compared to patients with HFrEF (hazard ratio =0.79 (0.67-0.93, 95% CI) (15). The greater prevalence of co-morbidities in HFpEF makes this phenotype more difficult to treat and explains why patients with HFpEF are more likely to die from a non-cardiovascular cause (15, 20, 22). Given the high co-morbidity burden in patients with HFpEF (19), behavioral lifestyle interventions such as exercise and/or weight loss, as compared to medication management, may be more useful for management in HFpEF.

Pathophysiology of Heart Failure

Despite epidemiological burden of HFpEF, less is known about its pathophysiology in comparison to HFrEF (6). When the heart “fails” the body attempts to compensate for the decreased cardiac output and tissue perfusion by activating the

sympathetic nervous system and the renin-angiotensin aldosterone systems to release catecholamines and natriuretic peptides in an attempt to increase myocardial contractility, heart rate, and vasoconstriction (3, 38–41). Despite the neurohumoral factors temporarily improving the cardiac output in patients with HF, this consistent neurohumoral activation can be detrimental over time (38). Kitzman et al. characterized heart failure pathophysiology into 4 domains to further understand the consequences of this condition (7). These four domains include: left ventricular structure and function, exercise performance, neuroendocrine function, and quality of life.

Left Ventricular Structure & Function

Cardiac output (CO) is the product of heart rate (HR) and stroke volume (SV) and represents the amount of blood pumped out of the heart over a period of time. A normal CO at rest is 4-5 L/min (3). Preload is one of the factors that affects SV and in turn, affects cardiac output. Preload is the volume of blood in the left ventricle before contraction and is also known as the end diastolic volume (EDV). Ejection fraction (EF) is calculated as SV divided by EDV and is normally 50-70%. Ejection fraction can either be significantly reduced (HFrEF with EF $\leq$ 35%) or preserved (HFpEF with EF $\geq$ 50%) as a result of the remodeling of the left ventricle due to the systemic changes (3). Dilation of the left ventricle results in systolic dysfunction, also known as HFrEF. With systolic dysfunction, the dysfunction of the left ventricular myocardium is likely a result of ischemic disease, uncontrolled hypertension, or myocardial infarction (3, 18). Therefore the risk factors for HFrEF include coronary artery disease, hypertension, hypercholesterolemia, diabetes mellitus, obesity, family history of HF, predisposition to cardiomyopathies, and exposure to cardiotoxic agents (18). Any injury to the

myocardium as a result of the above risk factors results in a loss of myocytes and increased ventricular strain resulting in the dilation of the left ventricle (18). Because this type of remodeling results in a reduced ejection fraction, there is less ejected blood from the left ventricle with each heartbeat so less blood makes it to the organs and peripheral tissue (3). This also results in an increased end diastolic pressure that consequently increases the pressure of the capillaries in the lungs that results in the common symptom of dyspnea (3).

Concentric left ventricular remodeling results in diastolic dysfunction, also known as HFpEF (22). The chamber size is decreased because of this type of inward hypertrophy, but the contractility of the heart is maintained despite limited LV filling (3, 7). As mentioned previously, risk factors for HFpEF include obesity, chronic kidney disease, anemia, hypertension, diabetes, and chronic obstructive pulmonary disease (18). It is believed that these risk factors result in a pro-inflammatory state that exacerbates the decreased compliance and contractility of the left ventricle, arterial stiffening, myocyte hypertrophy, increased collagen deposition, coronary microvascular regulation, and greatly impairs skeletal muscle oxygen extraction (4, 18). Therefore, regardless of the type of remodeling of the left-ventricle, HF symptoms are the result of a mismatch in cardiac output to metabolic demand (12).

Exercise Performance

Patients with HFrEF and HFpEF both have decreased exercise capacity due to the previously mentioned structural changes to the left ventricle that result in decreased cardiac output (7). Furthermore, the systemic inflammation common in both HFrEF and HFpEF from the combination of increased adiposity, insulin resistance, dyslipidemia, and

hypertension impair skeletal muscle function and therefore, physical function (6). When compared to healthy controls, both patients with HFrEF and HFpEF had decreased peak workload, exercise time, oxygen consumption, ventilatory anaerobic threshold, and higher levels of norepinephrine during exercise (7).

Neuroendocrine Function

Regardless of the HF phenotype, there is increased neuroendocrine activation when the heart "fails" to produce an adequate cardiac output (7). Kitzman et al. found that there was no significant difference between patients with HFrEF and HFpEF in norepinephrine levels, but that both HF phenotypes have higher norepinephrine levels when compared to healthy controls (7). They also found that brain natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were significantly higher in both HF phenotypes. Brain natriuretic peptide is found in the ventricles and is released following ventricular stretch (3). Brain natriuretic peptide as well as NT-proBNP plasma concentrations are helpful in the diagnosis and prognosis of both types of HF and elevated BNP is typically one of the first signs of HF (3, 4, 18). Natriuretic peptide concentration has a direct relationship with LV end-diastolic wall stress as lower LV end-diastolic wall stress results in lower BNP and NT-proBNP levels (4). One other neurohormonal adaptation in HF is elevated cytokine production (tumor necrosis factor α, interleukin-1α, and interleukin 6, and interferon α) (3). Elevated levels of cytokines in patients with HF are associated with worse clinical outcomes and decreased contractility (3).

In order to maintain cardiac output when the heart is not functioning at an optimal level, there is an activation of the sympathetic nervous system (SNS) that results in a

release of epinephrine and norepinephrine to increase HR and contractility (3). This activation of the SNS also promotes vasoconstriction in the periphery to help maintain/increase stroke volume to ensure adequate tissue perfusion (3). There are 3 types of receptors that are activated in the SNS in patients with HF: β1, β2, α1. Although this activation is initially helpful, when consistently overstimulated, it can eventually lead to myocardial toxicity and accelerate the HF progression (changing ejection fraction and/or arrythmias) (3, 4). The renin-angiotensin aldosterone system is also activated via the stimulation of β1 and α1 receptors to increase contractility, facilitate norepinephrine release, increase vasoconstriction, and promote sodium retention (3). Due to the vasoconstriction, there is an increased afterload (pressure that the left ventricle must overcome to pump blood into systemic circulation) in which the state of increased pressure in the left ventricle results in concentric remodeling via myocytes hypertrophy and increasing collagen deposition in order to adequately deliver blood to the body (4, 14, 18). But that collagen deposition and thickening of the myocytes is not always beneficial, as too much of these adaptations leads to decreased left ventricular compliance and myocardial stiffness (4, 14, 18). This type of remodeling makes it difficult for the left ventricle to relax (hence, the name diastolic dysfunction) and results in increased filling pressures (required to adequately fill the LV) exacerbating the high-pressure state within the heart (3, 4, 14). Constant sympathetic stimulation can lead to decreased baroreceptor sensitivity and is a potential mechanism underlying chronotropic incompetence (3, 42, 43). The constant increased levels of the aforementioned neurohormones exacerbate the hemodynamic response by worsening the chronotropic and inotropic responses that contribute to a further decline in cardiac structure and function (3, 14).

Quality of Life

Both phenotypes of HF result in decreased quality of life for patients (7). For individuals with HF the quality of life and functional independence are decreased for any given activity, due to increased fatigue and dyspnea (44–46). Dyspnea is likely the result of the increased left atrial pressures leading to lung congestion and fatigue is the result of hypoperfusion of the skeletal muscles and other metabolic abnormalities (18). Not surprisingly, Kitzman et al., found that patients with HFpEF and HFrEF had lower quality of life when compared to men and women ages 65-74 years old (7).

Symptoms of HF

There currently is not a definitive treatment for HFpEF, thus the focus of treatment is on symptom improvement (4, 11, 18). The main symptom that affects patients with HFpEF with exercise intolerance is dyspnea during daily activities and exercise (11, 30). As a result of decreased exercise tolerance, the quality of life for individuals with HFpEF is generally reduced (44, 45). Currently, there is a paradigm shift from treating HF at the cardiovascular level to treating the risk factors that contribute to the systemic syndrome (11). One factor that makes HFpEF symptom management more challenging to address is that patients with HFpEF may not display any symptoms or only experience mild symptoms at rest, and only exhibit symptoms only during exertion (4). Currently, the only type of medication that has been effective for reducing hospital admissions in patients with HFpEF has been a diuretic (spironolactone) (47). In contrast to limited benefits of pharmacotherapy, two meta-analyses and a review examined randomized controlled trials that used exercise therapy for HFpEF treatment and

concluded that exercise training improves both cardiorespiratory fitness and health related quality of life in these patients (11, 35, 36).

Exercise Intolerance and The Fick Equation

Exercise intolerance is present in both patients with HFrEF and HFpEF, but is considered the hallmark symptom of HFpEF (7, 9, 46, 48, 49). Exercise intolerance is objectively measured by a reduced peak exercise oxygen consumption (VO_{2peak}), and is characterized by fatigue and shortness of breath during daily activities or exercise (46, 50). Not only is the co-morbidity burden higher in patients with HFpEF, but it is also likely that these patients will have worse functional status (VO_{2peak}) and exercise intolerance (51).

To understand exercise intolerance in HFpEF, it is important to identify the components of the Fick Equation. The Fick Equation is: $VO_2 = CO \times a\text{-}vO_{2difference}$, where CO (cardiac output) is defined as HR x SV (11, 52). Heart rate and SV (or CO) are considered central components of the Fick Equation whereas $a\text{-}vO_{2difference}$ is considered a peripheral component. The central and peripheral factors that define VO_2 according to the Fick Equation indicates that there are multiple factors that may contribute to exercise intolerance in HFpEF. These include central mechanisms like the ability to increase SV and HR (or heart rate reserve), ventilatory reserve (or the ability to absorb oxygen at the lungs), and peripheral vascular function as well as the cellular metabolic function of skeletal muscles (11). Normally with increased metabolic activity (as seen during exercise or activities of daily living), there is increased heart rate (~150%) and stroke volume that constitute as increased blood flow, oxygen extraction, and consumption of oxygen by the skeletal muscles (49). Increases in HR and SV result in increases of

VO_{2peak}. The maximum amount of oxygen consumed during activity, increases until it reaches a plateau. This maximal or peak value is affected by how well the cardiovascular system can adequately deliver oxygen and how well the skeletal muscles can extract and utilize oxygen according to the metabolic needs.

At the central level, one of the mechanisms that affects increases in stroke volume in HFpEF is LV diastolic function (11). Diastolic dysfunction is more of a problem during exercise, than at rest, because the faster heart rates during exercise do not allow adequate time for the remodeled left ventricle to fill adequately. There is also a decrease in stroke volume as a result of the diastolic HF (about 50-65 mL in a HF patient vs. 100mL in a healthy person) (46, 53–56). During peak exercise, as a result of decreased stroke volume, patients with HF are likely to have impaired (<50%) cardiac output when compared to an individual with normal physiology (4, 46).

Peripheral abnormalities, indicated by a diminished a-$vO_{2difference}$, are also a contributor to the reduced VO_{2peak} in patients with HFpEF (46, 57, 58). One of the peripheral mechanisms driving exercise intolerance in HFpEF is a decreased peripheral vascular reserve which is demonstrated by reduced microvascular density in the periphery (11). Another is poor skeletal muscle quality that results in reduced oxygen uptake and utilization (11).

Although stroke volume contributes to increases in VO_2 during exercise, stroke volume only increases about 30%, whereas heart rate can increase maximally up to 150% in order to contribute to increased metabolic demand (49). Therefore, one of the other central drivers of exercise intolerance is a sub-optimal increase in HR (11). To increase cardiac output via increased HR, there is parasympathetic withdrawal up to 100 bpm and

sympathetic activation when the heart rate achieves >100 bpm (52, 59, 60). However, once the heart's beats per minute exceeds 110bpm-120bpm, the stroke volume is no longer able to increase, and the heart must rely only on increases in heart rate to meet the demands of increased cardiac output (52). Typically, the heart rate increases linearly with increases in VO_2, but toward near maximal levels of exercise the heart rate response tends to plateau (52, 61). The heart's ability to appropriately increase rate of contraction in order to increase cardiac output with increasing metabolic demands (i.e., activities of daily living, exercise, etc.) is important for oxygen delivery and proper tissue perfusion. Thus, studies have linked the inability of the heart to increase rate of contraction adequately to a reduced exercise capacity and exercise intolerance in patients with HFpEF(52, 62).

Chronotropic Response to Exercise

Chronotropic incompetence (CI) is defined as the heart's inability to adequately respond to increased physical demands during activity, and is strongly associated with the degree of exercise intolerance experience by patients with HF (4, 46, 49, 63–65). Although CI is associated with exercise intolerance in HFpEF, it is unclear if CI a cause of exercise intolerance or a result of exercise intolerance due to reduced exercise capacity (49, 62). Ton and Lewis posit that CI and exercise intolerance are related in one of two ways: alternative mechanisms limit access to higher heart rates during exercise or that the failure to increase heart rate is a part of the pathophysiology of HFpEF (49). Another contributor to the inadequate heart rate response is that $HR_{reserve}$ is decreased in this population (46, 56). The $HR_{reserve}$ is defined as the difference between HR_{peak} and HR_{rest}. Since HR_{max} remains relatively unchanged in patients with HFpEF compared to patients

without HF, $HR_{reserve}$ is decreased due to the elevated resting HR observed in this population (46, 56). Previously, there has been little work on how much HR contributes to exercise intolerance in patients with HF (46). As described earlier, while HR is only one aspect of the Fick equation, research clearly demonstrates the importance of an appropriate HR during exercise in patients with HFpEF.

Chronotropic Incompetence

The presence of chronotropic incompetence (CI) is diagnosed when an individual reaches a peak heart rate during exercise that is significantly lower than the average predicted heart rate for normal individuals of the same age (49). Typically heart rate and stroke volume increase linearly with increased levels of exercise and increased cardiac output (4). However, as an individual exceeds 50% of their maximal exercise capacity, SV levels off and this increasing HR becomes the sole contributor of cardiac output (52, 61). Often, cardiac output does not reach predicted maximal values in HFpEF due to the insufficient HR response (4, 59, 60). Individuals with CI have normal resting heart rates but an attenuated HR during exertion (52). Chronotropic incompetence can manifest in in a few different forms in patients with HF, decreased peak HR, HR instability during exercise, as well as an abnormal (slow) HR recovery, all of which exacerbates exercise intolerance by modifying cardiac output (42, 43, 49). This limitation of the heart rate reserve (defined as the difference in HR_{peak}-HR_{rest}) in HFpEF is central to the pathophysiology as this results in elevated left atrial pressures, impaired left ventricular filling, limited contractile reserve, chronotropic incompetence, vascular perfusion, and O_2 extraction (31). In fact, CI was identified, from a pooled meta-analysis of 17 HFpEF

studies, as the factor having the most impact on exercise intolerance (31, 35). Despite this relationship, the specific mechanism(s) that result in CI remain unclear (31, 66).

Unfortunately there is currently not a unanimously accepted definition of CI which results in significant variability in the reporting of prevalence in patients with HF (59, 67–71). The reported prevalence of CI in HFrEF is ~50%, but less is known about the prevalence of CI in patients with HFpEF (46, 72). The reported prevalence of CI in patients with HFpEF has ranged from 20-75% of patients (46, 62, 73–78), but the most recent study reported the prevalence of CI in HFpEF is ~55% (72). Jorde et al. reported that the highest prevalence of CI in patients with HFrEF was in those with more severe HF (60).

The clinical utility of CI has often been underappreciated (59), and the identification of CI is complicated as there are various definitions of the condition. Furthermore, there are confounding effects of aging and medications on the chronotropic response of the heart, as well as the requirement of an exercise stress test for the formal diagnosis of CI (59). Despite the complexities of CI, methods for diagnosis are inexpensive and are widely accessible (59). It is important to identify the presence of CI in the HF population as the prognosis of patients with CI is worse than those without it (62, 79, 80). Moreover, with increasing HF class severity, there is an associated increase in chronotropic impairment (81). Chronotropic incompetence has a significant impact on exercise intolerance in older patients with HF and is clinically important as it can be utilized to predict adverse cardiovascular events as well as overall mortality (46). Specifically in HFpEF, CI independently predicts major cardiovascular outcomes and mortality (42, 49, 59).

Measurement & Criteria

Exercise stress testing is used to assess the chronotropic response (52). A variety of exercise modalities (bicycle ergometer, treadmill, etc.) are appropriate to use for stress testing to determine the heart's chronotropic response, but the treadmill remains the preferred method for testing as the other modalities pose limitations in evaluating the chronotropic response to exercise (52). During exercise testing it is important to assess HR across the range required for activities of daily living (52). The results of the test to examine one's chronotropic response are affected by the quality of the environment and the state of the patient (52). Therefore, it is important to consider all extraneous variables that may affect HR, such as medications, dehydration, testing environment temperature, physical pain, and emotional stress, before starting exercise testing to examine one's chronotropic response (52). For example, it is well known that β-adrenergic blockers can blunt the heart's chronotropic response to exercise (52).

The chronotropic response can be quantified as the ability/inability to reach an age- predicted heart rate (52). CI is often identified when the HR does not achieve a certain percentage (i.e. 70%, 80%, 85%, but most commonly 80%) of their age-predicted HR_{max} (APHRM) during an exercise stress test (59, 62, 82–84). APHRM can be defined using the $220 - age$ equation. We acknowledge that this equation comes with a lot of variability, but for the purposes of this thesis and measurement of the chronotropic response, this was the most appropriate equation to use.

A more appropriate method to determine the presence of CI in clinical populations, including patients with HF, with a tendency to have higher resting HRs, is to calculate their CI based on their $HR_{reserve}$ (calculated as $HR_{peak} – HR_{rest}$) (59).

This $HR_{reserve}$ approach takes into account that a clinical population has higher resting heart rates is the *Adjusted Percent Heart Rate Reserve (APHRR),* (59, 85):

$$Adjusted\ Percent\ HR\ Reserve = \frac{HRreserve}{APHRM - HRrest}$$

Note. $HRreserve = HRpeak - HRrest.\ APHRM = 220 - age$

Although directly measuring HR is necessary for defining CI, there are also subjective measures that must also be considered. It is important to collect variables other than HR to ensure that the patient has reached maximal effort (52). Evaluating the respiratory exchange ratio (RER, the volume of carbon dioxide produced divided by the volume of oxygen utilized) and rating of perceived exertion (RPE) are important as the test endpoint should be fatigue, not lack of effort or limited by factors other than the cardiorespiratory system (52). Regardless of exercise testing modality, when evaluating the presence of CI, it is imperative that the participant go to exhaustive efforts by producing a sufficient rating of RER or RPE (59). Specifically, achieving an RER of 1.05 during exercise represents sufficient physiological effort and can be evaluated by CI. Failure to achieve an RER of $\geq$ 1.05 should warrant the use of other criteria that do not require exhaustive effort. Despite this one study, patients with HFpEF who did not reach an RER of $\geq$1.05 were excluded from further analysis (49).

In the situation where the patient does not achieve an RER $\geq$1.05 during an incremental exercise test, a method known as the Wilkoff approach or metabolic chronotropic relationship (MCR) (also known as the chronotropic index) should be utilized (52). The MCR utilizes the relationship between HR and oxygen consumption

while also adjusting for age, physical fitness, and functional capacity and appears to be unaffected by the exercise testing modality or testing protocol (52). The MCR equation is derived from the $HR_{reserve}$ equation as $Metabolic_{Reserve} = MET_{max}\text{-}MET_{baseline}$ (52). Chronotropic index is the ratio of the $HR_{reserve}$: $Metabolic_{Reserve}$ during submaximal exercise, making it more conducive for clinical populations where maximal or peak effort is sometimes more difficult obtain (52, 59). The metabolic reserve is equal to the percentage of $HR_{reserve}$ in adults with normal sinus rhythm, and thus there is a linear relationship between the increase in $\%HR_{reserve}$ and $\%Metabolic_{Reserve}$ (52). MCR predicts that those with a "normal" chronotropic response will achieve 1.0 (95% CI, 0.8-1.3) (52). In contrast, an MCR, that is <0.80 represents CI (52).

With the MCR approach, any HR obtained during an exercise stress test (HRstage) can be assessed for chronotropic function. The MCR equation for CI is (52):

Estimated HRstage =

$$[[(220 - age - HRrest) * (METSstage - 1)]/[(METSpeak - 1)]] + HRrest$$

Simplified as: $HRstage = (HRR * \%MR) + HR\,rest.$

Note. 1 MET= 3.5 ml/kg/min

As previously mentioned, it can sometimes be difficult for clinical (HF) populations to reach maximal or peak levels during stress testing. For this reason, the MCR can be used in addition to other CI defining methods to ensure that the presence of CI is confirmed. This approach is useful; when a participant does not reach ≥80%-85% $HR_{reserve}$ during an exercise test despite an but did achieve adequate effort (RER ≥1.05) or when they did not achieve adequate effort as indicated by RER ≤ 1.05 (52).

The Impaired HR Response in HFpEF

Insufficient HR and/or CI that results in a decreased cardiac output has been proposed as a physiological mechanism contributing to exercise intolerance in patients with HFpEF(6, 10, 73, 86–89). Exercise intolerance from CI is likely a product of autonomic imbalance at the central level of the Fick Equation as described earlier (90–93). Although the mechanism undermining CI is not well understood, research currently posits that CI is likely the result of the myocardial β-adrenergic receptor desensitization (or down-regulation) from constant autonomic imbalance in the HF state from of increased circulating catecholamine levels and as a result, the remodeling of the sinoatrial node (4, 46, 63–65, 91, 94–99). Sarma et al. examined sinoatrial node β-receptor sensitivity in HFpEF patient to age- and sex-matched healthy controls and young, healthy controls (62). The purpose of this study was to examine the integrity of cardiac β-receptor responsiveness. Participants completed exercise stress testing and graded isoproterenol infusion to quantify cardiac β-receptor mediated HR responses. In order to ensure there was no autonomic neural influence on individual's HR during the isoproterenol infusion, dexmedetomidine (a central α-2 adrenoceptor agonist) and glycopyrrolate (muscarinic cholinergic antagonist) were given to denervate the sinoatrial node from extracardiac influence (62). This study concluded that patients with HFpEF demonstrated functionally significant CI because of decreased β-receptor responsiveness. Furthermore, this study determined that the strongest, yet statistically insignificant, predictors of β-receptor dysfunction among HFpEF subjects were baseline plasma norepinephrine levels (standardized β, -0.39, p-value = 0.18) and peak exercise heart rate (standardized β, 0.36, p-value = 0.22).

Management of CI

Chronotropic incompetence is potentially manageable as previous research has suggested that interventions to reverse CI such as medications, cardiac devices, and lifestyle modifications, particularly exercise training and weight loss, may improve HR response to exercise and therefore improve exercise tolerance and their quality of life (46, 59).

β -*Adrenergic Blockers*

β-adrenergic blockers are one of the most widely prescribed medications in cardiology as they are indicated for the treatment of hypertension, heart disease, and cardiac arrhythmias. They are also widely used in the management of HFpEF (50-80% of patients) despite the limited evidence of their benefit this patient population (4, 89, 100–106). While it is appropriate to expect a decrease in HR with the use of β-adrenergic blockers, this is not always the case and is seen as a "paradox". Maldonado- Martín et al. found that there was no significant or clinically meaningful difference in HR responses (specifically HR_{peak}, $HR_{reserve}$, $HR_{recovery}$, VO_{2rest}, $VO_{2submax,}$ or VO_{2peak}) in patients with HF that were taking β-blockers compared to those who weren't (9). Consequently, despite conventional wisdom, this study concluded that β-blockers do not have a meaningful impact on the HR response during exercise in patients with HFpEF (9).

Hirsh et al. also examined the effects of β-blocker cessation on exercise tolerance and the prevalence of CI in patients with HF (107). They concluded that withdrawal of β-blockers increases the HR response during exercise, but that CI still persists. There was also no difference in exercise capacity between the groups on β-blockers and off β-blockers even though the HR response was restored (107). Therefore, the utility of β-

blockers for treatment of CI remains unclear (20) and warrants assessment of other treatments/therapies that may improve the chronotropic response to exercise in patients with HFpEF and improve their functional capacity and quality of life.

Cardiac devices/ Rate- Adaptive Pacing

Rate-adaptive pacemakers are a potential treatment for CI as this device based therapy can increases one's HR in response to increased metabolic demands (52, 62, 71, 108). Research examining the utility of rate-adaptive pacing with cardiac resynchronization therapy has been examined in patients with HFrEF (109). Tse et al. examined the use of these devices in patients with HFrEF with chronotropic incompetence and cardiac resynchronization therapy (n=20) and found that these devices resulted in increases of peak exercise HR and exercise duration, but did not improve VO_{2peak} (109). However, there still is some suggested utility in using rate adaptive pacing in patients with HF with more severe chronotropic incompetence (defined by <70% of APHRM) as they found that rate-adaptive pacing improved exercise time, increased HR_{peak}, and most importantly increased VO_{2peak} in this subset of the HFrEF population. Therefore, this research suggests that there is some utility in using rate-adaptive pacing in patients with HFrEF with severe CI.

More recently, there have been several studies that have examined the benefits of rate-adaptive pacing in patients with HFpEF (110). Serova et al. found that when compared to the control group (conventional pacing programming), rate adaptive pacing did significantly improve VO_{2peak} (1.64 ± 1.6 mL/min/kg, $p < .0001$), exercise time (170 ± 98 s, $p<0.001$), and quality of life (reduction in MLWHF score by 9 points, $p<0.0001$) after the 3-month intervention, but the patients with HFpEF in this study had

chronic atrial fibrillation and permanent pacing making the results only generalizable to some of the HFpEF population (110). One trial examining rate-adaptive pacing in HFpEF (RESET) was ended early due to low enrollment (105) and another is currently on-going with an estimated completion date of May 2022 (ClinicalTrials.gov Identifier: NCT02145351).

Recently, a systematic review examined 14 papers looking at the utility of rate-adaptive pacing in patients with HF from 1980 to January of 2021 (108). This review concluded that although rate-adaptive pacing may increase HR, the increase in HR did not necessarily improve their VO_2 (i.e., exercise tolerance) in patients with HF. Although rate-adaptive pacing may restore the chronotropic response in select patients, it is imperative to consider other treatments that may consistently improve cardiac function in patients with HF.

Lifestyle Modifications: Exercise and Caloric Restriction

Given the lack of beneficial medications and medical device treatment for patients with HFpEF with CI, the focus of managing this condition should be on lifestyle modifications such as exercise training and weight loss (4). Previous investigations have demonstrated use of these modalities for these patients.

Exercise Training Intervention

One possible way to improve the chronotropic response in patients with HFpEF may be through exercise-based intervention. A meta-analysis looking at randomized controlled trials of exercise training in HFpEF concluded that exercise interventions resulted in improved VO_{2peak} and quality of life (35). In healthy individuals, VO_2 increases during exercise as a result of an approximate 2.5-fold increase in HR, 1.2-fold

increase in SV, and an 2.5-fold a-$vO_{2difference}$ (31, 111). Therefore, HR is an important contributor to increase VO_{2peak} and that can worsen exercise intolerance in patients with HFpEF (46, 112). Generally, patients with HFrEF or HFpEF with CI have lower VO_{2peak} than similar patients without CI (46). Unfortunately, despite the high prevalence of CI in patients with HF, very few studies have evaluated the potential for exercise training to improve chronotropic responses and/or reverse this condition.

As described earlier it is well known that patients with HF have increased sympathetic activation (44). However, exercise training in this population has been shown to restore the autonomic balance in patients with HF (113). One way that exercise improves autonomic balance is by improving parasympathetic tone as a result of decreased norepinephrine and muscle sympathetic activity as well as improved heart rate variability and baroreflex sensitivity (114–124). Research has previously demonstrated that at any given work level, a trained individual will have lower heart rates (improved autonomic balance) and lower circulating catecholamines at submaximal levels compared to an untrained individual (52).

Keteyian et al. conducted a 24 week exercise training intervention in patients with HF (64). Twenty-one patients were randomized to exercise training and 22 to a no exercise control group. After 24 weeks, VO_{2peak} was significantly greater in the exercise group when compared to the control group (204 $\pm$ 57 ml/min vs. 72 $\pm$ 33 ml/min, respectively; $p<0.05$). Moreover, HR_{peak} ($R^2=0.50$) and $HR_{reserve}$ ($R^2=0.56$) changes were significantly related to the change in VO_2. The study also showed that HR_{rest} and $HR_{submaximal}$ decreased significantly more in the exercise training group than in the control group. In addition to improvements in VO_{2peak} and the HR response, there was also a

significant reduction in plasma norepinephrine at rest and during exercise ($p<0.05$) (64). Keteyian et al. also concluded that there was a partial reversal of chronotropic incompetence due to the increased exercise heart rate (n=14 with CI at baseline & 24-weeks).

Caloric Restriction

Over 80% of people with HFpEF are overweight or obese (6, 125, 126). This is especially concerning as being overweight/obese promotes inflammation and further contributes to the HFpEF pathophysiological cycle by resulting in hypertension, insulin resistance, dyslipidemia, cardiac and skeletal muscle dysfunction and generally decreased physical function (6, 30, 127–130). Specifically, inflammation from increased adiposity effects coronary and systemic endothelial function, impaired skeletal muscle mitochondrial function, and results in decreased skeletal muscle oxygen delivery and utilization (130). Therefore, weight loss via caloric restriction (CR) could be useful in HFpEF treatment and symptom management, especially for improving VO_2 (i.e., exercise intolerance).

Two review papers focused on the effects of CR on the HR response in non-heart failure populations (131, 132). One review examined the effects of CR on the HR response and found that CR was beneficial regardless of demographic but found the biggest benefit in its "sickest subjects" (those with similar physiological characteristics to the HFpEF population) (132). Moreover, they found that exercise training enhances the effects of CR in hypertensive subjects; this is especially important as hypertension is a common co-morbidity in HFpEF. Caloric restriction also improved subjects' HR response by lowering their HR_{rest} and increasing their heart rate variability (a more

favorable balance between the parasympathetic and sympathetic nervous system) (132). Similarly, a review on CR on the HR response and CI in animal models found that CR lessens catecholamine biosynthetic enzymes and reduce oxidative damage to the adrenal medulla while preserving the chronotropic response (131). Pagel et al. also suggest that diet modifications have the potential to reverse faulty hemodynamics in HF (4). Other previous work that has looked at diet modifications in HF include: a study that saw better LV diastolic function and decreased arterial stiffness as a result of a salt-restricted diet (133) and another study where HFpEF women underwent bariatric surgery had improvement in HF symptoms and reversed left ventricular remodeling (134).

Significance

To date, there has been very little research evaluating the role of lifestyle interventions (including exercise training and weight loss via caloric restriction) on heart rate response and/or the prevalence of CI patients with HFpEF (46). Thus, the purpose of this research is to determine the prevalence of CI in a contemporary cohort of 100 patients with HFpEF and to examine the effects of 20-weeks of aerobic exercise training and/or caloric restriction intervention to restore chronotropic competence in patients with HFpEF.

Hypotheses

I. The prevalence of CI in the SECRET I participants at study baseline will not be different from the most recent estimates (20-75%) of CI in HFpEF population (46, 62, 72–78).

II. Aerobic exercise training will increase HR_{peak}, $HR_{reserve}$, $HR_{recovery1}$, $HR_{recovery}$, while decreasing HR_{rest} and $HR_{submaximal}$, and, overall, decrease the prevalence of CI in this HFpEF population.

III. Caloric restriction will increase HR_{peak}, $HR_{reserve}$, $HR_{recovery1}$, $HR_{recovery}$, while decreasing HR_{rest} and $HR_{submaximal}$, and, overall, decrease the prevalence of CI in this HFpEF population.

IV. The combination of caloric restriction and aerobic exercise training will have a synergistic effect on increasing HR_{peak}, $HR_{reserve}$, $HR_{recovery1}$, $HR_{recovery}$, while decreasing HR_{rest} and $HR_{submaximal}$, and will further decrease the prevalence of CI compared to patients in either treatment alone.

METHODS

Overview

Data from the Study Examining Caloric Restriction and Exercise Training (SECRET I) Trial was used for this thesis. Study Examining Caloric Restriction and Exercise Training was a randomized, attention-controlled, 2x2 factorial trial that took place at Wake Forest University from February 2009 through November 2014. The trial was previously approved by the Institutional Review Board and registered at clinicaltrials.gov (NCT00959660). Prior to participation, participants provided written informed consent. The SECRET I trial consisted of a 20-week intervention of caloric restricted diet (CR), aerobic exercise training (ET), or both (CR + ET) as well as an attention control group (CON). The primary outcome measures for the SECRET I trial were exercise capacity and quality of life, whereas this thesis was a secondary analysis on heart rate variables and chronotropic incompetence.

Study Participants

Participants for SECRET I were obtained from search lists of medical records (135, 136). Initially, 577 participants were screened for participation. Inclusion criteria were: $\geq$60 years, body mass index (BMI; calculated as weight in kilograms/height in meters squared) of $\geq$30 kg/m^2, signs and symptoms of heart failure defined by the National Health and Nutrition Examination Survey Congestive Heart Failure criteria of 3 or higher, or criteria of Rich et al., or both; and left ventricular ejection fraction of $\geq$ 50% (137, 138). Participants also had to be clinically stable with no significant change in cardiac medications in the 4 weeks prior to enrollment. Participants could not be undergoing regular exercise or following specific diets prior to enrollment. Exclusion criteria included:

left ventricular segmental wall motion abnormalities and significant ischemic or valvular heart disease, pulmonary disease, anemia, or any other disorder that may explain a patient's heart failure symptoms. In total, 100, older, obese participants with chronic, stable HFpEF were enrolled in this trial. The principal investigator and all study investigators, except the biostatistician, were blinded to all study outcomes.

Randomization

After baseline assessments were completed, participants were randomized using a computer-generated list using SAS software (SAS Institute), version 9.0, maintained by the study statistician and stratified by β-blocker medication and sex to 1 of 4 groups: CR, ET, ET + CR, or CON.

Lifestyle Interventions

Participants randomized to either group receiving aerobic exercise training (ET or ET + CR) completed 1-hour of supervised exercise sessions 3 times per week for 20 weeks consisting primarily of walking on a track using an individualized exercise prescription based on the cardiopulmonary exercise test results. The intensity level was "moderate" and progressed as tolerated, based primarily on heart rate reserve and ratings of perceived exertion (135, 136).

Participants randomized to either group receiving CR (CR or ET+ CR) were prescribed a hypocaloric diet using meals (lunch, dinner, and snacks) prepared by the Wake Forest University General Clinical Research Center metabolic kitchen under direction of a registered dietitian. Participants prepared their own breakfast from a menu. Individual energy needs were calculated from resting metabolic rate (CCM Express, MGC Diagnostics), following an overnight fast, and an activity factor based on self-

reported physical activity. Prescribed calorie intake deficits were approximately 400 kcal/d for the CR group and approximately 350 kcal/d for the ET + CR group (the difference between the groups allowed for the energy expenditure of the exercise intervention), but not less than 1000 kcal/d for all diet intervention participants. The CR diet provided approximately 1.2 g of protein/kg ideal body weight, 25% to 30% fat calories, and the remainder as carbohydrate. Participants were provided daily calcium supplements (600 mg) and kept records of all food consumed, which was monitored weekly.

Participants randomized to attention control (CON) received neither diet nor exercise interventions and voluntarily agreed to not make diet or exercise changes during the 20-week study. The CON received telephone calls every 2 weeks from staff to discuss general health issues and enhance retention prior to follow-up testing.

Outcomes

Standardized procedures known to elicit maximal exercise performance were used during baseline and follow-up (at 20 weeks) cardiopulmonary exercise testing (CPET), including a standardized treadmill protocol, guidance by the respiratory exchange ratio (RER, an objective indicator of effort) and Borg scale of perceived exertion, and reading of a standardized participant instruction script prior to each exercise test. Heart rates were measured/recorded via electrocardiogram after 5 minutes of supine rest, during each stage of the CPET including peak exercise, as well as during recovery. Breath-by-breath gas exchange data were measured continuously during exercise and averaged every 15 seconds, and peak values were averaged from the last two 15-second intervals during peak exercise. Data from the CPET were used to calculate chronotropic incompetence.

Chronotropic Incompetence- Calculation & Prevalence

The first, and most widely used approach to evaluate the presence of CI requires the determination of an *Adjusted Percent Heart Rate Reserve*. This method was used in the present investigation as it adjusts for elevated resting heart rate common in this population (59, 85):

$$Adjusted\ Percent\ HR\ Reserve = \frac{HRreserve}{APHRM - HRrest}$$

Note. $HRreserve = HRpeak - HRrest.$

$$Age - predicted\ HR\ maximal\ (APHRM) = 220 - age$$

Example. During CPET the participant (70 years of age) has a resting HR of 80 beats per minute and a peak exercise HR of 130 beats per minute. Thus, using the equation above, this participant achieved [(130 – 80)/ (150-80)] an Adjusted Percent Heart Rate Reserve of 0.71 (71%).

Failure to obtain 80% of *Adjusted Percent HR Reserve* at peak exercise indicates the presence of CI, only if the subject reached an RER at peak exercise of ≥1.05. If the subject did not meet an RER ≥1.05 at peak exercise, another approach, called the metabolic chronotropic relationship (MCR) was used to assess the presence of CI (52). An MCR score from any testing stage that is <0.80 indicates the presence of CI (52). In this analysis, submaximal (stage 3) data were used to calculate the MCR if the pre-specified RER value was not met. The MCR equation is (52):

Estimated HRstage = $[[(220 - age - HRrest) * (METSstage - 1)]/[(METSpeak - 1)]] + HRrest$

Simplified as: $HRstage = (HRR * \%MR) + HR\,rest.$

Note. 1 MET= 3.5 ml/kg/min

Example. During CPET, another participant (75 years of age) has a resting heart rate of 85 beats per min and when they terminated the CPET, their RER was 1.01. Their submaximal (stage 3) heart rate was 95 beats per minute. Their $VO_{2submax}$ *at stage 3 was 14.1 ml/kg/min and their* VO_{2peak} *was 15.7 ml/kg/min. Therefore, the Adjusted Percent Heart Rate Reserve equation to determine CI cannot be used as they did not achieve an adequate RER and the MCR equation must be used:* $[[(220 - 75 - 85) * (4.03 - 1)]/[(4.29 - 1)]] + 85$. *This calculated that their estimated HR at stage 3 should have been 140 beats per minute, but this participant's heart rate at stage 3 was 95 bpm, meaning that they only achieved 68% of their HR at stage 3 and therefore have CI.*

For all participants who met a prespecified RER of ≥1.05 during baseline and follow-up CPET testing, the ≥80% *Adjusted Percent HR Reserve* equation was used to calculate the presence/ absence of CI. According to the *Adjusted Percent HR Reserve* equation, there were 53 participants (out of 90) without CI at baseline (59%). In the 37 participants who were determined to have CI at baseline from the *Adjusted Percent HR Reserve* equation, their RER value at peak effort was considered. If any of those 37 participants did not meet the prespecified RER of ≥1.05 (baseline, n=3; 20-weeks, n=2), the MCR equation was then used. The MCR equation uses submaximal data, so stage 3 values were used to calculate presence of CI using the MCR in those who didn't meet the pre-specified RER. If submaximal stage 3 values were not available due to missing data, the MCR could not be used, so the presence of CI could not be determined for that

participant (baseline, n=10, 20-weeks, n=7). This process was repeated with the follow-up CPET data to determine prevalence of CI at 20-weeks. Chronotropic incompetence is considered a dichotomous variable (either present or absent). Prevalence of CI, for each group at both time points, was calculated by the number of subjects that did not achieve an adequate HR response, based on the aforementioned criteria, during the CPET.

Statistical Analysis

All analyses were performed with SPSS (Version 26.0.0.1). The data were examined for normality and inspected for outliers. The level of statistical significance for all analyses was established at with a two-side *P-value* of <0.05 (46). All available outcome data were analyzed with intention-to-treat analysis. Fisher-Freeman-Halton Exact test was used to evaluate the prevalence of CI in groups at baseline and at 20-weeks. Covariates for the Analysis of Covariance (ANCOVA) were baseline $HR_{response}$, sex, and beta-blocker usage. Analysis of Covariance was used to compare HR_{rest}, $HR_{submaximal}$, HR_{peak}, $HR_{reserve}$ (HR_{peak}-HR_{rest}), $HR_{recovery1}$ (1 minute of active recovery), $HR_{recovery}$ (HR_{peak}-$HR_{recovery1}$) among the four intervention groups at 20-weeks. Bonferroni post-hoc testing was used to compare specific differences between groups at 20-weeks. Pearson-product moment correlation was used to examine the relationship between the change in relative VO_{2peak} and the change in $HR_{reserve}$, change in absolute VO_{2peak} & $HR_{reserve}$, and change in body weight and change in $HR_{reserve}$ in all of the intervention groups combined as well as individual group correlations.

RESULTS

Participants

From the 1,586 records reviewed, 577 participants were further screened by telephone and 167 were scheduled for a screening visit. Ultimately, 100 participants with HFpEF were enrolled and randomized to ET (n=26), CR (n=24), ET + CR (n=25), CON (n=25) (Table 1). Of these, 92 participants (92%) (ET=24, CR=24, ET + CR=22, CON= 22) completed the intervention and follow up testing (Table 1). Participants discontinued the study due to: personal reasons (CON, n=2; ET, n=1; ET +CR, n=1), knee pain (ET, n=1; ET + CR, n=1), hospitalization (ET +CR, n=1), and a violation of the protocol (defined as undertaking formal, aggressive diet and exercise interventions outside of the protocol, (CON, n=1)).

Participant characteristics were generally in accord with those observed in prior HFpEF studies and were predominately women (n=81; 81%), there was a high prevalence of hypertension and diabetes, as well as reduced exercise capacity (~50% of predicted) (Table 1). As previously reported in the main effects analysis of this trial (SECRET I), Kitzman and colleagues found significant increases in physical function (VO_{2peak}) for the exercise training group (1.2ml/kg/min, 95% CI, 0.7 to 1.7; $p<0.001$) and the caloric restricted diet group (1.3ml/kg/min, 95% CI, 0.8 to1.8; $p<0.001$) (6). Furthermore, they found a synergistic effect of combining ET + CR, on the main outcome of VO_{2peak} (increase of 2.5ml/kg/min). None of the interventions resulted in a statistically significant improvement in participants quality of life, although this was attributed to the instrument (MLWHF) used for this outcome measure.

Table 1. Baseline Characteristics of Study Participants

Characteristic	Control (N=25)	ET (N=26)	CR (N=24)	ET + CR (N=25)	P-Value
Age (years)	65.6 ± 4.8	67.5 ± 5.9	66.5 ± 4.9	66.3 ± 5.2	0.63
Women	20 (80%)	21 (81%)	20 (83%)	20 (80%)	0.99
White	16 (64%)	15 (58%)	11 (46%)	13 (52%)	0.61
Body Weight (kg)	105 ± 13	107± 24	99 ± 12.1	111 ± 19	0.10
BMI (kg/m^2)	39.4 ± 5.6	39.9 ± 8.4	37.3 ± 3.6	40.7 ± 5.6	0.24
Body fat (%)	46.0 ± 7.2	44.8 ± 6.1	45.1 ± 6.5	46.0 ± 6.1	0.88
Ejection Fraction (%)	59.9 ± 6.8	62.1 ± 5.8	63.0 ± 5.6	59.6 ± 5.7	0.71
NYHA class					
II	17 (68)	12 (46%)	16 (67%)	15 (60%)	0.36
III	8 (32)	14 (54%)	8 (33%)	10 (40%)	
B-type natriuretic peptide	30 ± 34	33 ± 22	29 ± 22	31 ± 17	0.68
Diabetes mellitus	9 (36%)	10 (38%)	5 (21%)	11 (44%)	0.37
Hx hypertension	24 (96%)	25 (96%)	23 (96%)	23 (92%)	0.89
Systolic BP (mmHg)	137 ± 17	136 ± 16	134 ± 14	137 ± 16	0.83
Diastolic BP (mmHg)	77 ± 7	78 ± 8	76 ± 7	79 ± 10	0.78
Current medication					
ACE-inhibitors	8 (32%)	11 (42%)	9 (38%)	9 (36%)	0.90
Diuretics (all)	20 (80%)	21 (81%)	18 (75%)	17 (68%)	0.70
Loop diuretics	3 (12%)	9 (35%)	6 (25%)	7 (28%)	0.30
Beta-blockers	11 (44%)	10 (38%)	9 (38%)	10 (40%)	0.97
Calcium Antagonists	7 (28%)	10 (38%)	10 (42%)	8 (32%)	0.74
Nitrates	4 (16%)	1 (4%)	2 (8%)	2 (8%)	0.50
Angiotensin Receptor Blockers	8 (32%)	12 (46%)	8 (33%)	7 (28%)	0.55
Peak VO_2 (ml/kg/min)	14.0 ± 2.1	14.4 ± 2.4	14.8 ± 2.4	14.7 ± 3.3	0.76
Peak VO_2 (ml/min)	1463 ± 213	1505 ± 332	1455 ± 318	1608 ± 361	0.30
Peak RER	1.14 ± 0.08	1.10 ± 0.06	1.11 ± 0.10	1.14 ± 0.08	0.23

Heart Rate Responses to Exercise & Recovery

Figures 1a-f. represent the unadjusted mean ± SE heart rate responses for all four groups from CPET conducted at baseline and 20-weeks. As described in the analytic plan, analysis of covariance (adjusting for sex, β-blockers, and baseline HR response) was conducted on these HR variables. The ANCOVA indicated there was a significant difference among the 4 intervention groups for HR_{rest} (p-0.001), $HR_{submaximal}$ (p-0.001), and $HR_{recovery}$ (p-0.016). Consequently, Bonferroni post hoc testing revealed significant differences in HR_{rest} at follow-up between CR and CON (p= 0.003), ET and CON (p=0.020), and ET + CR and CON (p=0.006). $HR_{submaximal}$ was significantly different between CR and CON (p=0.001), ET and CON (p= 0.019), and ET + CR and CON (p< 0.001). A significant difference in $HR_{recovery}$ was revealed between ET + CR and CON (p=0.016).

Figure 1a. Unadjusted means (±SE) HR_{rest} at Baseline & 20-Weeks in the Intervention Groups. ***ANCOVA p-value = 0.001.***

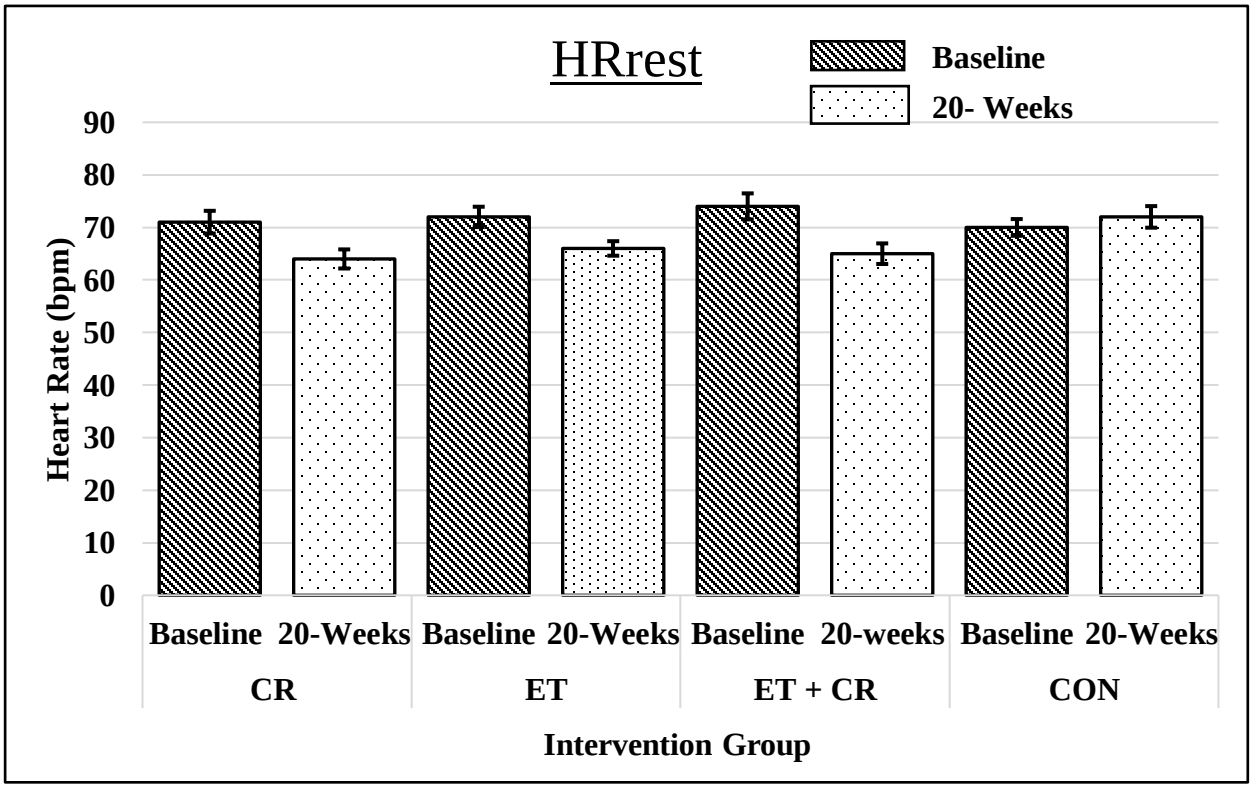


Figure 1b. Unadjusted means (±SE) $HR_{submaximal}$ at Baseline & 20-Weeks in the Intervention Groups. ***ANCOVA p-value = 0.001.***

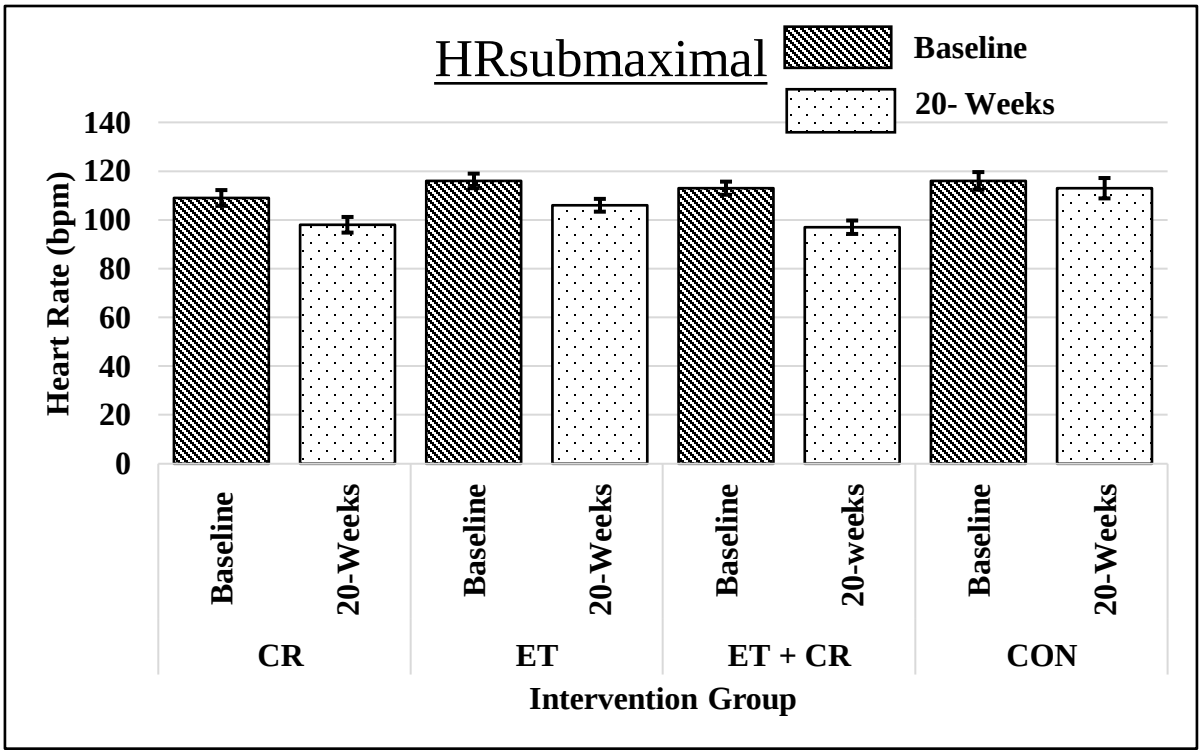


Figure 1c. Unadjusted means (± SE) HR_{peak} at Baseline & 20-Weeks in the Intervention Groups. ***ANCOVA p-value= 0.759****.*

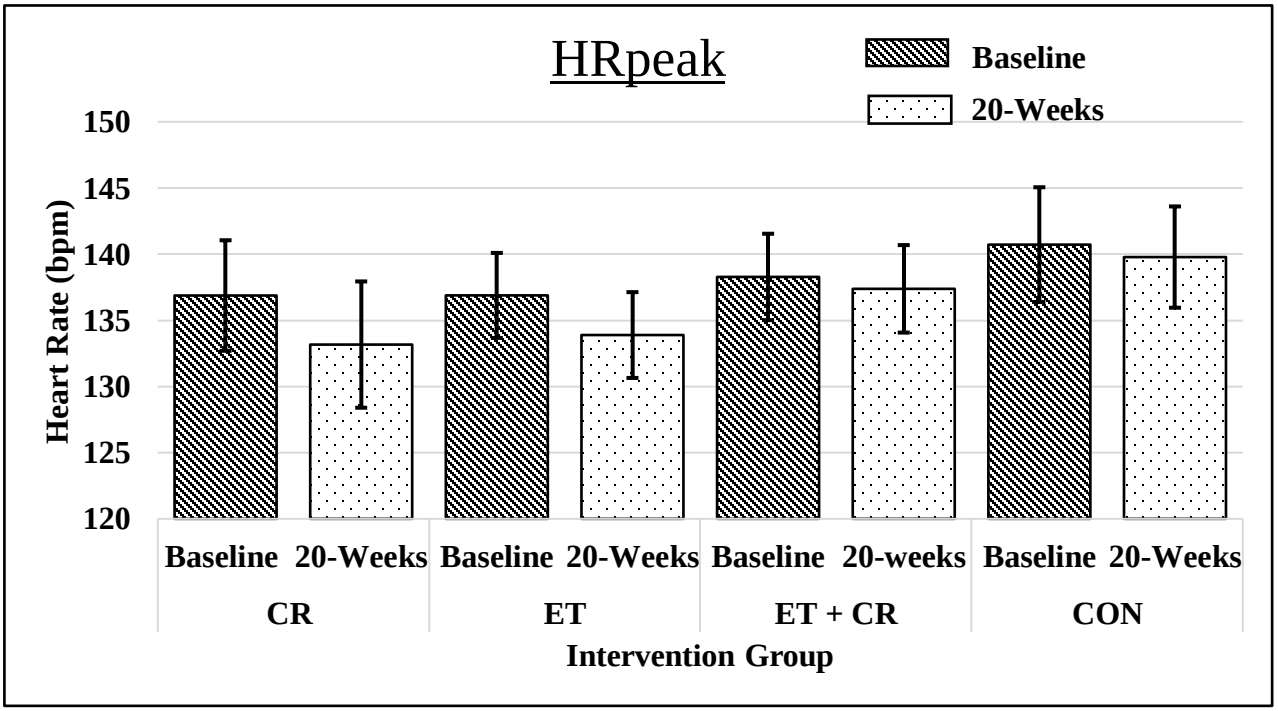


Figure 1d. Unadjusted means (±SE) $HR_{reserve}$ at Baseline & 20-Weeks in the Intervention Groups. ***ANCOVA p-value = 0.186***.

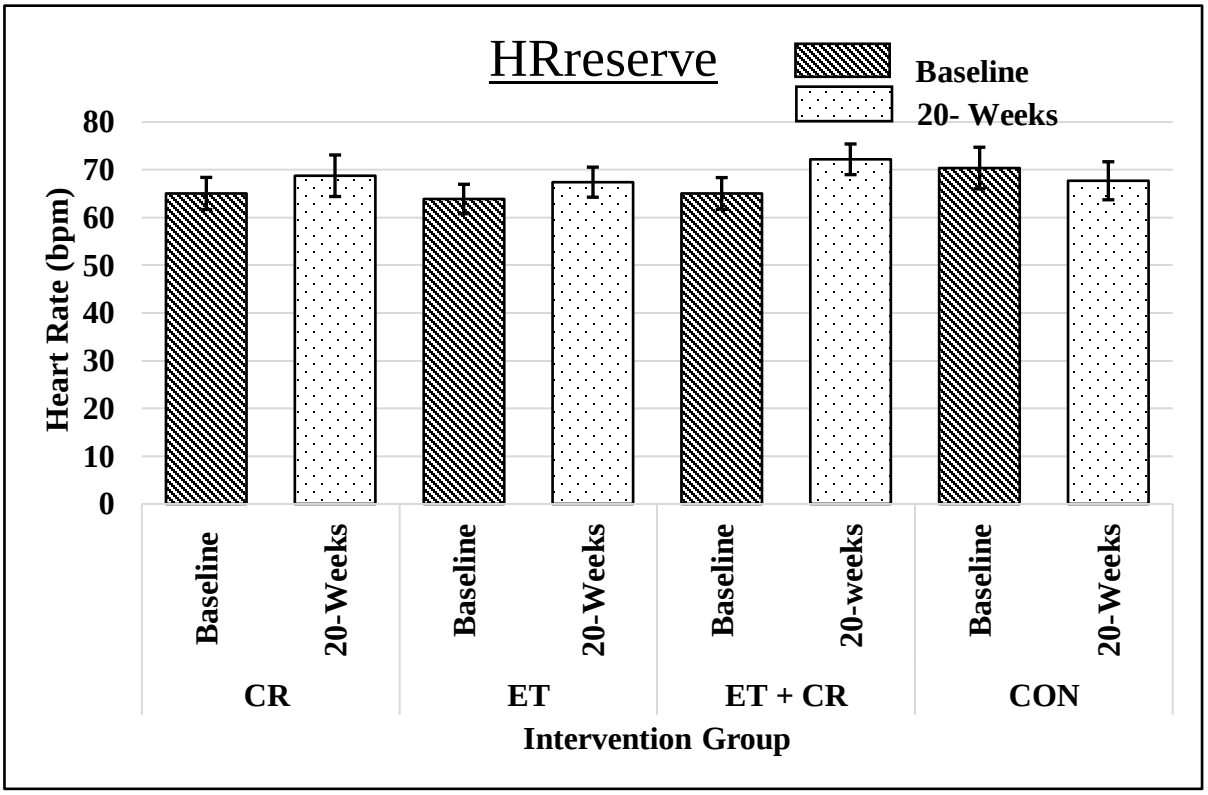


Figure 1e. Unadjusted means (± SE) $HR_{recovery1}$ at Baseline & 20-Weeks in the Intervention Groups. ***ANCOVA p-value= 0.116.***

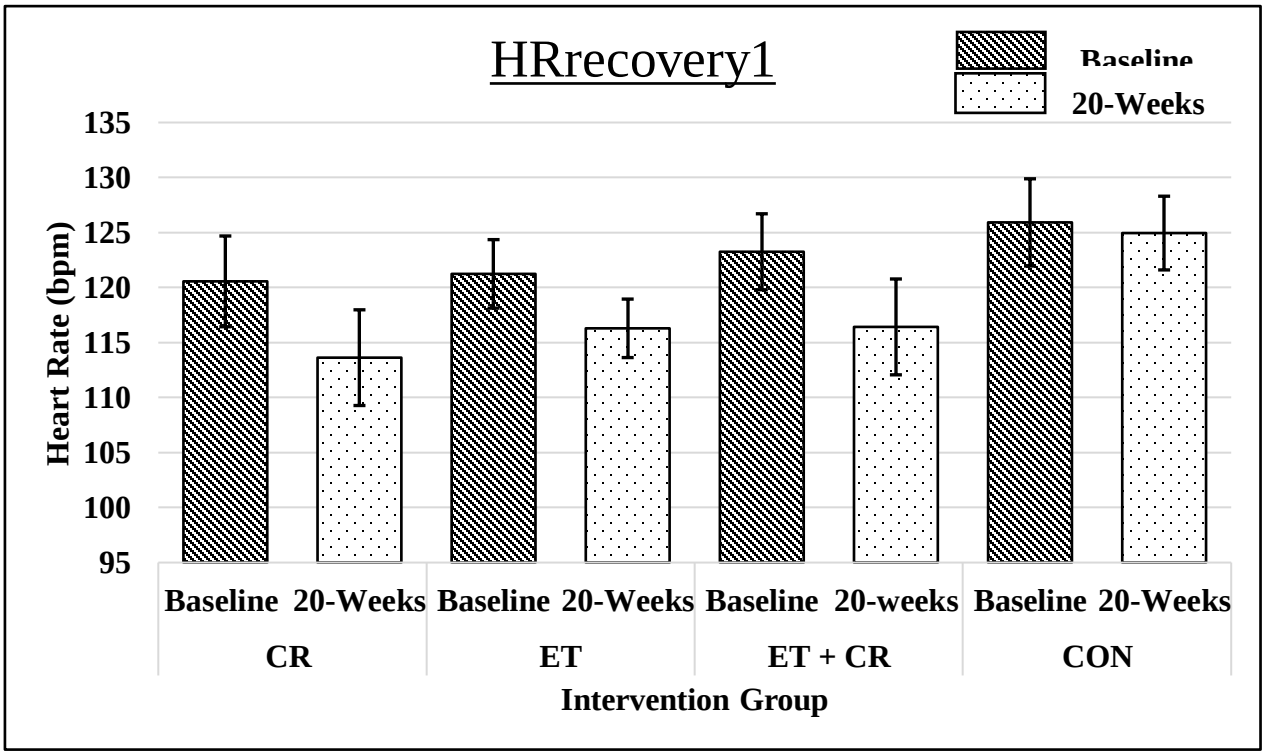
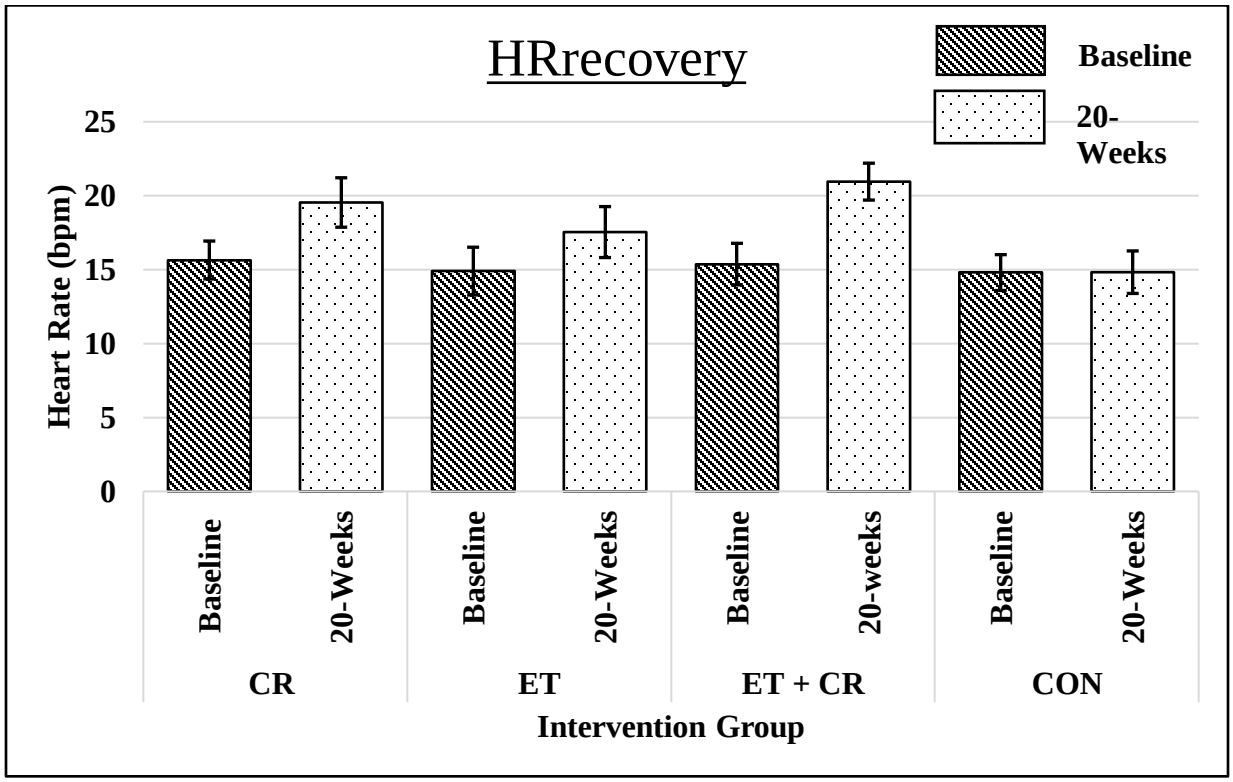


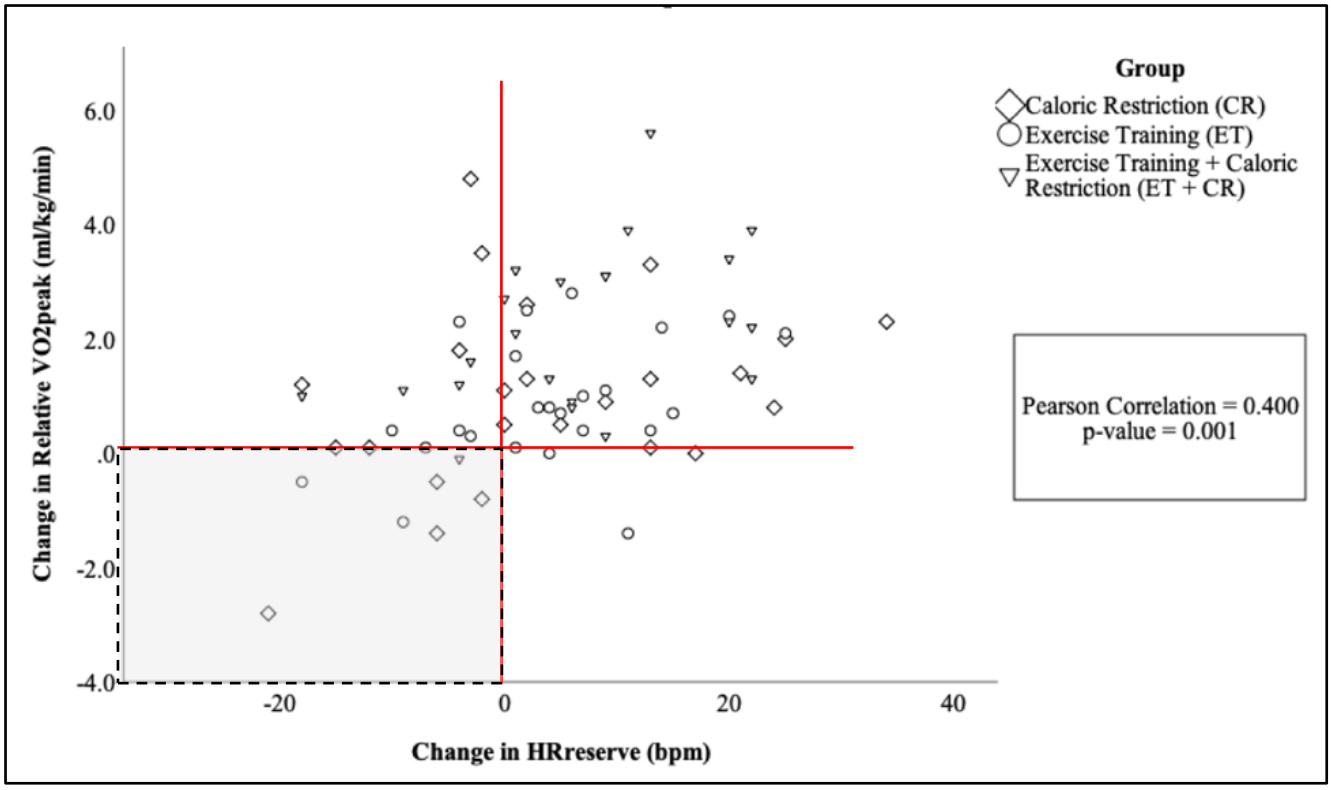
Figure 1f. Unadjusted means (± SE) $HR_{recovery}$ at Baseline & 20-Weeks in the Intervention Groups. ***ANCOVA p-value=0.016*.**



To explore the impact of the intervention on change in HR in relation to changes in relative VO_{2peak} (ml/kg/min), Pearson product moment correlations were performed. As seen in Figure 2, after pooling the data, there was a significant correlation between the change in $HR_{reserve}$ (from baseline to follow-up) and change in relative VO_{2peak} (from baseline to follow-up) in the three intervention groups (Pearson Correlation = 0.400, p-0.001). The control group was excluded in this correlational analysis in order to specifically look at the effects of the intervention. Also, in Figure 2, lines are drawn to indicate no change, from baseline to follow-up in both HR and VO_{2peak}. As seen in Figure 2, there appears to be 7 participants in the lower-left quadrant, 4 from CR group, 2 from ET, and 1 from ET + CR that did not "respond" to the SECRET I lifestyle interventions of CR or ET. For the purpose of this analysis, we defined "non-responders" as participants who did had decreases in their $HR_{reserve}$ and relative VO_{2peak}, however, we recognize that may not translate to clinically meaningful changes.

Individual intervention group Pearson product moment correlations were also analyzed to examine the relationship in the change in $HR_{reserve}$ (from baseline to follow-up) and change in relative VO_{2peak} (from baseline to follow-up) (Table 2). These results indicate that $HR_{reserve}$ (change from rest to peak exercise) explains ~12, 18, and 20 percent of the variance in the change in relative VO_{2peak} (ml/kg/min) from baseline to follow up in the CR, ET, and ET + CR groups, respectively (Table 2).

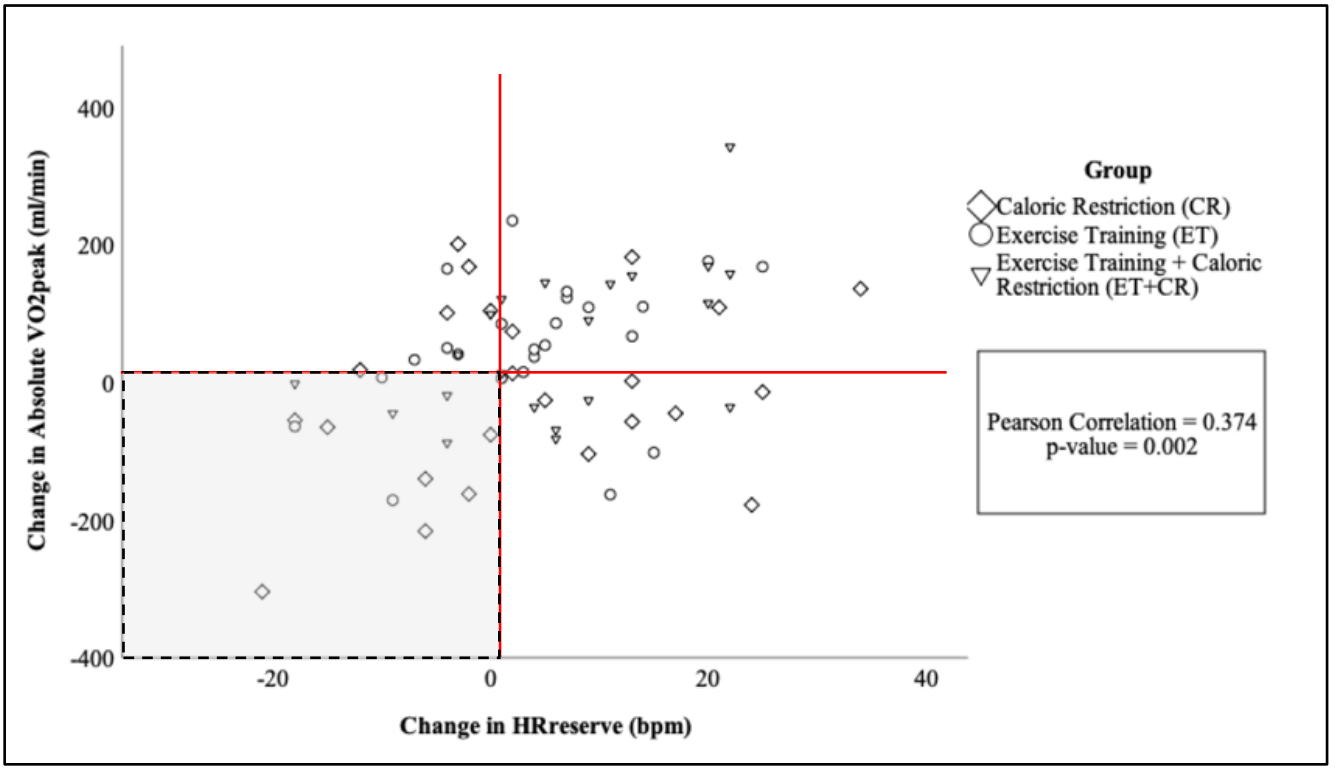
Figure 2. Relationship Between Change in Relative VO_{2peak} & $HR_{reserve}$



To explore the impact of the intervention on change in HR in relation to changes in absolute VO_{2peak} (ml/min), Pearson product moment correlations were performed. As seen in Figure 3, after pooling the data, there was a significant correlation between the change in $HR_{reserve}$ (from baseline to follow-up) and change in absolute VO_{2peak} (from baseline to follow-up) in the three intervention groups (Pearson Correlation = 0.374, p=0.002). The control group was excluded in this correlational analysis in order to specifically look at the effects of the intervention. Also, in Figure 3, lines are drawn to indicate no change, from baseline to follow-up in both HR and VO_{2peak}. As seen in Figure 3, there appears to be 12 participants in the lower-left quadrant, 6 from CR group, 2 from ET, and 4 from ET + CR that did not "respond" to the SECRET I lifestyle interventions of CR or ET. For the purpose of this analysis, we defined "non-responders" as participants who had decreases in their $HR_{reserve}$ and absolute VO_{2peak}, however, we recognize that may not translate to clinically meaningful changes.

Individual intervention group Pearson product moment correlations were also analyzed to examine the relationship in the change in $HR_{reserve}$ (from baseline to follow-up) and change in absolute VO_{2peak} (from baseline to follow-up) (Table 2). These results indicate that $HR_{reserve}$ (change from rest to peak exercise) explains ~9, 12, and 29 percent of the variance in the change in absolute VO_{2peak} (ml/min) from baseline to follow up in the CR, ET, and ET + CR groups, respectively (Table 2).

Figure 3. Relationship Between Change in Absolute VO_{2peak} & $HR_{reserve}$



To explore the impact of the changes in body weight (kg) on changes in HR, Pearson product moment correlations were performed. As seen in Figure 4, after pooling the data, there was a significant correlation between the change in body weight (kg) to change in $HR_{reserve}$ in the three intervention groups (Pearson Correlation = -0.288, p-0.016). The control group was excluded in this correlational analysis in order to specifically look at the effects of the intervention. Also, in Figure 4, lines are drawn to indicate no change, from baseline to follow-up in both HR and VO_{2peak}. As seen in Figure 4, there appears to be 3 participants in the lower-right quadrant all from the ET group that did not "respond" to the SECRET I lifestyle interventions of ET. For the purpose of this analysis, we defined "non-responders" as participants who had a decrease in their $HR_{reserve}$ and an increase in their body weight, however, we recognize that may not translate to clinically meaningful changes.

Individual intervention group Pearson product moment correlations were also analyzed to examine the relationship in the change in body weight to change in $HR_{reserve}$ in the 3 intervention groups (Table 2). These results indicate that the change in body weight explains ~8, 6, and 18 percent of the variance in the change in $HR_{reserve}$ from baseline to follow up in the CR, ET, and ET + CR groups, respectively (Table 2).

Figure 4. Relationship Between Change in Body Weight & $HR_{reserve}$

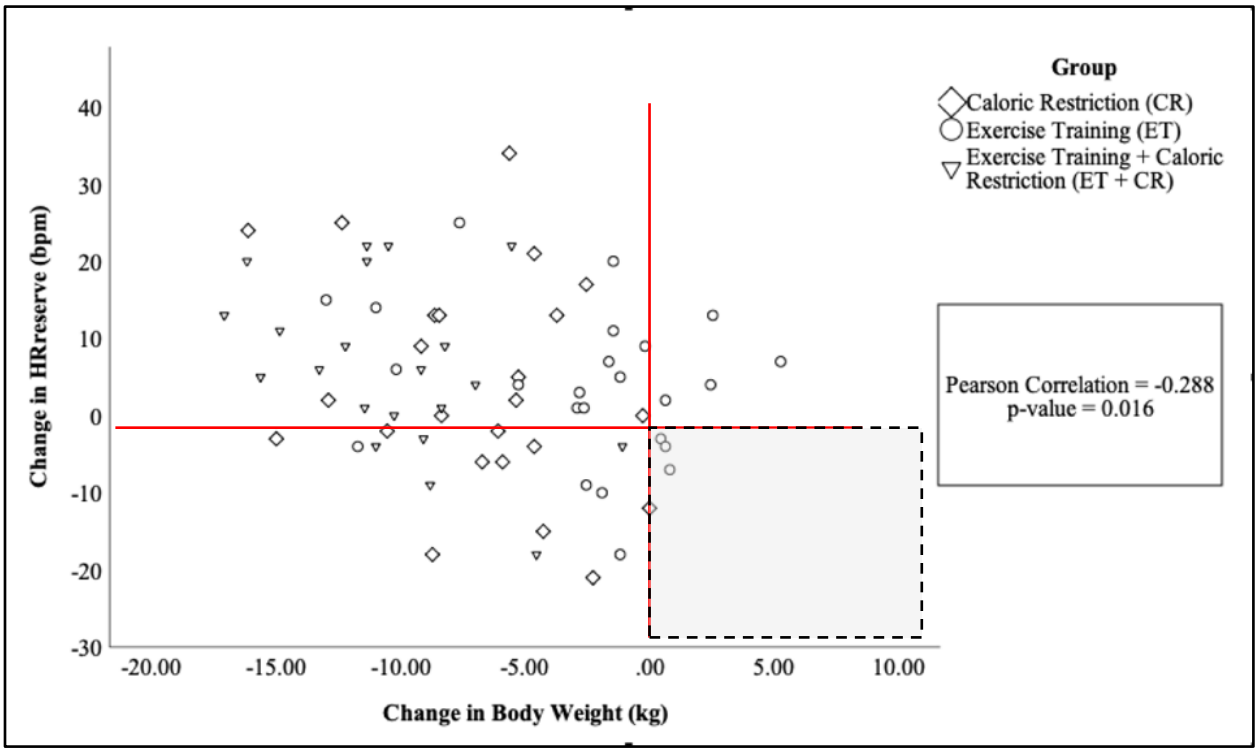


Table 2. Pearson Correlation Analyses

Change in $HR_{reserve}$ to Change in Relative VO_{2peak}			
Intervention Group	*r*	r^2	*p-value*
CR	0.348	0.121	0.096
ET	0.428	0.183	0.037*
ET + CR	0.446	0.199	0.043*
CON	0.301	0.091	0.174
Change in $HR_{reserve}$ to Change in Absolute VO_{2peak}			
Intervention Group	*r*	r^2	*p-value*
CR	0.297	0.088	0.159
ET	0.344	0.118	0.100
ET + CR	0.541	0.293	0.011*
CON	0.343	0.118	0.118
Change in Body Weight to Change in $HR_{reserve}$			
Intervention Group	*r*	r^2	*p-value*
CR	-0.276	0.076	0.192
ET	-0.245	0.060	0.249
ET + CR	-0.429	0.184	0.052*
CON	0.057	0.003	0.800

Note: CR= Caloric Restriction, ET= Exercise Training, ET + CR = Exercise Training and Caloric Restriction, CON= Control. One outlier in the control group was excluded from the above correlational analyses that include $HR_{reserve}$ as that participant's change in $HR_{reserve}$ surpassed that of anyone's change in HRreserve in any of the intervention groups (likely due to a data entry error or the participant completed exercise training and/or weight loss via caloric restriction without the study team members awareness)

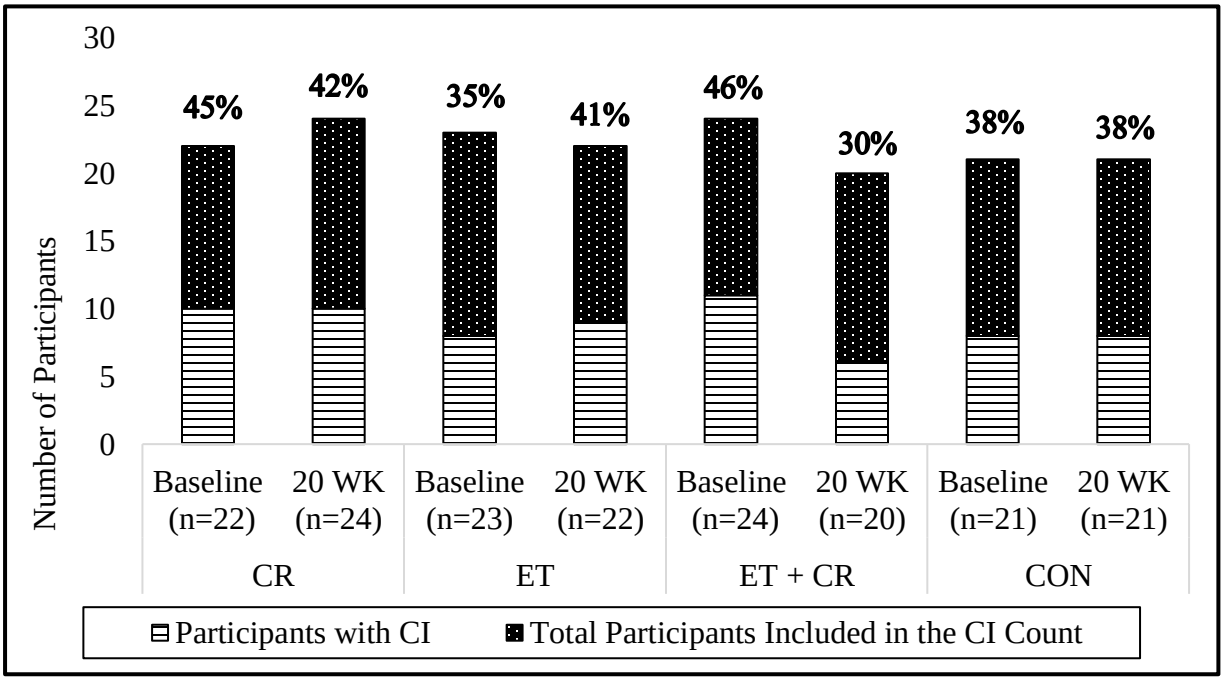
Prevalence of Chronotropic Incompetence

For all participants who met a prespecified RER of ≥1.05 during baseline and follow-up CPET testing, the ≥80% *Adjusted Percent HR Reserve* equation was used to calculate the presence/ absence of CI. According to the *Adjusted Percent HR Reserve* equation, there were 53 participants without CI at baseline (59%). In the 37 participants who were determined to have CI at baseline from the *Adjusted Percent HR Reserve* equation, their RER value at peak effort was considered. For any of the 37 participants did not meet the prespecified RER of ≥1.05 (baseline, n=3; 20-weeks, n=2), the MCR equation was then used. The MCR equation uses submaximal HR and VO_2 data (stage 3 of CPET) values to calculate CI. If submaximal stage 3 values were not available due to missing data, the MCR approach could not be used, thus the presence of CI could not be determined for that participant. Consequently, the presence/absence of CI could not be determined in 10 participants at baseline and 7 at follow-up. Chronotropic incompetence is considered a dichotomous variable (either present or absent). Prevalence of CI, for each group at both time points, was calculated by the number of subjects that did not achieve an adequate HR response, based on the aforementioned criteria, during the CPET.

As shown in Figure 5, out of participants with available maximal exercise testing data, thirty-seven (out of 90 = 41%) participants met the definition of CI at baseline, whereas only thirty-three (out of 87, 38%) participants met the same definition of CI at 20-weeks.

Fisher-Freeman-Halton Exact testing indicated there was not a statistically significant difference (p-value= 0.143) in the prevalence of CI from baseline to follow-up testing (Table 3) among the four groups. This test compared the percent of participants within each intervention group whose CI had resolved by the 20-week mark of the intervention. The CR group saw 12.5% of the participants with CI at baseline resolve at follow-up. The ET group saw 0% of the participants with CI at baseline resolve at follow-up. The ET + CR group saw 16% of participants with CI at baseline have their CI resolve over 20-weeks, whereas the control group saw 8% of its participants with CI resolve over 20-weeks. Although not statistically significant, caloric restricted diet alone tended to decrease the prevalence of CI, whereas exercise training alone did not. Caloric restriction and exercise training were additive (complementary) and together produced a larger, albeit non-statistically significant, decrease in the prevalence of CI.

Figure 5. Chronotropic Incompetence Prevalence at Baseline & 20- Weeks



Note. Percent denoted at the top of the bars represent the percent of people with CI in the total number of people whose data was included in the count based off previously mentioned criteria.

Table 3. Fisher- Freeman Halton Exact Results for CI Prevalence

CI resolved? (*p-value=0.143*)			
Intervention Group	Total (n=)	Absence of CI ***OR*** CI Un-Resolved (n=)	CI Resolved (n=)
CR	24	21	3
ET	26	26	0
ET + CR	25	21	4
CON	25	23	2

DISCUSSION

This thesis examined the impact of exercise training (ET) and/or caloric restriction (CR) on HR response and CI in patients with HFpEF. To our knowledge, this is the first study to evaluate lifestyle interventions (ET and weight loss via CR) on HR response and the prevalence of CI in the HFpEF population. The results of the present investigation determined the prevalence of CI in SECRET I participants at baseline of the study was ~41%, which is within the range reported in the most recent estimates of CI in the HFpEF population (~20-75%) and was consistent with our hypothesis (Hypothesis I) (46, 62, 72–78). We also found that, in general, aerobic ET and weight loss via CR did significantly decrease HR_{rest} and $HR_{submaximal}$ and increase $HR_{recovery}$ (Figures 1a., 1b., 1f.) which was in line with our hypotheses (Hypotheses II & III). However, HR_{peak} remained unchanged which is consistent with literature demonstrating that lifestyle changes, particularly exercise training, does not change HR_{peak} (Figure 1c.) (46, 56, 59). $HR_{recovery1}$ decreased but not significantly (Figure 1e.) which were contrary to hypotheses II & III. Consistent with hypothesis IV, it does appear that there is a synergistic combination of ET + CR on both the HR response.

Participants

Participants in this secondary analysis of the SECRET I trial had typical clinical features of the HFpEF population as they were older (67 $\pm$ 5 years), were predominately female (81%), were obese (based on BMI), had decreased exercise capacity (50% of predicted VO_{2peak}), and high prevalence of co-morbidities such as hypertension and diabetes (Table 1). Out of the 100 participants randomized, 92 participants (92%) completed the trial.

Exercise Training on the HR Response

Typical changes in HR in response to exercise training in normal, healthy individuals include: a decreased HR_{rest} and $HR_{submaximal}$ with improved $HR_{recovery}$ and little changes, if any, in HR_{peak} (59). These alterations in the HR response are the result of a more favorable autonomic balance between the sympathetic and parasympathetic nervous systems (59). One way that exercise improves autonomic balance is by improving parasympathetic tone as a result of decreased norepinephrine and sympathetic activity as well as improved heart rate variability and baroreflex sensitivity (114–124). Research has demonstrated that at any given work level, a trained individual will have lower HRs and lower circulating catecholamines at submaximal levels when compared to untrained individuals (52). However, patients with HF as a result of their systemic condition, have increased sympathetic activation at rest and during exercise (44). A meta-analysis looking at randomized controlled trials of exercise training in HFpEF concluded that exercise interventions resulted in improved VO_{2peak} and quality of life (35).Therefore, exercise training in this population has been shown to be useful in restoring a more favorable autonomic balance (113). In HF specifically, exercise training interventions (including aerobic exercises like walking and cycling) have been shown to have beneficial reductions on the activation of the sympathetic nervous system activity in patients with HFrEF (120, 126).

Our data supports these previous findings as we found decreased HR_{rest}, $HR_{submaximal}$, and improved $HR_{recovery,}$ all of which support a more favorable balance in the autonomic nervous system as a result of lifestyle interventions (Figures 1a.,1b.,1f.). However, our data demonstrated that HR_{peak} did not change in this population from

exercise interventions (Figure 1c.). Although this is interesting in terms of CI as research in the HFrEF population saw an increase in HR_{peak} after aerobic exercise training (64), our finding is plausible as one's HR_{peak}/HR_{max} is more of a function of aging rather than deconditioning (59, 131). This would also suggest as to why $HR_{reserve}$ did not significantly change (Figure 1d.) as HR_{peak} is used in the calculation of $HR_{reserve}$. In our analyses, $HR_{recovery1}$ remained unchanged (Figure 1e.) despite improved HR_{rest} and $HR_{submaximal}$. This was contrary to our hypotheses as we anticipated $HR_{recovery1}$ to improve as a result of lifestyle intervention. However, it is likely that there was improved autonomic balance suggested by the decreases in HR_{rest} and $HR_{submaximal}$. Despite $HR_{recovery1}$ not improving, post-hoc testing revealed a significant improvement in $HR_{recovery}$ when comparing the ET + CR to the CON group.

Caloric Restriction on HR Response

A caloric restricted diet has also been suggested by research to have improved HR responses in normal, healthy populations and populations with similar physiological characteristics to the HF population (131, 132). Previous research concluded that exercise training enhances the effects of CR in hypertensive subjects, a co-morbidity common in HFpEF (131, 132). Specifically, Nicoll et al. showed that CR improved their HR response by lowering their HR_{rest} which is consistent with our findings (Figure 1a.) (132). A review examining CR on the HR response in animal models found that CR helped preserve the chronotropic response (131). This was also true in our findings as we found improved HR responses in the groups that included CR (CR and ET + CR) when compared to the CON group (Table 3). This is likely because caloric restriction that results in weight loss means that for any given activity, patients with HF are moving

around less body mass, and therefore the heart does not have to generate as much cardiac output. There are also likely other benefits like decreased systemic inflammation accompanied by improved autonomic balance with weight loss (4, 131).

The Combination of ET + CR on the HR Response

As mentioned previously, the combination of ET + CR is likely to have a synergistic effect on physiological responses in healthy and clinical populations (6, 131, 132). Consistent with hypothesis IV and previous literature, it does appear that there is a synergistic combination of ET + CR. Our data shows that the greatest improvement in the HR response was in the combined ET + CR group (Figures 1a.,1b.,1f., Figures 2 & 3, Table 2). Despite $HR_{recovery1}$ not improving, post-hoc testing revealed a significant improvement in $HR_{recovery}$ when comparing the ET + CR to the CON group, which further demonstrates the synergistic combination of the lifestyle interventions on HR responses. This synergistic combination was also supported by our correlational analyses as the strongest, significant positive correlation in the change in relative VO_{2peak} (ml/kg/min) and change in $HR_{reserve}$ was in the ET + CR group (Figure 2). This was also the case for the change in absolute VO_{2peak} (ml/min) and change in $HR_{reserve}$ correlational analysis (Figure 3). Consistent with these correlational analyses, the correlation between change in body weight and change in $HR_{reserve}$ showed the strongest, significant negative correlation in the ET + CR group (Figure 4). The prevalence of CI decreased the most (16%), although not significantly, in the ET + CR group when compared to ET or CR alone (Table 3). This synergistic combination of ET + CR was previously shown to be the most impactful on the main outcomes (exercise capacity and quality of life) of the SECRET I randomized controlled trial (6).

The Prevalence of CI and Impact of Lifestyle Changes

The present investigation determined that 37 out of 90 (41%) of participants were classified with CI at baseline. This is consistent with several previous investigations of subjects with HFpEF and CI. The reported prevalence of CI in patients with HFpEF has ranged from 20-75% of patients (46, 62, 73–78), but the most recent systematic review reported the prevalence of CI in HFpEF is ~55% (72). One notable study whose purpose was to determine the prevalence of CI in HFpEF and HFrEF populations in comparison to a healthy control group, reported a CI prevalence of 19.6% in those with HFpEF (11 participants with CI out of 56) (46). However, this study used the criteria of 85% of APHRM during an exercise test (but the same RER criteria as the current thesis) to define CI. It is likely that using 85% of APHRM excluded some people in the HFpEF population with CI because this prevalence of 19.6% is lower than the suggested range (20-75%) and the prevalence of CI in this thesis (~41%). This thesis defined CI based off 80% of APHRR and adjusts for high resting HRs, so it is likely that that our criteria included more people with CI as compared to 85%, which is likely why the reported prevalence in this thesis is higher than Joo et al. (46). The difference in prevalence from the reported studies emphasizes the need for a standardized definition of CI.

This study demonstrates that although 20-weeks of aerobic ET and/or weight loss via CR resulted in improved HR responses in older, obese patients with HFpEF, these lifestyle changes independently had minimal effect on the prevalence of CI. This is in contrast to a study by Keteyian et al. who concluded a partial reversal of CI with an aerobic exercise intervention in patients with HFrEF (64). In contrast to our results, Keteyian et al. found an increase in HR_{peak} (141 $\pm$ 5, p-0.05) and $HR_{reserve}$ (73$\pm$4, p-0.04)

in participants with CI who engaged in 24 weeks of aerobic exercise training. Although Keteyian et al. saw improvements in HR_{peak}, the amount of people with CI at baseline (n=14) and 24-weeks (n=14) did not change which is consistent in with the results of the exercise group of this thesis. The significant change in HR_{peak} may have been because the study conducted by Keteyian et al. was in HFrEF participants or that the current thesis covaried baseline HR response through the use of ANCOVA rather than using a paired t-test. The current thesis and the work by Keteyian et al. found a significant correlation in the change in $HR_{reserve}$ (bpm) and change in relative VO_{2peak} (ml/kg/min), however this relationship was stronger in the findings of Keteyian et al. ($r = 0.75$, p-value not reported but noted statistically significant).

However, the present study does suggest the combination of ET + CR resulted in a substantial decrease in the prevalence of CI from baseline to follow-up. While a relatively small number of participants in ET + CR resolved CI after the 20-week intervention (n=4), this has important clinical implications as studies have demonstrated that the presence of CI in patients tends to have worse clinical outcomes than those without CI (62, 79, 80). Regardless of HF phenotype, people with CI and HF have a 24% higher mortality rate (OR -1.24, 95% -2.20 to -0.28, p-0.01) and lower VO_{2peak} compared to those without CI (-3.30 ml/kg/min (95% CI -4.25 to -2.35 $p<0.01$))(72). This means that patients with HF and CI experience more exercise intolerance during activities of daily living than those without CI, so it does impact those people regularly. CI is also a prognostic marker of adverse events (42).

Komadja et al. suggest possible mechanisms in which exercise training in HF may improve CI and restore quality of life (20). Possible mechanisms include reversal of the

autonomic imbalance resulting in improved endothelial function, central hemodynamics, inflammatory markers, neurohormonal activation, and skeletal muscle structure and quality (20, 71). More specifically, physical activity decreases sympathetic outflow and plasma catecholamine levels at rest (59, 125). The results of this thesis do not allow us to further understand the mechanisms behind CI, but rather help us understand CI management options.

Non-Responders to Lifestyle Interventions

The results of the correlational analyses at the combined intervention group level suggest that there were some non-responders to the lifestyle interventions. For the purpose of these analyses, we defined "non-responders" as participants who did not improve in both variables included in the correlational analyses, however, we recognize that may not translate to clinically meaningful changes. This is indicated by the shaded region in lower left quadrant of the Figure 2 and Figure 3 and the lower right quadrant of Figure 4. In Figure 2, there were n= 4 non- responders in the CR group, n=2 in ET, and n=1 in ET + CR. Of those 7 non-responders, 5 of them (71%) had CI at either baseline, follow-up, or both timepoints. In Figure 3, there were n= 6 non- responders in the CR group, n=2 in ET, and n=4 in ET + CR. Of those 12 non-responders, 8 of them (67%) had CI at either baseline, follow-up, or at both timepoints. In Figure 4, there were no non-responders in the CR group, n=3 in ET, and none in the ET + CR. Of those 3 non-responders, only one of them (33%) had CI at baseline and follow-up. This suggests that CI could be contributing to their non-responsiveness to the lifestyle interventions.

Limitations and Future Directions

Despite the significant findings of this investigation, there are several important limitations. The SECRET I trial was a single site, blinded, randomized controlled trial with levels of high control. Although these aspects of studies are typically seen as a strength, they limit the external validity of these findings. Although we used two equations to help determine the prevalence of CI in this population, we acknowledge that numerous participants were excluded because they did not meet the RER criteria and were further excluded with the use of the MCR equation. This exclusion probably affected the prevalence of CI that we found in this group. It is possible that some of the participants who were excluded by these methods had CI because they did not meet a near maximal RER (a possible result of an attenuated HR response). We also acknowledge that the 220 - *age* equation utilized in the CI calculations comes with a lot of variability, but for the purposes of this thesis, this was the most appropriate equation to use. Lastly, the SECRET I trial's duration was 20-weeks. We recognize that if this trial were longer, that we may have seen the effects of the continuation of the lifestyle interventions on HR responses and CI. Although it was not part of this trial, it would also be of importance to follow-up with participants at some point post-trial to see if the benefits on the HR response of the 20-week intervention were sustained or if the benefits reversed over time. Future research should consider further understanding the mechanisms behind CI in the HFpEF population and expanding upon the findings of CI management in HFpEF (rate-adaptive pacing, β-blockers, lifestyle interventions, etc.).

Conclusions

Aerobic exercise training and/or weight loss via caloric restriction resulted in improved heart rate responses but with minimal impact on the prevalence of CI in patients with HFpEF. This study has important clinical implications as improved HR responses, particularly at submaximal levels of exertion, can improve exercise tolerance and quality of life in older, obese patients with HFpEF. Unfortunately, previous research has indicated that neither medications nor rate-adaptive pacing were able to reverse this condition. This study also suggests that ET and/or CR has limited impact on reversing CI in older, obese patients with HFpEF. Given the high prevalence and important prognostic value of CI in HFpEF (62, 79, 80), more research needs to be conducted to identify therapies to reverse this condition.

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CURRICULUM VITAE

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Education

Wake Forest University
Master of Science Candidate, Health and Exercise Science, expected May 2022
Elon University
Bachelor of Science in Exercise Science, Magna Cum Laude, May 2020
Minor in Biology

Research Experience

Master's Thesis *(Advisor- Dr. Peter Brubaker):*
Impact of Exercise Training and/or Caloric restriction on Heart Rate Response in Patients with Heart Failure with Preserved Ejection Fraction (HFpEF)
Improving Exercise Capacity with a Tailored Physical Activity Intervention in Lymphoma Patients Undergoing Treatment, Physical Activity in Lymphoma Study (PALS),
Graduate Student Assistant May 2021 - Present
ExTra-MATCH III: Meta-analysis of exercise training in HFpEF,
Data Assistant Jan 2021 - May 2021
Undergraduate Research Project *(Advisor- Dr. Simon Higgins):*
The Utility of Telemetric Devices for the Measurement of Heart Rate Variability and Orthostatic Intolerance in Older Adults

Clinical Experience

Healthy Exercise & Lifestyle ProgramS (HELPS),
Morning Coordinator May 2021 - Present
Graduate Student Staff Aug 2020 - May 2021
Health Outreach Program of Elon (HOPE) Clinic,
Undergraduate Student Volunteer Aug 2019 - Dec 2019

Work Experience

Wake Forest Human Anatomy Cadaver Lab,
Teaching Assistant Aug 2020 - Present
Elon University Office of the Provost and Academic Affairs,
Lead Student Assistant Feb 2017 - May 2020
Elon University Human Donor Anatomy Lab,
Teaching Assistant Aug 2017 - May 2020
Elon University Office of Admissions,
Campus Tour Guide May 2017 - May 2020

Awards

2020 Exercise Science Outstanding Senior Service Award, *Elon University*
Exercise Science Chair's Award – Spring 2019 and Spring 2020, *Elon University*

Funding

2019-2020 Elon University Glen Raven Endowed Grant Recipient
Fall 2019 Elon University Research Grant-in-Aid

Certifications & Membership

Administration of Neurocognitive Battery	July 2021 - Present
SilverSneakers Yoga	April 2021 - Present
SilverSneakers Classic	Aug 2020 - Present
American College of Sports Medicine, Certified Personal Trainer	May 2020 - Present
Omicron Delta Kappa Leadership Honors Society	Aril 2020 - Present
American Heart Association, Basic Life Support (CPR & AED)	Nov 2019 - Present
Kappa Omicron Nu National Honor Society for the Human Sciences	April 2019 - Present
Beta Beta Beta Biological Honors Society	April 2018 - Present

Microsoft Word & PowerPoint 2010

Conference Participation

National American College of Sport Medicine 2020- San Francisco, CA

Abstracts:

- Sleep Quality is Associated with Nighttime Heart Rate Variability in Young Adults
  - Emerson Bennett, Lauren Q. Higgins, Simon Higgins
- Classification Accuracy of Wrist-Worn Physical Activity Monitors Relative to Free-Living Heart Rate
  - Simon Higgins, Emerson Bennett, Richard Blackmon

Publications

Anticipated: *The Utility of Telemetric Devices for the Measurement of Heart Rate Variability and Orthostatic Intolerance in Older Adults*