EFFECTS OF A RANDOMIZED CONTROLLED TRIAL OF DIET AND/OR EXERCISE ON OBJECTIVELY MEASURED PHYSICAL ACTIVITY LEVELS IN OLDER HEART FAILURE PATIENTS

BY

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A Thesis Submitted to the Graduate Faculty of

WAKE FOREST UNIVERSITY GRADUATE SCHOOL OF ARTS AND SCIENCES

in Partial Fulfillment of the Requirements

for the Degree of

MASTER OF SCIENCE

Health and Exercise Science

May 2012

Winston-Salem, North Carolina

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DEDICATION

I would like to dedicate this thesis to my amazing parents. I am blessed beyond measure to be able to say the two most incredible people I know are my parents. First, to my mother Nancy: thank you for your unconditional love and support. You have always been there for me, through life’s successes and trials. You continue to show me every day how to be Christ-like, by putting the needs and desires of others before your own. I am incredibly thankful for your example, as well as your guidance. You taught me to follow my heart even though it might not always be the easiest decision. And to my father, Jeff: I would not be the man I am today if it was not for your influence. It is my hope and prayer that someday I will be half of the man that you were. You showed me what it means to be a Godly man and take care of your family, even among less than ideal circumstances. Despite your weaknesses, you displayed strength – a strength you found in Christ. You were the definition of persistence, courage, and determination. I am fortunate to have developed these characteristics you always portrayed.
ACKNOWLEDGEMENTS

I would like to formally thank:

Dr. Peter Brubaker, for being my thesis advisor, professor, and mentor. I am so thankful to have been able to work so closely with such a renowned faculty member at Wake Forest. I am forever grateful for the wealth of knowledge you have shared with me and for your guidance and direction for my future professional career. I appreciate how you treated me as a colleague and worked so hard with me to finish this thesis. You made this process less overwhelming, and without your help it would not have been possible.

Dr. Michael Berry, for being on my thesis committee. I have thoroughly enjoyed having you as a professor. You taught me that the academic world does not always have to be professional; it can be fun and entertaining as well. I will never forget your sense of humor and ability to make stressful environments more easy going.

Dr. Patricia Nixon, for also agreeing to be on my thesis committee. I learned a great deal from you as a professor and always enjoyed your upbeat attitude. Thank you for further developing my understanding of the field we study through a larger scope.

Jordan Hauser, for being an amazing supervisor and friend. You were a great example for how to manage and run a clinic. I am so fortunate to have worked so closely with you during my second year and I know I will pull from these experiences during my professional career.

HELPS Participants, who taught me just as much during my time here as the coursework did. Thank you for the life lessons you taught me and for always being an incredible resource for advice. I will forever cherish the conversations I had with you all.

My Classmates, for the amazing love and support you gave me over the past 22 months. I could not have asked for 7 better people to go through this program with. I can honestly say you know me as well as some of my closest family and friends. You always knew how to best motivate and encourage me. Each one of you has taught me something I will forever cherish and I will always consider all of you friends.

Mom, David, Bre, Aaron, and Abbey, for your continuous support. I am so incredibly blessed to have such amazing people in my life. Despite the difficulty of living so far away, you were always there to provide encouragement and an escape from the stresses of my education. At the end of the day, I know you are always there to pick me up when I need it. I could not ask for better people to call family.
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LIST OF ABBREVIATIONS

6MW: Six-Minute Walk Distance
6MWT: Six-Minute Walk Test
ACE – inhibitors: Angiotension-Converting Enzyme - inhibitors
ACSM: American College of Sports Medicine
ALVD: Asyptomatic Left Ventricular Dysfunction
AS: Activity Score
a-vO₂ difference: Arterial-Venous Oxygen Difference
BMI: Body Mass Index
BNP: Brain Natriuric Peptide
bpm: Beats per Minute
BRFSS: Behavioral Risk Factor Surveillance System
CAD: Coronary Artery Disease
CDC: Center for Disease Control and Prevention
CHAMPS: Community Health Activities Model Program for Seniors
CLIP: Cooperative Lifestyle Intervention Program
CO: Cardiac Output
COPD: Chronic Obstructive Pulmonary Disease
CPET: Cardiopulmonary Exercise Test
CRC: Colorectal Cancer
CRP: Cardiac Rehabilitation Program
CVD: Cardiovascular Disease
DEE: Daily Energy Expenditure
DEXA: Dual Energy X-ray Absorptiometry

EDV: End-Diastolic Volume

EE: Energy Expenditure

EF%: Ejection Fraction

ESV: End-Systolic Volume

G: Gravitational Constant

HCS: Healthy Control Subject

HF: Heart Failure

HF-ACTION: Heart Failure and A Controlled Trial Investigating Outcomes of exercise training

HFrEF: Heart Failure with a Reduced Ejection Fraction

HR: Heart Rate

HTN: Hypertension

Hz: Hertz

IADL: Instrumental Activities of Daily Living

IPAQ: International Physical Activity Questionnaire

kcal: kilocalorie

kg: Kilogram

LPA: Light Physical Activity

LV: Left Ventricle

LVEF: Left Ventricular Ejection Fraction

m: Meters
max: Maximum
MET: Metabolic Equivalent
MI: Myocardial Infarction
min: Minimum
MLHF: Minnesota – Living with Heart Failure Quality of Life Questionnaire
mmHg: Millimeters of Mercury
MPA: Moderate Physical Activity
MVPA: Moderate-Vigorous Physical Activity
NHANES: National Health and Nutrition Examination Survey
NHW: Non-Hispanic White
NYHA: New York Heart Association
OR: Odds Ratio
PA: Physical Activity
PAAS: Physical Activity Analysis Software
PADL: Personal Activities of Daily Living
PAEE: Physical Activity Energy Expenditure
PARIS: Prospective Aerobic Reconditioning Intervention Study
PC: Computer
PCA: Principal Components Factors Analysis
QOL: Quality of Life
r: Correlation
RPE: Rating of Perceived Exertion
SD: Standard Deviation
SECRET: Study of the Effects of Caloric Restriction and Exercise Training

SEE: Standard Error of the Estimate

Slope: VE/VCO₂ Slope

SPSS: Statistical Package for the Social Sciences

SV: Stroke Volume

TEE: Total Energy Expenditure

US: United States

VAT: Ventilatory Anaerobic Threshold

VO₂ max: Maximum Oxygen Consumption

VO₂ peak: Peak Oxygen Consumption

VPA: Vigorous Physical Activity

vs: Versus

WFUBMC: Wake Forest University Baptist Medical Center

yrs.: Years
ABSTRACT

Daniel Clevenger

EFFECTS OF A RANDOMIZED CONTROLLED TRIAL OF DIET AND/OR EXERCISE ON OBJECTIVELY MEASURED PHYSICAL ACTIVITY LEVELS IN OLDER HEART FAILURE PATIENTS

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

PURPOSE: To evaluate the changes in primary outcomes (VO\textsubscript{2} peak and body weight) and physical activity levels (PA) from baseline to follow-up between four intervention groups of a weight loss study in older heart failure patients with a preserved ejection fraction (HFpEF). Additionally, a second purpose was to explore the relationships between the changes in PA levels and changes in the primary outcomes of the SECRET trial: VO\textsubscript{2} peak and body weight.

METHODS: Subjects were assessed at baseline and follow-up of a RCT examining the effects of an exercise and/or weight loss intervention in older HFpEF patients. Patients were randomized to one of four intervention groups: Exercise Only (Ex), Diet Only (Diet), Exercise Plus Diet (E+D), or Attention Control (AC). Inclusion for the RCT included: a HF Clinical Score of > 3, a normal ejection fraction (> 50%), a BMI of > 30 kg/m\textsuperscript{2}, and > 60 years of age. Body weight was measured using a standardized scale. Peak oxygen consumption (VO\textsubscript{2} peak) was obtained from a maximal effort exercise test on a motorized treadmill. A uniaxial accelerometer (Lifecorder) was worn for 7 continuous days, and evaluated for adequate wear time and days. The average steps/day, physical activity energy expenditure (PAEE) in kcal/min, minutes of light (LPA) and moderate-vigorous physical activity (MVPA) were determined for each participant.
RESULTS: The 43 HFpEF subjects included in this study were older (mean age 68 yrs), mostly female (74%), and overweight/obese (mean BMI of 38.8 kg/m$^2$). The only variable that was significantly different between the intervention groups was a difference in age of 6 years between the Ex and E+D groups. The Diet and E+D groups had a significantly lower body weight at follow-up (94.0 ± 1.27 and 93.5 ± 1.30 kg, respectively) compared to the AC group (102.9 ± 1.47 kg). The Diet and E+D groups had a significantly higher VO$_2$peak at follow-up (16.2 ± 0.36 and 16.8 ± 0.37 ml·kg·min$^{-1}$, respectively) compared to the AC group (13.9 ± 0.41 ml·kg·min$^{-1}$). The E+D group had significantly more steps/day at follow-up (6590.55 ± 445.01 steps/day) compared to the Diet and AC groups (4086.56 ± 450.54 and 4331.70 ± 502.15 steps/day, respectively). The E+D had significantly more minutes of MVPA at follow-up (29.42 ± 2.50 min) compared to all three other intervention groups (Ex: 15.50 ± 3.12 min; Diet: 12.19 ± 2.53 min; AC: 11.91 ± 2.82 min). The E+D group had a significantly higher PAEE at follow-up (261.94 ± 20.96 kcals/day) compared to the Diet and AC groups (152.05 ± 21.22 and 161.42 ± 23.65 kcals/day, respectively). Changes in minutes of MVPA was the only PA variable found to be significantly correlated with both changes in VO$_2$peak ($r = 0.329$) and changes in body weight ($r = 0.387$).

CONCLUSION: Results of this 20 week study suggest that exercise and diet is the most effective short-term combination for weight loss and for increasing VO$_2$peak in this population. Another unique finding of this study was that diet alone compared to exercise alone was superior for producing improvements in VO$_2$peak and weight loss. Results of this trial also suggest that the E+D group demonstrated the largest increase in PA measures and that changes in PA levels only modestly correlate with changes in
VO₂peak, suggesting other factors, particularly diet changes, also play an important role in the weight loss in HFpEF patients.
REVIEW OF LITERATURE

Overview of Heart Failure

_Epidemiology of Heart Failure_

Chronic heart failure (HF) affects 5.7 million adults in the United States, leading to nearly one million hospitalizations and 300,000 deaths annually\(^1\). The estimated annual cost to manage this disease is approximately $40 billion\(^1,2\). Of all categories of cardiovascular diseases, HF is the only one in which the prevalence, incidence, hospitalization rate, mortality, and total cost have continued to increase over the past 25 years\(^3,4\). The prevalence of HF in men ages 40-59 is 1.9 percent and progressively increases to 11.5 percent in men over the age of 80. Women show a similar increase in prevalence from 0.8 to 11.8 percent from ages 40-59 to over the age of 80, respectively\(^2\). The incidence of HF increases 2-fold for each decade of age and approximately 750,000 new cases are diagnosed each year\(^3\). The overall risk of developing HF, across a lifespan, is 20 percent for both men and women\(^5\). These increases in prevalence and incidence rates over recent decades can be attributed to a longer life-expectancy in addition to advances in medical care and management of cardiovascular and other diseases\(^3,4\). By 2040, it is projected there will be 77.2 million new HF cases\(^6\). Even more alarming, an underestimation of rates most likely occurs because some patients who have left ventricular dysfunction are asymptomatic and are therefore undiagnosed\(^3\). This increasing trend is, and will continue to be, a major public health concern.
Risk Factors for Heart Failure

Although there are many potential risk factors associated with the development of HF, the most common causes of HF are hypertension (HTN), coronary artery disease (CAD), and diabetes; however, the strongest risk factor is still a topic of debate in the literature. The Framingham Heart Study has produced important information in regards to the development of HF. Framingham participants, who were free of HF at baseline, were followed to determine the overall lifetime risk for developing HF as well as potential risk factors for HF. The Framingham Heart Study found 75 percent of HF cases were preceded by HTN. It was also found that at 40 years of age, the overall lifetime risk for developing HF was 21 and 21.3 percent for men and women, respectively. However, this risk doubled for participants who had a blood pressure at or above 160/100 mmHg compared to those below 140/90 mmHg. The Framingham Offspring Study was then conducted to determine familial clustering as well as other potential risk factors. In a study examining both the Framingham Heart Study and Framingham Offspring Study, HTN preceded HF in 91 percent of the cases and was associated with a two-to-threefold increase in risk for the development of the HF.

Gibson et al. examined the prevalence of HF in two rural communities and found that CAD was associated with HF in 38.9 and 48.9 percent of the two study groups. Data from the Framingham Heart Study also has shown CAD to be a major risk factor for HF. Prevalence of CAD was less common in women than men (48% vs. 59.9%, respectively), for developing HF. However, when further analyses were conducted to see the impact of HTN, only 9.9 percent of the HF cases had CAD without HTN. The differences noted between these studies can potentially be accounted for by
inconsistencies in criteria for diagnosing CAD, HTN, and HF\(^7\). In addition to CAD, the presence of a previous myocardial infarction (MI), a hard manifestation of CAD, has been shown to increase the lifetime risk of developing HF in persons over the age of 40. Therefore a history of HTN or MI significantly increases the risk of developing HF\(^5\).

In order to determine the progression from CAD to HF, Bibbins-Domingo et al.\(^1\) prospectively studied 2,391 diagnosed CAD, postmenopausal women from 1993-2006. The results from their investigation suggested that diabetes was the strongest predictor for the development of HF. Women with diabetes and no additional risk factors had a 3.0 percent incidence of HF compared to 0.4 percent for those who were non-diabetic and no additional risk factors. However, women with diabetes and \(\geq 3\) risk factors had an 8.2 percent incidence of HF. A difference in risk was also seen for controlled versus uncontrolled diabetics. Diabetics with fasting blood glucose \(>300\) mg/dL had a threefold increase in risk compared with those with controlled fasting blood glucose levels after adjusting for possible covariates\(^1\)\(^1\). Although these investigators found diabetes to increase the risk for HF, this increased risk has been shown to be higher in women than in men\(^8\).

Research has also shown that obesity (BMI \(\geq 30\) kg/m\(^2\)) increases the risk of developing HF\(^1\)\(^2\). The Physician’s Health Study examined 21,094 men without a history of CAD. Compared with normal weight participants, overweight participants (BMI \(\geq 25\) kg/m\(^2\)) and obese participants had a 49 percent and 180 percent increase in HF risk, respectively. In fact, for every 1 kg/m\(^2\) increase in BMI there was an 11 percent increase in risk of HF\(^1\)\(^2\). However after adjusting for potentially confounding variables such as
HTN, diabetes, and hypercholesterolemia, the relative risk for developing HF decreased from 3.38 to 2.80 in obese participants compared to normal weight individuals.\textsuperscript{12}

Whereas many of the aforementioned risk factors can be modified by lifestyle changes and/or medications, age is a risk factor for HF that cannot be modified. Increasing age has been shown to be related to the development of HF.\textsuperscript{7,10,13–15} The Framingham Heart Study and the Framingham Offspring Study followed 9,405 males and females to examine the development of cardiovascular disease.\textsuperscript{10} In this analysis, age was found to be a major risk factor for the development of HF. The annual incidence rate increased from 3/1,000 in men ages 50-59 to 27/1,000 in men ages 80-89. A similar pattern was observed in the women, with the annual incidence rate increasing from 2/1,000 to 22/1,000 in women ages 50-59 to 80-89, respectively. Even after adjustment for age, the incidence of HF in women was still one-third that of men.\textsuperscript{10} Therefore beyond the modifiable risk factors of HTN, CAD, and diabetes, age alone affects the structure of the left ventricle (LV) and contributes to the pathophysiological changes that result in HF.

\textit{Pathophysiology of Heart Failure}

Heart failure can be defined as the inability of the heart to meet the demands of the tissues due to a reduced cardiac output (CO).\textsuperscript{16} Heart failure is often described as a “syndrome” (see Figure 1) as various pathophysiological responses and symptoms stem from a reduced CO.\textsuperscript{2,17}

Initially, the reduced CO to the lungs causes pulmonary mismatching and manifests in symptoms of fatigue and shortness of breath on exertion. In addition to the
lungs, the kidneys are also affected by the reduced perfusion. This leads to the activation of the renin-angiotensin-aldosterone and sympathetic nervous systems. As a result of the neurohormonal activation of the renin-angiotensin-aldosterone system, the peripheral arteries undergo vasoconstriction and consequently increase the afterload on the heart. Brain natriuretic peptide (BNP) is produced by the ventricular myocardium attempt to vasodilate the arterioles. Moreover, a decrease in blood flow to the skeletal muscle occurs as a result of the activation of the sympathetic nervous system and neurohormones. This activation overrides local metabolites attempting to vasodilate the arterioles within the active skeletal muscle. The inability to decrease vascular resistance of the skeletal muscle is one of the predominant causes of the exercise intolerance experienced by HF patients.

Figure 1. Pathophysiologic Syndrome of Heart Failure
HF is generally a progressive disease by nature where pathologic remodeling of the left ventricle compounds the problem by furthering weakening the myocardium. This leads to diminished contractile functioning of the ventricles which further reduces the ejection fraction and cardiac output. Because of the numerous physiological changes discussed above, HF patients experience exercise intolerance in addition to fatigue and/or dyspnea on exertion. Consequently, exercise intolerance is shown to be the most common symptom of the HF population.

**Acute Exercise Responses in Heart Failure**

Exercise intolerance is best evaluated by VO$_2$peak which is determined by the Fick equation. In this equation, VO$_2$peak = cardiac output x arterial-venous oxygen difference (a-vO$_2$ difference). Through the Fick equation, both central and peripheral hemodynamics are taken into account to allow one to understand the specific factors that contribute to the exercise intolerance. In normal subjects, cardiac output (CO) increases 4-6 fold from rest to peak exertion. This increase is due to increases in both heart rate (HR) and stroke volume (SV). During an acute bout of exercise in normal subjects, SV increases 20-50% due to an increase in venous return which increases the end-diastolic volume (EDV). A decrease in end-systolic volume (ESV) is also seen due to an increase in myocardial contractility. In HF patients, the reduced LV function fails to maintain a sufficient CO, generally less than 50% of a normal individual. The SV fails to increase to normal levels because the LV is unable to relax and/or contract in a normal manner. The reduced CO is primarily attributed to a decrease in SV and frequently an inadequate HR.
response. A recent study found chronotropic incompetence to occur in 42% of HF patients. 

Along with the “central” hemodynamic changes, there are also changes seen in the periphery. In HF patients, an insufficient widening of the a-vO₂ difference occurs which limits the oxygen delivered to the working skeletal muscles during exertion. In response to the reduced perfusion, the skeletal muscle adapts by decreasing both the number and size of the “aerobic” Type I muscle fibers. In order to adapt to the reduced perfusion, there is a decrease in oxidative enzymes and an increase in anaerobic enzymes within the skeletal muscle. Furthermore, there is a decrease in skeletal muscle mitochondrial volume as well as density in HF patients. Vasoconstriction also occurs due to an increase in endothelial dysfunction and vasomotor activity. From rest to peak exertion in normal subjects, a-vO₂ difference increases three fold, whereas only a two fold increase is seen in HF patients.

**Signs/Symptoms, Diagnosis, and Treatment of Heart Failure**

Although HF patients suffer from a variety of symptoms, dyspnea and excessive fatigue, predominantly with exertion, are the two most common. However, these symptoms are very prevalent among a variety of other conditions and therefore cannot serve as diagnostic criteria of HF. This further complicates the diagnostic process of HF. Patients are first treated for other medical conditions and when they continue to present with a presence of symptoms over a period of time, these other medical conditions are slowly ruled out leading to a diagnosis of HF. Repeatedly measuring the body
weight of the patient has been shown to aid in the diagnosis of HF by alerting the clinician and the patient of possible fluid retention. Typically HF patients are categorized into subgroups based on both functional capacity and symptoms using the New York Heart Association (NYHA) and/or the American College of Cardiology Scale (See Appendices).

Heart failure signs/symptoms manifest when there is significant systolic and/or diastolic dysfunction of the left ventricle (LV). Aging and increased angiotensin II production causes the heart to undergo morphological changes which limit its optimal functioning. The primary assessment used to evaluate the cardiac functioning is the ejection fraction (EF%). Ejection fraction is calculated by stroke volume (SV)/end-diastolic volume (EDV). In normal individuals, EF% is between 55-65 percent. Patients who present with signs and symptoms of heart failure can be classified into one of two categories: HF with a reduced EF% (HFrEF) or HF with a preserved EF% (HFpEF). Those with HFrEF have considerable LV dysfunction, displayed through a reduced EF% of <35 percent. The heart of a patient with HFrEF is characterized by an enlarged LV and poor LV contractility. In contrast HFpEF patients have a preserved or normal EF% of 50 percent or greater and are characterized by having normal LV systolic function, but a reduced EDV due to diminished LV relaxation and filling. This leads to in concentric hypertrophy of the LV resulting in a thick and stiffened heart.

Ejection fraction, LV size, and LV contractility are all used in the evaluation of the HF patient and categorization of the patient as having either HFrEF or HFpEF. The echocardiogram is the most useful tool to evaluate HF and to determine systolic or diastolic dysfunction. The standard 2-D echocardiogram can be used to evaluate EF%,
LV wall diameter and thickness, as well as wall motion\textsuperscript{2,4}. Other assessment tools used to evaluate LV dysfunction including: nuclear myocardial perfusion imaging, positron-emission tomography, cardiac magnetic resonance imaging, and cardiac catheterization\textsuperscript{2}. In addition, these tests can determine whether the LV dysfunction is either ischemic or non-ischemic. Heart failure which is ischemic in nature is usually due to a lack of blood flow to the myocardium associated with coronary artery disease (CAD). Moreover, ischemic HF can be due to previous myocardial infarction and/or chronic myocardial ischemia. Conversely, non-ischemic HF is typically attributed to heart valve dysfunction or infections of viral origin affecting the myocardium and/or myocytes\textsuperscript{19}.

Treatment for HF patients depends primarily on the disease progression. The American College of Cardiology scale (see appendix) can be used to categorize the patients based on disease progression in stages A-D. Patients in stage A do not have overt HF and present with risk factors such as HTN, CAD, and diabetes. However, these patients do not have HF signs or symptoms. The main treatment goal of patients in this stage is to manage the risk factors in the attempt to prevent overt HF. Trials have shown reducing blood pressure reduces left ventricular hypertrophy and cardiovascular mortality, as well as lowering the incidence of heart failure by 30-50\%\textsuperscript{2,17}. Patients with HTN are often prescribed ACE-inhibitors or angiotensin-receptor blockers in order to delay or prevent LV remodeling and disease progression\textsuperscript{17}. In addition, ACE-inhibitors have also been shown to significantly reduce the incidence of stroke and MI, as well as mortality\textsuperscript{23-25}.

Patients with structural heart disease may or may not have signs or symptoms and are thus categorized as stage B, C, or D. The main objectives for these patients are to
slow the progression of the disease, minimize symptoms, manage risk factors, and improve survival. These objectives can be met through modifying the patient’s lifestyle through reducing sodium intake, monitoring body weight, and closely adhering to the prescribed medications. Medications that are commonly prescribed to patients in these HF stages are ACE-inhibitors, beta blockers, and diuretics. Beta blockers are used to treat HTN, angina, and arrhythmias as well as counteract the potentially harmful effects of the sympathetic nervous system in HF. When used in the HF population beta blockers have been shown to improve morbidity, mortality, LV remodeling, quality of life, hospital admission rates, as well as sudden death. Life-threatening ventricular arrhythmias are common in patients with HF and can be managed with an implantable cardioverter defibrillator or pacemaker to control both heart rate and rhythm. In those HF patients who suffer from CAD, myocardial revascularization can also be beneficial. This can be done either through coronary artery bypass or percutaneous coronary intervention (i.e. angioplasty/stent). Despite extensive research over the past 30 years consistently showing the benefits of exercise/physical activity in stable HF patients, most HF management guidelines fail to include this beneficial therapy.

Recommendation of Physical Activity

Physical activity (PA) has a multitude of benefits and has also been shown to decrease the all-cause mortality rate for all ages. In addition, primary and secondary prevention of a variety of chronic diseases may be attainable through exercise training. Individuals with coronary artery disease, type 2 diabetes, metabolic syndrome, colon
cancer, and breast cancer who are physically active have a reduction in risk of premature death due to their chronic condition \(^{29-35}\). Hypertensive individuals benefit from PA as well, with improvements in blood pressure, muscular strength, feelings of depression and anxiety through improving mental health, mood, and quality of life. Physical activity also has a positive effect on weight management by helping to reduce weight and body fat \(^{36,37}\).

According to the Centers for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM), both men and women of all ages benefit from daily PA. Both organizations recommend that adults participate in aerobic exercise consisting of either 30 minutes of moderate intensity (i.e. brisk walking or cycling at less than 10 miles per hour) or 15-20 minutes of vigorous intensity (i.e. jogging, running, swimming laps, or cycling at greater than 10 miles per hour) per day. Following these recommendations has been shown to reduce the risk of developing cardiovascular disease (CVD) \(^{38}\). Consistent with these daily recommendations, the United States Department of Health and Human Services encourages at least 150 minutes of PA, at a moderate intensity, per week in order to significantly lower the risk of developing CVD and maintain overall health. Moreover, research has shown a dose-response relationship between PA and health benefits; thus increasing PA levels beyond 150 minutes per week may result in additional benefits. Moderate PA for at least 30 minutes/day results in an approximate energy expenditure of 150 kcals/day, or 1000 kcals/week, a level thought to be a minimal threshold for health benefits \(^{39}\). However if weight loss is the primary goal, the weekly PA target should increase to at least 180 minutes at a moderate intensity. It
has been suggested that some individuals may require at least 300 minutes of moderate PA per week to effectively lose weight \textsuperscript{40}.

Despite well-established PA guidelines, most Americans do not meet these recommendations. According to the 2008 National Health Interview Survey, only 14\% of American adults participated in vigorous leisure-time PA three to four times per week and even fewer (11.5\%) participated at least five times per week. Furthermore, this survey also found that 36\% of adults were sedentary during leisure-time and 59\% did no vigorous PA during their leisure-time \textsuperscript{41}. Additionally, the National Health and Nutrition Examination Survey (NHANES) found that only 5\% of the adult population met the recommendation of at least 30 minutes per day of moderate PA \textsuperscript{42}.

Although there are numerous benefits associated with PA, there is also potential risk for cardiac complications such as a heart attack and/or sudden cardiac death. Research has shown these adverse events are associated with a hazard period during or within one hour of completing heavy physical exertion \textsuperscript{43-45}. Mittleman et al., found that 54\% of those who experienced a myocardial infarction (MI) had participated in heavy physical exertion within the previous hour prior \textsuperscript{44}. Research has also shown that habitually sedentary individuals are most at risk of a MI during the hazard period associated with heavy physical exertion \textsuperscript{43,44}. Ultimately the risk of sudden cardiac death in healthy individuals is low, varying from 0.01-0.20 cases per 10,000 hours \textsuperscript{45}. Furthermore when individuals are screened properly and supervised by competent medical staff, this risk is 0.03 cases per 10,000 hours \textsuperscript{45}. In spite of a low risk for cardiac complications among healthy adults, the risk is increased in those with heart disease. Rogosta et al. found that 88\% of the exertion-related deaths had underlying
atherosclerotic disease and only 7% of the deaths were in individuals with no known history or risk factors for atherosclerotic disease. The risk of adverse events during exercise in secondary prevention programs (i.e. cardiac rehabilitation programs) is slightly higher than that of healthy individuals. Even though MIs are the most common cardiovascular complication within these programs, Haskell et al. found only 1 MI per 32,593 patient hours of exercise. Overall, the risk of cardiovascular complication during exercise in a cardiac rehabilitation program is 0.08-0.15 cases per 10,000 hours. Even though there is some risk associated with exercise, habitual exercise has been shown to strongly decrease the risk of sudden cardiac death, especially in those unaccustomed to vigorous exertion.

Methods of Quantifying Physical Activity

The intricate and multidimensional nature of PA makes it difficult to measure and quantify. By definition, PA is any bodily movement produced by movement of skeletal muscles. Physical activity can be prescribed based upon its intensity, frequency, type, and duration of the activity. The intensity of PA is commonly categorized according to the minutes of light (LPA), moderate (MPA), and vigorous (VPA). Energy expenditure (EE) is another way to determine the PA amount by quantifying the amount of energy required by the body to perform a certain activity. Evidence suggests that EE may be a more accurate predictor of health-related outcomes than the type of PA performed. Energy expenditure can also be further classified according to the energy expended solely during PA (PAEE), which is quantified in kilocalories (kcals).
There are a variety of subjective and objective approaches available to evaluate PA levels. Several subjective measures are available to quantify PA patterns over a predetermined period of time. These methods include: PA records, logs, and recalls/interviews. Physical activity records serve as diaries for the individual in an attempt to capture all sources and patterns of PA during a certain time frame. Similarly, PA logs attempt to collect the same information but they are structured more like a checklist of specific activities commonly performed in a given target population. The disadvantages of PA records, logs, and recalls are they are very time-consuming to both the participant and have a significant recall bias. The most commonly used subjective measure to monitor PA levels is the recall questionnaire.49 The primary advantage to subjectively measuring PA is that these methods are relatively inexpensive and easy to administer to a large group. Additionally, these methods are population-specific and do not require nearly as much time as PA records or logs. Recall questionnaires typically have 10-20 items which assess frequency, duration, and types of PA during the past day, week, or month. These questionnaires have several advantages over other techniques, which is why they are so commonly used. However, questionnaires are also subjected to significant recall error and bias.49 These subjective measures have been shown to over-report levels of vigorous activity and under-report light activity levels compared with accelerometry data.53

Given the potential for recall error and bias of these subjective approaches, a more objective measure of PA is often preferred. Examples of these objective measures of PA include doubly labeled water, heart rate monitoring, pedometers, and accelerometers. The most accurate method for determining energy expenditure is doubly labeled water.
However, this method is expensive, only quantifies total EE, and does not provide information on frequency, intensity, or duration of the PA.\textsuperscript{49}

The pedometer is a small, inexpensive, device that is commonly used to objectively measure PA levels. Pedometers provide estimations of total steps, distance covered, and some devices estimate EE.\textsuperscript{57–61} To increase accuracy, most units require the user to enter stride length and body mass into the device. Pedometers can provide instant feedback to the user and thus can also potentially be used as a motivational tool. While widely used, pedometers have several important limitations; including the inability to quantify non-ambulatory activities, the inability to internally store data, the inability to determine amount of time the device is worn each day, and possibly the most significant is their inability to quantify the frequency, intensity, or time of the activity.\textsuperscript{57} Furthermore, the speed of ambulation can negatively affect the accuracy of the pedometer used. Walking speeds < 1.86 miles per hour\textsuperscript{61} and running speeds > 9.94 miles per hour have been shown to elicit significant measurement error\textsuperscript{62}. Adiposity of the waist causes a tilt of the device that affects the pedometer’s accuracy. Increased BMI and waist circumference have also been shown to decrease the accuracy of pedometers by tilting of the device at the waist which affects the pedometer’s mechanism of measurement.\textsuperscript{61}

In order to determine the accuracy and reliability of various pedometers, Schneider et al.\textsuperscript{59} compared ten different models over a 400-meter walk. Although eight models were found to be reasonably accurate, the Kenz-Lifecorder, New Lifestyles-2000, and the Yamax Digiwalker were shown to be the most accurate with values within ± 3% of the actual step counts.\textsuperscript{59} In 2004, Schneider et al.\textsuperscript{60} studied 13 motion sensors, including the Kenz-Lifecorder, and compared the output of each device to the Yamax
SW-200 which served as the criterion pedometer. Based on mean values some models underestimated steps by as much as 25% and others overestimated by as much as 45%. The Kenz-Lifecorder was one of four models which produced accurate step counts compared to the criterion model. Consequently these researchers concluded that the Kenz-Lifecorder was an appropriate PA assessment tool in research settings. In addition to the work done by Schneider et al., other studies have also concluded the Kenz-Lifecorder to be a valid tool for quantifying PA in a variety of populations. Specifically, the Kenz-Lifecorder has been shown to accurately assess energy expenditure and exercise intensity both during exercise periods and non-structured activities. Kumahara et al. found significant correlations between both total energy expenditure (TEE) and PAEE (r = 0.928 and 0.564, respectively) when measured by the Lifecorder and direct calorimetry. In addition, these researchers found a positive relationship between MET levels and exercise intensity levels measured by the Lifecorder (r = 0.963). These investigators determined the Lifecorder produced exercise intensity levels of light, moderate, and vigorous which correspond to < 3.0 METs, 4.0-6.0 METs, and > 7.0 METs, respectively. Furthermore since most PA occurs between 2-8 METs, the Kenz-Lifecorder is accurate in quantifying PA and measuring PAEE in a various populations.

Comparison of Subjective and Objective Measures of Physical Activity

Numerous studies have compared different subjective and objective methodologies for measuring PA levels. The general consensus among these studies is
subjective measures of typically overestimate the time spent in PA, particularly for vigorous PA, compared to objective measures.

Macfarlane et al. 53 examined the convergent validity of six different methods used to assess daily PA. It was determined that heart rate monitors significantly overestimated light activity and underestimated moderate activity compared to the International Physical Activity Questionnaire (IPAQ), PA log, pedometer, uniaxial accelerometer, and a triaxial accelerometer. The investigators propose that these errors could be attributed the cut points of the heart rate monitor for what constitutes light activity 53. Although the HR-VO₂ relationship has been shown to be linear over a wide range of intensities, this is not always the case during low and very high intensity PA 71. Since many daily activities are low to moderate intensity, heart rate monitoring may not produce accurate estimations of daily EE 49.

Ainsworth et al. 51 compared three methods used to assess time spent in PA among 83 adults over a three week period. Each subject participated in a telephone survey to recall non-occupational walking, moderate intensity activity, and hard/very hard intensity activities over the previous week. Additionally, each participant wore a CSA accelerometer and completed a 48-item PA log. This log quantified the amount of time during which the participant did household activities, occupational activities, their mode of transportation, participation in sports, and leisure-time PA. Weak correlations were observed between CSA and PA logs for moderate intensity activity (r = 0.22 and 0.36) and hard/very hard intensity activity (r = 0.31 and 0.36). The relationships between PA intensity levels obtained during telephone surveys and PA logs were more variable. Correlations between 0.26 and 0.54 were observed between these methods for moderate
intensity PA as well as walking. However, no significant correlation was seen between the reporting of hard/very hard intensity activities ($r < 0.09$) suggesting there was no significant difference between PA logs and telephone surveys in regards to the reporting of activities at this intensity level. While this study concluded that telephone surveys, PA logs, and accelerometers all reasonably quantify levels of moderate and hard/very hard PA, there was very little agreement between these three approaches, suggesting they cannot be used interchangeably $^{51}$.

Using a subset of participants from the Cooperative Lifestyle Intervention Program (CLIP) study in 2008, Amico and Brubaker $^{68}$ quantified PA levels in 184 sedentary, overweight and obese older adults with mobility disability and established CVD and/or the metabolic syndrome. Participants’ PA levels were subjectively measured using the Community Health Activities Model Program for Seniors (CHAMPS) PA questionnaire and objectively measured using the Kenz-Lifecorder accelerometer. Both measures were analyzed separately in regards to steps, PAEE, LPA, and MVPA. Results from this study showed there were no significant correlations between CHAMPS and the accelerometer derived steps, PAEE, LPA, and MVPA ($r = 0.002, 0.060, 0.063, \text{ and } -0.028, \text{ respectively}$). The CHAMPS questionnaire tended to overestimate MVPA but underestimate light intensity PA compared to the accelerometer $^{68}$.

In order to better understand the relationship between subjective and objective PA measures in heart failure patients, Brubaker and Shedd $^{72}$ evaluated baseline PA patterns in a subset of participants from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise training (HF-ACTION) trial. Investigators used the International
Physical Activity Questionnaire (IPAQ) and the Kenz-Lifecorder accelerometer to subjectively and objectively quantify PA levels. There was no significant difference between the amount of moderate PA (178 ± 27 vs. 441 ± 175) and total PA (1209 ± 83 vs. 1406 ± 385) observed between the accelerometer and the IPAQ, respectively. However, significant differences were observed in the MET min/wk of light (1018 ± 69 vs. 460 ± 124) and vigorous (12 ± 6 vs. 400 ± 155) activities between the accelerometer and the IPAQ, respectively. These results indicate the IPAQ tended to underestimate light PA and overestimate vigorous PA compared to the accelerometer-derived data.

Quantifying Physical Activity Levels in Different Populations

Healthy Adults

The National Health and Nutrition Examination Survey (NHANES) in 2003-2004 collected accelerometer data on 4,867 individuals ranging from children (6-11 years), adolescents (12-19 years), and adults (20+ years) \(^{42}\). It was found that objectively measured PA declined dramatically with age. Tudor-Locke and Myers also observed a decline in activity with age in their review of 32 studies that examined PA patterns in American children, adults, and older adults \(^{73}\). Children accumulated more steps (12,000-16,000 steps/day) compared to healthy adults (7,000-13,000 steps/day), and older adults (6,000-8,500 steps/day). Additionally, individuals suffering from chronic disease conditions reported even fewer steps/day (3,500-5,500).

In an attempt to provide a more universal agreement on target PA levels, Tudor-Locke and Bassett proposed a classification system to allow for evaluation of PA levels in adults: “sedentary = <5,000 steps/day; “low-active” = 5,000-7,499 steps/day;
“somewhat active” = 7,500–9,999 steps/day; “active” = 10,000–12,499 steps/day; and “highly active” = ≥ 12,500 steps/day. While it has been recommended that adults should achieve 10,000 steps/day, this goal might be too high and inappropriate for older adults as well as individuals with chronic disease conditions.

Elderly

Regardless of age, regular PA of moderate to vigorous intensity, has been shown to be beneficial, yet many older adults are not physically active. In 2009, it was reported that roughly 60% of Americans ≥ 65 years of age did not participate in at least 30 minutes of moderate PA five or more days/week, or at least 20 minutes for three or more days/week. While a multitude of research studies have examined PA levels of older adults, the general conclusion among researchers is that the total duration of exercise tends to decrease with age. One study observed 56 older, community dwelling adults to evaluate their walking, postural transition, and sedentary behavior. Participants wore an accelerometer for seven days allowing investigators to quantify volume, frequency, intensity and the variability of participants’ PA. It was found that participants had an average step count/day of 6,343.2 with a range of 864.8 – 15,847 steps/day. Younger age and lower BMI were shown to be significant predictors of PA levels. Researchers also concluded that walking, sedentary behavior, and postural transition measure different things, yet when used together they help explain the complexity of daily function in older community dwelling adults. Based on the scale by Tudor-Locke and Bassett, these older adults are considered “somewhat-active”.
Bruce et al. 83 studied women between the ages of 70 and 85 years, all of whom were considered both physically and mentally healthy. Investigators found that 39% of these women achieved enough PA from their recreational activities, however 26% did no recreational PA. Of the non-active women, 42.5% attributed their inactivity to a fear of falling. Of the physically active women, only 27% reported a fear of falling. Results from this study suggest that a fear of falling is a major contributor to physical inactivity in older adults 83.

Another study 80 looked the mean PA level (PAL) in older versus younger adults (mean ages: 61 versus 27 years). In order to calculate the mean PAL, the average daily metabolic rate (ADMR) was divided by the basal metabolic rate (BMR). A tri-axial accelerometer was used to measure PA. Activity counts of ≤ 200/min were categorized as light PA (<3 METs). Moderate intensity PA was defined by activity counts of 200-500/min and was associated with MET levels of 3-6, such as walking. Lastly, high intensity PA was defined as at least 500 counts/min and include activities such as domestic activities performed around the house, exercise, and/or sport activities all of which resulted in > 6 METs. Results showed that PAL values were significantly correlated with activity counts produced from the tri-axial accelerometer (r = 0.78) and VO2max (r = 0.59). Results also demonstrated that elderly subjects spent significantly more time performing light intensity activities compared to moderate or high intensity activities. The opposite pattern was observed for younger individuals.
**Overweight/Obese Individuals**

Several studies have examined the PA levels of overweight/obese individuals\(^8^5^–^8^8\). As expected, these populations are almost always less physically active than their normal weight counterparts. One published review of 58 studies over the past 40 years evaluated PA levels in overweight/obese persons and found an inverse relationship between PA level and percent body fat (\(r = -0.5\) to \(-0.16\))\(^8^7\). Additionally, results from this review showed that those classified as overweight showed lower levels of PA compared to those classified as having a normal weight\(^8^7\). Another study\(^8^8\) administered pedometers to participants and evaluated the steps/day of 1,136 adults. On average these adults took 5,117 steps/day, yet the number of steps/day significantly decreased as BMI levels increased (Normal = 5,864, Overweight = 5,200, Obese = 4,330 steps/day, respectively)\(^8^8\).

Tudor-Locke et al.\(^8^6\) evaluated PA and physical inactivity based on BMI from the 2005-2006 National Health and Nutrition Examination Survey (NHANES) accelerometry data. Individuals were separated according to BMI categories in order to determine if each group met the public health recommendation of accumulating 30 minutes (or the equivalent in 10 minute intervals) of PA per day of moderate or vigorous intensity on 5 or more days per week. The BMI categories were grouped into normal (< 25 kg/m\(^2\)), overweight (25-30 kg/m\(^2\)), and obese (≥ 30 kg/m\(^2\)). Results showed that only 3.2% of American adults met the Surgeon General’s recommendation for PA. The data also revealed that fewer adults achieved the recommended PA levels as BMI increased. In addition to decreasing PA levels, increased sedentary levels were also observed. Within a 24-hour period the time spent in sedentary, light, moderate, and vigorous activities
differed significantly for obese males (486.8 min/day, 142.4 min/day, 22.4 min/day, 3.7 min/day, respectively) compared to the overweight males (484.2 min/day, 155.4 min/day, 30.7 min/day, 5.3 min/day, respectively) and normal weight males (466.9 min/day, 160.2 min/day, 34.6 min/day, 6.0 min/day, respectively). Conversely, females only displayed significant differences in PA distribution during a 24-hour period in the moderate and vigorous categories for obese (13 min/day, 2.5 min/day), compared to the overweight (17.5 min/day, 5.3 min/day) and normal (19.9 min/day, 8.7 min/day) women. This study validates that both BMI and gender differences have an impact on PA levels among American adults.

Adams et al. analyzed data from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance (BRFSS) to examine PA levels in adults living in South Carolina. The goal of these investigators was to determine if these individuals met the PA recommendations of the Centers for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM), which are defined as ≥ 30 minutes of moderate intensity PA on ≥ 5 days per week or ≥ 20 minutes of vigorous intensity PA on ≥ 3 days per week. Individuals were categorized according to BMI: lean (< 25 kg/m²), overweight (25-29.9 kg/m²), and obese (≥ 30 kg/m²). Physical activity levels were also dichotomized into inactive (no PA participation), insufficiently active (physically active, but did not meet the CDC-ACSM PA recommendations), and sufficiently active (met the CDC-ACSM PA recommendations). Investigators found that even though 29.5% of lean, 27.8% of overweight, and 19.3% of obese males were sufficiently active, 23.6% of lean, 23.4% of overweight, and 31.9% of obese males were inactive. Furthermore, 46.9% of lean, 48.8% of overweight, and 48.9% of obese males
were insufficiently active. Females showed similar results, with 22.4% of lean, 32.3% of overweight, and 41.7% of obese women being inactive and 48.1% of lean, 44.5% of overweight, and 41.9% of obese women being insufficiently active. However, 29.4% of lean, 23.3% of overweight, and 16.4% of obese women were sufficiently active 85. Results from this study conclude that both obese and overweight males and females participated in significantly less leisure-time PA and had significantly more physical inactivity than their normal weight counterparts. In general, this study showed an inverse relationship between PA levels and BMI in men and women 85.

Cardiac Patients

Multiple studies 89–91 have evaluated the PA levels of cardiac rehabilitation program (CRP) participants. Ayabe et al. 91 used Kenz-Life recorder EX accelerometers to examine PAEE, light PA (LPA), moderate PA (MPA), and vigorous (VPA) on both CRP and non-CRP days. Researchers found that PAEE was significantly less on non-CRP days than on CRP days (177 ± 113 vs. 299 ± 161 kcals/day). Additionally, CRP participants had significantly less LPA, MPA, and VPA on non-CRP days compared to CRP days (49.3 ± 19.3 vs. 59.7 ± 19.8; 10.5 ± 14.6 vs. 26.4 ± 20.4; 0.4 ± 1.7 vs. 1.4 ± 3.0 minutes/day, respectively). Based on these results, it appears that CRP participants were close to accumulating the PA recommendation of 30 minutes of MVPA/day on days they participated in the exercise program. However on non-CRP days, PA levels were far less than recommended. Consequently, it was concluded that patients who only participate in three days of CRP without additional activity on non-CRP days are not achieving enough activity to maintain cardiovascular health (> 1,500 kcals/week) 91.
Jones et al.\textsuperscript{90} evaluated 25 males, ranging in age from 39 to 69 years of age, with a history CAD who were participating in a phase III CRP. Using an Actigraph accelerometer, PA levels were measured in steps and EE over the course of 7 days. Researchers then made comparisons between CRP and non-CRP days as well as additional PA outside of the CRP. Consistent with the findings of Ayabe et al.\textsuperscript{91}, PA levels were significantly higher on CRP days compared to non-CRP days (10,087 ± 631 vs. 5,287 ± 520 steps/day). Results also showed those who participated in home exercise in addition to CR were significantly more active than individuals who only participated in CR (7,993 ± 604 vs. 5,277 ± 623 steps/day). Researchers concluded that even though attending CRP sessions helps patients accumulate adequate PA on CRP days, only 8\% of patients reached the recommended minimum level of weekly PA. However, patients who did some form of home-exercise on non-CRP days in addition to CRP sessions were able to increase their total volume of PA closer to recommended levels\textsuperscript{90}.

Another study\textsuperscript{89} examined the PA levels of 31 phase IV CRP patients that participated in an “Active for Life” class. This study found no significant changes in PA levels from phase III to phase IV CRP, regardless of attendance in the “Active for Life” classes after phase III. Based on patients PA diaries, it was estimated that leisure-time PA energy expenditure averaged 1,376 kcals/week (range: 128 – 3,380 kcals/week). This amount is less than what is associated with increased fitness (1,400 kcals/week), inhibiting disease CAD progression (1,600 kcals/week), or CAD regression (≥ 2,200 kcals/week)\textsuperscript{89}. Since these were self-reported PA levels, these values are likely to be overestimated. Thus, several studies provide objective evidence that most CRP participants do not get enough PA to reduce progression of CAD or lose weight.
Heart Failure

Despite the multitude of benefits, exercise and PA had been contraindicated in HF patients until recently. This contributes to the lack of PA often observed in HF patients as exercise/PA may still not be recommended by their health care provider. Additionally, HF patients may not participate in exercise as they are often limited by symptoms of exercise intolerance and/or there is no reimbursement for HF patients to exercise within a CRP. A handful of studies have attempted to quantify, both subjectively and objectively, the level of PA in HF patients.

Garet et al. administered a PA questionnaire to 105 patients with HF to evaluate the validity, reliability, and sensitivity of the PA questionnaire in this population. This PA questionnaire not only quantified PA levels, but also quantified daily energy expenditure (DEE). Physical activity levels were categorized into 3 different groups: \( PA_{low} \) (< 3 METs), \( PA_{high} \) (3-5 METs), \( PA_{intensive} \) (> 5 METs). Daily energy expenditure was shown to decline with both age and NYHA functional class. The test-retest correlation coefficient for activities between 3-5 METs was 0.82. Investigators determined that this questionnaire produced a reproducible estimate of DEE and suggest that HF patients spend the majority of their time in \( PA_{low} \) (< 3 METs). It is hypothesized that these HF patients spent less time in \( PA_{high} \) or \( PA_{intensive} \) (> 3 METs) in order to avoid worsening of their symptoms.

Walsh and colleagues investigated predictors of long-term prognosis in 84 HF patients (based on performance on a treadmill exercise test and daily levels). To measure exercise capacity, researchers used both the modified Bruce treadmill protocol and a self-
paced corridor walk. Daily PA was measured using a Digiwalker pedometer. This study concluded that the duration of exercise tests results were not significant predictors of long-term prognosis. However, the pedometer scores (> 25,000 steps per week) were shown to be significant predictors of prognosis in both univariate and multivariate analysis. Therefore, a reduced daily amount of PA in HF patients appears to be an important prognostic measure.

Oka et al. examined the relationship between exercise capacity, measured from a treadmill exercise test, and objectively measured PA levels of 45 HF patients. Vitalog activity monitors were used to quantify PA levels over a two day period. In addition, participants also recorded the amount of time spent in each activity, the rating of perceived exertion (RPE) of each activity, and any symptoms they experienced. Daily PA resulted in shortness of breath (SOB) (22%), fatigue (16%), and muscle/joint soreness (13%) in these HF patients. However, 46% of these participants reported they did not experience any HF symptoms during daily PA. Investigators suggest that daily PA levels of HF patients are reduced in order to avoid further exacerbating symptoms. Furthermore the amount of daily PA performed by these HF patients was fairly low. Only 6.6% of subjects reported exercising regularly at a moderate intensity. Thus, it appears that HF patients often restrict levels of PA in order to avoid unpleasant symptoms.

**Exercise Training Interventions**

*Heart Failure with a Reduced Ejection Fraction (HFrEF)*

Many HF patients suffer from exercise intolerance, and thus do not participate in exercise related activities due to exacerbation of HF symptoms or a fear of being active.
Over the past 20 years, there have been multiple studies evaluating the effect of an exercise training (ET) intervention on exercise capacity, health-related quality of life (HRQOL), as well as morbidity and mortality in HFrEF patients\textsuperscript{96–104}. The results of these studies have consistently demonstrated a significant increase in peak exercise workload, exercise time to exhaustion, and 6-minute walk test (6MWT) distance\textsuperscript{96,97,99–102,104}. The majority of these studies also demonstrated a significantly increased (≥ 10%) VO\textsubscript{2}peak from baseline\textsuperscript{96,99–102,104}. Conversely, two studies showed an increase in VO\textsubscript{2}peak of greater than 10% \textsuperscript{96,100,105}. The multi-center randomized control trial, Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) of 2,300 patients showed a non-significant 4% increase in VO\textsubscript{2}peak from baseline to 12 months. However, investigators concluded that regular ET is safe for these patients and reduces all-cause mortality and hospitalization\textsuperscript{98}. With the exception of an early study by Sullivan et al.\textsuperscript{97}, no other exercise intervention trials of HFrEF patients reported any significant adverse events\textsuperscript{96–104}.

In 1999, Belardinelli et al.\textsuperscript{103} randomly assigned 99 clinically stable HFrEF patients (Age: 59 ± 14 years, EF% in Training: 28.4 ± 6%, EF% in Control: 27.9 ± 5%) to either an ET group or a control group. The ET group underwent 12 months of exercise, 3 times per week at 60% of their measured VO\textsubscript{2}peak. During the 12-months, participants performed the exercise as follows: warm-up (stretching) 15-20 minutes and 40 minutes on a cycle ergometer. Investigators performed exercise testing at baseline, 2 months and 14 months\textsuperscript{103}. Resting heart rate significantly decreased in the training group (88 ± 12, 80 ± 10, 78 ± 10 bpm, respectively, P < 0.005 between groups) compared to the control group (93 ± 10, 91 ± 11, 89 ± 9 bpm, respectively). A significant increase
in VO$_2$peak was observed in the ET group (15.7 ± 2, 18.6 ± 1, 19.9 ± 1 ml·kg·min$^{-1}$, respectively) compared to the control group (15.2 ± 2, 15.6 ± 2, 16 ± 2 ml·kg·min$^{-1}$, respectively) $^{103}$. The training group also showed a reduced mortality rate compared to the control group (9 vs. 20, respectively; Relative Risk (RR): 0.37 (0.17-0.84)) and a significant reduction in hospital re-admissions (ET: 5 vs. Control: 14; RR: 0.29 (0.11-0.88)). The findings of this randomized controlled trial show that ET can be beneficial for clinically stable HFrEF population as VO$_2$peak, mortality, and hospital re-admissions all improved $^{103}$.

Hambrecht et al. $^{101}$ utilized a prospective randomized trial to evaluate the benefits of ET for 73 men with HFrEF. At baseline, thirty-six participants were randomized to the ET group, and 37 participants were randomized into the control group. The first part of the ET regimen took place inside the hospital for the 2 weeks. During this time, the subjects worked out 4-6 times per day for 10 minute increments on a cycle ergometer. Patients exercised at 70% of their VO$_2$peak that was attained during the CPET at baseline. After the first 2 weeks, the ET participants underwent another CPET to revise the exercise intensity for a home-based program (70% VO$_2$peak) that involved exercise on a cycle ergometer for 20 minutes per day for a 6 month period. The ET subjects also had to attend one group exercise session per week that included a one hour session of walking, ball games, or calisthenics. At the 6 month follow-up, those randomized to the ET group showed a significant improvement in VO$_2$peak compared to the control group (18.2 ± 3.9 vs. 23.0 ± 4.7 ml·kg·min$^{-1}$, 17.8 ± 4.5 vs. 18.1 ± 4.1 ml·kg·min$^{-1}$, respectively). It was also found that there was a significant increase in cardiac output at peak exercise in the ET group, while there was a significant decrease in cardiac
output in the control group (14.4 ± 6.2 vs. 17.1 ± 6.1 L/min, 14.2 ± 4.9 vs. 13.9 ± 5.1 L/min, respectively). These researchers found that there were significant changes in both exercise capacity as well as hemodynamic changes in regards to those with HFrEF\textsuperscript{101}.

A meta-analysis on 35 randomized control trials was performed by van Tol and colleagues in order to evaluate the effect of ET in those with HFrEF using summary effect sizes (SESs)\textsuperscript{96}. A total of 1,486 subjects with HFrEF were evaluated. There were 701 subjects who participated in ET while 651 subjects were in the control group (Age: 60.6 ± 7.5 years, BMI: 26.9 ± 1.3, EF: 27.7 ± 4.2%). The average aerobic training period for the ET groups was 13.0 ± 7.8 weeks with an average duration of 50.0 ± 22.0 minutes per session. The frequency of the exercise sessions per week were 3.7 ± 1.7 times per week. The intensities at which the subjects worked varied between 50-80\% VO\textsubscript{2}peak, 60-80\% maximum heart rate, or 60-80\% heart rate reserve. Some studies used resistance training or interval training, while others used a combination of aerobic training with resistance training. Cardiac output at peak exercise, VO\textsubscript{2}peak, anaerobic threshold, and 6 minute walk distance significantly increased from baseline (+2.51 L/min, 21.3\% increase from baseline, SES: 0.58 (0.19-0.97), \(P = 0.004\); +2.06 mL/kg/min, 13\% increase from baseline, SES: 0.60 (0.42-0.79) \(P = 0.000\); +1.91 mL/kg/min, 17.4\% increase from baseline, SES: 0.84 (0.48-1.20), \(P = 0.000\); +46.2 m, 11.6\% increase from baseline, SES: 0.52 (0.36-0.69), \(P = 0.000\), respectively). The meta-analysis shows that there are significant benefits of ET in those with stable HFrEF\textsuperscript{96}.

Brubaker et al.\textsuperscript{102} evaluated the effects of aerobic ET on 59 older HFrEF patients (Age: \(\geq 60\) years). Patients were randomized to 16 weeks (48 sessions) of either a control group or an aerobic ET group. Each ET session lasted for one hour at a lower intensity
(40-50% of their heart rate reserve (HRR)) during the first two weeks then at a slightly higher intensity (60-70% HRR) for the remaining 14 weeks. Although the ET subjects attended an average of 45 ET sessions and significantly increased their combined walking and cycling distance (4.11 ± 1.09 vs. 4.81 ±0.99 miles per session), there was no significant overall change in VO₂peak, peak ventilation, or VE/VCO₂ slope. However, 23 of the ET subjects demonstrated an increase in VO₂peak, six (26%) increased by ≥ 10%, which represents a clinically significant change, and nine (39%) increased their VO₂peak by 0-9.9%. The major finding of this study alone is that not all HFrEF patients respond favorably to ET. More research is needed in HFrEF patients to determine the differences between “responders” vs. “non-responders”.

Heart Failure with a Preserved Ejection Fraction (HFpEF)

Despite the fact that HFpEF has similar incidence and prevalence rates, only five studies to date have evaluated the effects of ET on HF patients with a preserved ejection fraction (HFpEF). Gary et al. was the first to examine exercise training in the HFpEF population. The primary purpose of this study was to evaluate the effects of exercise training on exercise self-efficacy. Thirty-two older women with HFpEF were included in the study (NYHA III, Age Range: 50-85). After undergoing baseline testing, patients were randomized to either a home-based walking intervention or an education control group for 12 weeks. Those in the home-based walking group walked 3 days/week outside their homes. Patients initially exercised at 40% heart rate reserve monitored by a heart rate monitor and gradually increased to 60% heart rate reserve, while maintaining a duration of 20-30 minutes. Patients in the home-based exercise
significantly improved their 6 minute walk distance compared to the control group (Δ203 vs. Δ93 feet, respectively). Participants in the exercise group significantly increased their exercise self-efficacy which was correlated with increased 6 minute walk distance. This study indicates that low to moderate walking can increase exercise self-efficacy in older HFpEF women thus giving them the confidence to exercise 107.

Smart et al. 106 was the first to compare the ET response between those with HFrEF (N = 24, Age: 62 ± 8 years, EF: < 35%) and HFpEF (N = 9, Age: 65 ± 5 years, EF: > 45%). After baseline testing, both groups of clinically stable HF patients participated in 16 weeks of ET on a cycle ergometer at 60-70% VO2peak for 3 one hour sessions per week. Both HFpEF and HFrEF groups were similar at baseline in regards to VO2peak (12.5 ± 4.1 vs. 11.9 ± 2.5 ml·kg·min⁻¹, respectively), ventilatory threshold (7.7 ± 2.5 vs. 7.9 ± 1.9, respectively), and VE/VCO2 slope (32.8 ± 8.3 vs. 33.8 ± 5.7, respectively). Both the HFpEF and HFrEF groups demonstrated significant changes from pre- to post-ET for VO2peak (HFpEF: 12.5 ± 4.1 vs. 16.2 ± 5.6 ml·kg·min⁻¹; HFrEF: 11.9 ± 2.5 vs. 14.8 ± 4.1 ml·kg·min⁻¹) and ventilatory threshold (HFpEF: 7.7 ± 2.5 vs. 9.5 ± 2.6; HFrEF: 7.8 ± 1.9 vs. 10.3 ± 2.3). The percent change in VO2peak for HFpEF and HFrEF (30% and 24%, respectively) are larger than typically reported 105.

Kitzman et al. 110 utilized a randomized, controlled, single-blind trial to evaluate the response to ET in those with HFpEF. Fifty-three clinically stable HFpEF patients (Age: 70 ± 6 years (60-82), EF: ≥ 50%), were randomized to either a control group or ET intervention. After ET, the ET subjects had a greater exercise time, peak workload, and VO2peak (ET: 13.8 ± 2.5 vs. 16.1 ± 2.6 ml·kg·min⁻¹, Control: 12.8 ± 2.6 vs. 12.5 ± 3.4
ml·kg·min\(^{-1}\), \(P = 0.0001\)\). This study was the first randomized, controlled, single-blind study to evaluate the effects of exercise training in HFpEF patients\(^{110}\).

Edelmann et al.\(^{108}\) conducted the first multicenter, prospective RCT on exercise training in HFpEF patients. Sixty-four patients with HFpEF (Age: 65 ± 7 years, 56% female) were randomized to either endurance/resistance training in addition to usual care or to usual care alone for 12 weeks. Patients in the ET group cycled at an HR that corresponded to 50-70% of their VO\(_2\)peak. After 4 weeks, resistance training was incorporated twice per week. Fifteen repetitions were performed at an intensity of 60-65% of their 1-RM. At follow-up, VO\(_2\)peak increased in the ET group (16.1 ± 4.9 to 18.7 ± 5.4 ml·kg·min\(^{-1}\)) and remained unchanged in the usual care group (16.7 ± 4.7 to 16.0 ± 6.0 ml·kg·min\(^{-1}\)). This study shows that a short-term supervised exercise program consisting of both endurance and resistance training is safe, feasible, and effective for patients with HFpEF.

Alves et al.\(^{109}\) studied the effects of exercise training on exercise tolerance in heart failure patients with mild and moderate-severe HFpEF, as well as HFpEF. Ninety-eight patients with moderate-severe (N = 34), mild (N = 33), and preserved (N = 31) were randomized to exercise training plus usual care or usual care alone. The exercise training group underwent 5-7 intervals of 3-5 minutes in duration at 70-75% of HR\(_{\text{max}}\) with 1 minute of active recovery at 45-55% of HR\(_{\text{max}}\). All 3 training groups significantly improved their exercise tolerance compared to the usual care group (moderate-severe: 62% vs. 22%; mild: 48% vs. 11%; preserved: 45% vs. 0%). The results of this study indicate that interval exercise training can improve exercise tolerance of heart failure patients independent of the degree of baseline LV dysfunction.
**Body Composition and Weight Loss in Heart Failure**

Large population-based studies, such as the Health, Aging and Body Composition (HABC) and the Cardiovascular Health Study (CHS), indicate that 89% of HFrEF patients are overweight (BMI>25) and 61% are obese (BMI>30). Additionally, patients with HFrEF have many significant abnormalities in body composition including, increased total and regional fat mass, decreased type I/type II muscle fibers, increased intramuscular fat, decreased capillary density, and increased levels of circulating inflammatory markers, including IL-6 and C-reactive protein. These abnormalities contribute to the exercise intolerance commonly seen in HFrEF patients. Consequently, more studies are needed to evaluate the impact of body composition on the pathophysiology of exercise intolerance in HFrEF patients.

Adipose tissue near and/or within the skeletal muscle significantly affects skeletal muscle function. Adipose tissue located in this area increases inflammatory cytokines, and can worsen exercise intolerance. Adipose tissue can be deposited between skeletal muscle bundles during aging and is more pronounced in patients with physical disability. Kouba et al. found that HFrEF patients to have an increase in intermuscular fat (IMF), that is inversely related to VO\(_2\)peak. Moreover, IMF can be modifiable through exercise training and weight loss thus making it a potential target for improving exercise intolerance in overweight HFrEF patients.

Obesity and fat mass are directly associated with many abnormalities that can potentially lead to the development of HFrEF including, abnormal left ventricular diastolic function, left ventricular hypertrophy, atherosclerosis, increased markers of inflammation, increased blood lipids, increased blood pressure
and decreased glycemic control. Obese individuals who lose weight not only improve survival but also improve physical function. Exercise training and caloric restriction have complementary effects on body composition and physical function. Alone, exercise training maintains and improves skeletal muscle function but often results in minimal weight loss. On the other hand, caloric restriction generally results in significant weight loss but in addition to a loss of fat mass there can also be a significant loss of muscle mass. Thus, it appears that combining caloric restriction is the optimal method to decrease fat mass yet maintain muscle mass and improve physical function. Furthermore, the combination of the two interventions also increases thigh muscle mitochondrial size and content. To date, there has not been a trial utilizing caloric restriction in the HFpEF population, alone or in combination with exercise.

Although the prevalence of older HFpEF patients with obesity is increasing, physicians are often hesitant to recommend weight loss in this population. Much of this concern is due to the reports of observational studies that indicate a significant relationship between body fat and survival in HF patients. A recent review of this obesity “paradox” suggests there may be a “U-shaped” curve of BMI vs. mortality in elderly heart failure patients. Thus the highest mortality is seen in patients with the lowest and highest BMI. Moreover, physicians are often concerned that HFrEF patients who have involuntary weight loss associated with loss of skeletal muscle, depletion of energy stores, and cytokine activation are in a terminal phase of the disease process.

However, HFpEF patients generally differ significantly from HFrEF patients with regard to body composition. These HFpEF patients are more likely to be overweight
and/or obese than HFrEF patients and are more predominantly female. Very obese hospitalized heart failure patients are more likely to have HFpEF. In contrast to HFrEF patients, involuntary weight and/or muscle weight loss and catabolism are rarely seen in HFpEF patients. Furthermore, Kitzman et al. has demonstrated that muscle mass may actually be well preserved in HFpEF patients, but that the muscle tissue is dysfunctional, possibly due to adipose infiltration. Despite the uncertainty about the relationship between body weight and survival in HF, the relationship between obesity and weight gain are strongly associated with increased morbidity and reduced physical function in most clinical populations.  

SECRET Study  

To date, no study has look at the effects of weight loss in HF patients. This led to the design of the Study of the Effects of Caloric Restriction and Exercise Training (SECRET), which was funded by the National Institute of Health (NIH), in which participants for this particular study were utilized. The SECRET study was designed to determine if exercise intolerance and quality of life (QOL) could be improved through exercise training and caloric restriction in elderly patients with heart failure with a preserved ejection fraction (HFpEF). Once eligible, the SECRET participants were randomized into one of four groups: diet only (Diet), exercise only (Ex), exercise and diet combined (E+D), or an attention control group (AC). This thesis has two aims: (1) to evaluate the change in objectively measured physical activity levels from baseline to follow-up in the intervention groups; and (2) to explore the relationship between change
in physical activity levels and the primary outcomes of this study (VO_{2peak} and body weight).

**Aims and Hypotheses**

Heart failure with a preserved ejection fraction is a significant public health concern, yet little is known about the PA levels this population and the effects of weight loss. Thus, this SECRET sub-study has two primary aims. The first aim of this study is to objectively measure PA levels and evaluate the changes in PA variables (steps/day, PAEE, LPA, and MVPA) between the intervention groups. We hypothesize the patients participating in the exercise intervention groups (exercise only and exercise plus diet) will demonstrate significant increases in objectively measured PA levels compared to non-exercise intervention groups (diet only and attention control). If an increase in PA levels are observed, a second aim will be to explore the relationships between the change in PA levels and change in the primary outcomes of the SECRET trial: VO_{2peak} and body weight. We hypothesize that there will be a significant correlation between increases in PA levels and increases in VO_{2peak}, but no significant correlation will be seen in the relationship between PA levels and weight loss.
METHODS

Overall SECRET Design

The recruitment goal for SECRET was to obtain 100 participants within the area of Wake Forest University Baptist Medical Center. Participant inclusion required a heart failure diagnosis based upon a clinical score > 3 and a normal ejection fraction (> 50%), determined by echocardiography. In addition to the above criteria, the participant must have been at least 60 years of age, had a body mass index of > 30 kg/m², been managed for heart failure using the appropriate medical therapy, and be able to perform exercise at a moderate intensity. See Appendix D for detailed inclusion and exclusion criteria for SECRET.

The testing procedures for the entire SECRET study took place over four different testing visits. During the first visit, each participant signed an informed consent and completed medical history forms. This visit also included a medical screening, anthropometric measurements (height and weight), a basic 2-D echocardiogram, and a dietary evaluation. Additional assessments during the next three visits included: resting metabolic rate, phlebotomy for biomarkers, lipoproteins, and brain natriuretic peptide (BNP), cardiac magnetic resonance imaging (MRI), dual energy x-ray absorptiometry (DEXA), echocardiography including doppler, maximal isokinetic knee extensor strength (KinCom), leg muscle power, a skeletal muscle biopsy, and administration of the Minnesota Living with Heart Failure Questionnaire (MLHF). Furthermore, the 6 minute walk test (6MWT) and cardiopulmonary exercise test (CPET) with breath-by-breath expired gas measurements were measured in order to evaluate functional capacity.
In elderly patients with HF, the CPET provides reproducible measures of VO\textsubscript{2}peak as well as ventilatory anaerobic threshold (VAT)\textsuperscript{150}. The CPET was conducted on a motorized treadmill, using the modified Naughton protocol to determine VO\textsubscript{2} peak, VE/VCO\textsubscript{2} Slope, and ventilatory anaerobic threshold (VAT) measures. Expired gas analysis was conducted using a commercially available system (CPX-2000; MedGraphics; Minneapolis, MN). The system was calibrated according to specification before testing so that expired gases could be analyzed. The SECRET participants were encouraged to give a maximal effort during the CPET. Maximal effort during CPET was determined by an RER > 1.05, RPE > 15, and > 90% age predicted maximal HR. The participant’s blood pressure, heart rate, and ECG were continuously monitored by a Master’s level exercise physiologist and a board-certified cardiologist. Peak VO\textsubscript{2} was determined by calculating the average VO\textsubscript{2} over the last 15 seconds of the test. Ventilatory anaerobic threshold was determined with the V-slope method by an experienced exercise physiologist who was blinded to the participant’s group assignment\textsuperscript{149}.

The NYHA functional classification scale was used to determine the extent of symptom exacerbation during physical exertion or rest (See Appendix A). New York Heart Association functional classification was determined by the attending cardiologist.
Intervention Groups

Attention Control (AC): The attention control group received a counseling session regarding general health education at baseline. Throughout the 20 week study timeframe, the subjects in this group were contacted every 2 weeks by SECRET staff members via telephone to discuss the participant’s general health status without specific reference to exercise, diet, or weight loss.

Exercise Only (Ex): The exercise group participated in a center-based exercise program 3 times per week at the Geriatrics Research Center under medical supervision. Upon the participant’s arrival, body weight; pre-exercise heart rate (HR) and blood pressure was obtained. Participants then participated in an aerobic warm-up (lap walking), aerobic exercise (lap walking or treadmill), and a cool-down. Throughout the exercise session, the staff periodically monitored the participant’s HR and O₂ saturations using a pulse oximeter to ensure the participant’s safety during exercise. Rating of perceived exertion (RPE) was also monitored to gauge the intensity of exercise (35). The exercise information (HR and RPE) was recorded on a monthly log form.

Each participant in the Ex group received his or her own exercise prescription based on the CPET performed at baseline before randomization. The standard exercise prescription for each participant started at a low intensity (40-50% of VO₂ reserve) and corresponding HR range. As the participant became more tolerant to exercise, the exercise specialist increased the intensity of the aerobic exercise at a gradual rate. Exercise intensity was increased until the participant could maintain 60% of his/her VO₂ reserve for at least 20 minutes. It should also be noted that the exercise prescription
and/or modality was altered for those with physical limitations or injuries during the study. The NuStep (a seated, reclined elliptical) was utilized if participants were unable to walk sufficiently.

*Diet Only (Diet)*: The Diet group of SECRET included a dietary consultation at baseline with a registered dietician (RD) at the Geriatric Research Center at Wake Forest University Baptist Medical Center. Each participant received a breakfast menu from which they choose a breakfast to prepare for themselves every morning. Two hypocaloric meals were provided for lunch, supper, and snacks for the rest of the day. The participant chose between 24 dietary items on a menu and were prepared by the GCRC metabolic kitchen. This 24 item menu was designed to promote a balanced diet with <30% of calories from fat and 1.2 grams of protein/kg of ideal body weight/day. The hypocaloric meals were picked up three times per week by the participant at the GCRC metabolic kitchen. A dietary log was kept by each participant to monitor their intake of foods and beverages. The diet was adjusted, as needed, to achieve a 2,500 kcals/week deficit in order to produce an approximate 1 pound per week weight loss. No patient received a diet <1,000 kcals per day. For safety measures, total weight loss for each subject was capped at 15% initial body weight at baseline or at a BMI of <27 for that individual. Participants in the exercise interventions (both with and without weight loss) participated in a weekly weigh-in. If the participants experienced an excessive weight loss, then their caloric needs and diet plan were recalculated so that the participant would achieve the appropriate weight. Weekly individual counseling sessions with a RD were utilized to enhance compliance to the diet.
Exercise and Diet (E+D): If the participant was randomized to the E+D group, then the participant received both the exercise and diet interventions described above.

During the final week of the 20-week intervention, participants in all four groups wore the accelerometer to measure follow-up PA levels. The accelerometry data was processed following the procedures described for baseline measures. Participants then underwent follow-up testing at the end of the 20-week intervention. This testing included the same measures that were obtained at baseline and were completed over the same number of visits. A 12-month follow-up was also conducted with a SECRET staff member over the phone to determine the participant’s current clinical status, weight, and physical function. In addition, the SECRET personnel performing outcomes assessments were blinded from group randomization when feasible \(^{149}\).

Sub-Study Design

All SECRET participants were given a programmed Kenz Lifecorder Ex accelerometer, prior to randomization, on their second clinical visit and were instructed to wear it for at least 7 days. Each accelerometer was programmed with the participant’s age, weight, height, gender, and time of day before being given to the participant to wear. Instructions on how to wear the accelerometer were verbally given to the participant. The device was sealed so the participant was unable to obtain any feedback about their activity level. The subject was told to consistently wear the device on either the left or right hip with the safety cord attached to clothing. They were instructed to begin wearing the device as soon as they woke up, and to continue to wear the accelerometer during all
waking hours except for when showering, swimming, or sleeping. Ideally the device should be worn between 7-10 days to obtain stable baseline measures of the participant’s physical activity levels. A slight variability in the number of days the device was worn occurred because the accelerometer could be returned in person during one of the other visits or through the mail in a protective envelope. Once the device was returned, the device was connected to a PC and the information collected by the device was downloaded.

The Kenz Lifecorder is a device that is 6 x 4.6 x 2.6cm and lightweight (40 grams) and analyzes vertical accelerations ranging from 0.06 to 1.94 G, where 1 G is equal to the acceleration of earth’s gravity, at a frequency of 32 Hz. The movement intensity is determined by the frequency and magnitude of the accelerations and recorded every 4 seconds. The movement intensity is measured on a scale of 1 to 9, with 1 being the lowest intensity of movement and 9 being the highest movement intensity. These intensity levels have been previously shown to correlate highly with metabolic equivalents (METs) and divided into categories of 1 to 3, 4 to 6, and 7 to 9 METs, for light, moderate, and vigorous levels of PA, respectively. It should be noted that light physical activity may be underestimated with this device as the intensity level of 1 correlates to approximately 2 METs. Given the population explored in this thesis, light PA (LPA) was defined as 1-2 METs and moderate-vigorous PA (MVPA) was defined as 3-9 METs. Also, it is important to note that these cut-points are not relative to each individual patient.

Physical activity analysis software (PAAS) allows for data to be downloaded from the accelerometer to the PC. Data is then viewed on a Microsoft Excel CSV
spreadsheet as well as in a customized report. The spreadsheet contains the following information: dates of wear, the participant’s height, weight, gender, and age, total daily energy expenditure (DEE) expended in kilocalories. Physical activity energy expenditure (PAEE) expressed in kilocalories (kcal), daily step count, and minutes spent in light, moderate, and vigorous activity levels are quantified for each day. The customized report reflected the same information, but also includes graphs describing the frequency of device usage and number of minutes at each movement intensity level.

From the customized report, each subject’s physical activity data was evaluated to determine if he or she would be included or excluded further data analysis. The total time for each day was determined and had to meet or exceed 10 hours for inclusion. When the participant fulfilled the first criteria of wear time (≥ 10 hrs.) for a particular day, the percent of wear time for each day was also calculated. If the participant did not wear the device for at least 80 percent of the total wear time, then that day was excluded from further analysis. To be included in this SECRET sub-study, the participant had to have at least three days that met the accelerometry inclusion criteria. These inclusion and exclusion criteria for the physical activity measures were based on previous research 154,155. Thus, for each participant in this sub-study we were able to obtain the following measures: steps/day, minutes of light (LPA) and moderate/vigorous physical activity (MVPA), and physical activity energy expenditure (PAEE).

Statistical Analyses

All of the data were entered into SPSS Statistics 19.0 for Windows and analyzed for normality. Descriptive statistics, including mean, standard deviations, and ranges,
were run on all data sets. A Two-Way Repeated Measures ANCOVA was used to examine the changes in PA measures, physical fitness, and body composition from baseline to 20 weeks. During this analysis, adjustments were made for both age and baseline values. Pearson Product Moment Correlations were performed to examine the relationships between the primary outcomes (VO₂peak and body weight) and PA measures. Paired sample t-tests were also conducted to compare PA measures between Exercise and Non-Exercise days. A P-value of < 0.05 was considered statistically significant for all analyses.
RESULTS

The primary aim of this thesis was to objectively quantify the changes in physical activity (PA) levels in those with heart failure and a preserved ejection fraction (HFpEF) during a 20 week intervention. The PA levels were evaluated using a Kenz-Lifecorder Ex accelerometer at baseline and follow-up of a single-blinded, randomized controlled trial. The PA measures obtained from the accelerometer were steps/day, minutes of light (LPA) and moderate-vigorous (MVPA) PA, as well as PA energy expenditure (PAEE). The second objective of this thesis was to explore the relationships between the change in PA measures and the primary outcomes of the study, VO\textsubscript{2peak} and body weight. Eighty participants from the SECRET study at Wake Forest University Baptist Medical Center were recruited for this study. Eighty HFpEF patients were included in the SECRET study, of which 54 had sufficient accelerometer data at baseline, of which 43 subjects met the inclusion criteria for this particular sub-study and were included in this analysis. See the diagram in Figure 1 for a detailed explanation of participant exclusions after baseline.

Participant Demographics

Descriptive statistics of the SECRET participants included in this investigation are listed in Table I. This sample included a greater number of females (N = 32) compared to males (N = 11). There were a higher percentage of whites (N = 27, 62.8%) compared to blacks (N = 15, 34.9%) and Hispanics (N = 1, 2.3%). This sample was comprised only of NYHA Class II and III patients (N = 29 and N = 13, respectively). Ninety-eight percent of these patients had a history of hypertension and 44.2% were diagnosed with type 2 diabetes. Among the patients in the study, 37% were on beta
blockers, 49% were on ACE inhibitors, and 67% were on diuretics. Additionally, there were no differences in medications between the groups and the medications did not change during the course of the study. The participants included in this study were well managed for their HF and hypertension. The only significant difference between the intervention groups was age (the Ex group was significantly older than the E+D group).

Figure 1: Flow diagram for patient exclusions
Table I: Descriptive Characteristics of Study Participants

<table>
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<tr>
<th>Variables</th>
<th>ALL (N = 43)</th>
<th>Exercise (N = 9)</th>
<th>Diet (N = 13)</th>
<th>Exercise Plus Diet (N = 12)</th>
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<td>Min – Max</td>
<td>Min – Max</td>
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<td>68.4 ± 5.6</td>
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<td>60 – 78</td>
<td>60 – 79</td>
<td>61 – 78</td>
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<td>BMI (kg/m²)</td>
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<td>30.1 – 55.6</td>
<td>30.8 – 55.6</td>
<td>30.1 – 42.1</td>
<td>32.7 – 48.3</td>
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<td>Ejection Fraction (%)</td>
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<td>61.7 ± 7.2</td>
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<td>Body Fat (%)</td>
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<td>6MW (m)</td>
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<td>435.4 ± 60.3</td>
<td>416.7 ± 59.9</td>
<td>412.6 ± 83.0</td>
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</table>

*Significant Difference between Exercise and Diet Plus Exercise (P < 0.05)

BMI = Body Mass Index; 6MW = Six Minute Walk

Treatment Effect on the Primary Outcomes, VO₂peak and Body Weight

Patients were randomized into one of four interventions: Exercise Only (Ex), Diet Only (Diet), Exercise Plus Diet (E+D), and Attention Control (AC). Both body weight and VO₂peak were normally distributed. Analysis of covariance indicated there was a significant group main effect for body weight (p < 0.001). Post hoc analysis determined that at follow-up, participants in the Diet and E+D groups had a significantly lower adjusted mean body weight (94.0 ± 1.27 and 93.5 ± 1.30 kg, respectively) than the AC
group (102.9 ± 1.47 kg) (Figure 2). The adjusted body weight at follow-up for the Ex group (99.0 ± 1.60 kg) was not significantly different from any of the other groups. Additionally, there was no statistical difference in adjusted body weight at follow-up between the Diet and E+D groups. The absolute mean (and %) change in body weight from baseline to follow-up for the AC, Diet, Ex, and E+D was 0 (0%), -8.4 (-9%), -4.3 (-4%), and -10.3 (-9%) kg, respectively.

Figure 2: Unadjusted Mean Body Weight at Baseline and Follow-Up for the Groups

* Indicates a statistically significant difference at follow-up based on adjusted means (from ANCOVA) compared to Attention Control group (P < 0.01)

Average unadjusted values for VO2peak for the four groups at baseline and follow-up are presented in Figure 3. Analysis of covariance indicated there was a significant group main effect for VO2peak (p < 0.001). Post hoc analysis indicated that at follow-up, participants in the Diet and E+D groups had a significantly higher adjusted VO2peak (16.2 ± 0.36 and 16.8 ± 0.37 ml·kg·min⁻¹, respectively) than the AC group (13.9 ± 0.41 ml·kg·min⁻¹) (Figure 2). However after adjusting for body weight by examining VO2peak in ml·min⁻¹, there was no significant difference between the Diet and AC
groups. Furthermore, no significant differences in adjusted VO$_2$peak values were observed between the Ex ($15.5 \pm 0.45$ ml·kg·min$^{-1}$) group and the other three groups (Diet, E+D, and AC) at follow-up. The absolute unadjusted mean (and %) change in VO$_2$peak from baseline to follow-up for the AC, Diet, Ex, and E+D was -0.8 (-5%), 1.3 (9%), 0.9 (7%), and 2.3 (13%) ml·kg·min$^{-1}$, respectively.

Figure 3: Unadjusted Mean VO$_2$peak at Baseline and Follow-Up for the Groups

* Indicates a statistically significant difference at follow-up based on adjusted means (from ANCOVA) compared to Attention Control group ($P < 0.01$)

**Treatment Effect on Physical Activity Measures**

Analysis of covariance, controlling for age and baseline values, was used to analyze differences in PA measures (steps/day, minutes of LPA and MVPA, and PAEE) between the groups. A significant group interaction was found for steps per day ($P <$
Post hoc analysis indicated that participants in the E+D group obtained significantly more adjusted steps per day (6590.55 ± 445.01 steps/day) at follow-up than the Diet (4086.56 ± 450.54 steps/day) and AC (4331.70 ± 502.15 steps/day) groups (Figure 4). The adjusted mean for the Ex group (4754.70 ± 554.37 steps/day) was not significantly different than the other groups. The absolute mean (and %) change in steps/day from baseline to follow-up for the AC, Diet, Ex, and E+D was 532 (16%), 543 (13%), 1349 (46%), and 2649 (67%) steps/day, respectively.

Figure 5 displays the changes in unadjusted mean LPA values for the four groups. Analysis of covariance determined there was no significant group main effect (p = 0.644) for minutes of LPA. However there was a significant group interaction for minutes of MVPA (p < 0.001). Post hoc analysis determined that participants in E+D group had significantly more adjusted minutes of MVPA at follow-up (29.42 ± 2.50 min) when compared to the other three groups (Ex: 15.50 ± 3.12 min; Diet: 12.19 ± 2.53 min; AC: 11.91 ± 2.82 min) (Figure 6). No other significant differences were observed at follow-up between the intervention groups. The absolute mean (and %) change in minutes of MVPA from baseline to follow-up for the AC, Diet, Ex, and E+D was 2.1 (25%), 2.6 (23%), 5.9 (90%), and 20.2 (202%) minutes of MVPA, respectively.
Figure 4: Unadjusted Mean Steps per Day at Baseline and Follow-Up for the Groups

* Indicates a statistically significant difference at follow-up based on adjusted means (from ANCOVA) compared to Attention Control group (P < 0.01)
‡ Indicates a statistically significant difference at follow-up based on adjusted means (from ANCOVA) compared to Diet group (P < 0.01)

No significant differences were observed for minutes of LPA per day between groups.
Figures 6: Unadjusted Mean Minutes of MVPA and Baseline to Follow-Up for the Groups

* Indicates a statistically significant difference at follow-up based on adjusted means (from ANCOVA) compared to Attention Control group (P < 0.01)
† Indicates a statistically significant difference at follow-up based on adjusted means (from ANCOVA) compared to Diet Only group (P < 0.01)
‡ Indicates a statistically significant difference at follow-up based on adjusted means (from ANCOVA) compared to Exercise Only group (P < 0.01)

Analysis of covariance demonstrated a significant group interaction (P < 0.01) for PAEE and therefore post hoc analysis was conducted. The E+D group had significantly higher adjusted mean PAEE at follow-up (261.94 ± 20.96 kcals) compared to the Diet (152.05 ± 21.22 kcals) and AC (161.42 ± 23.65 kcals) groups (Figure 7). The adjusted PAEE for the Ex group (183.00 ± 26.12 kcals) was not statistically different from any of the other groups at follow-up. The absolute mean (and %) change in PAEE from baseline
to follow-up for the AC, Diet, Ex, and E+D was 19.2 (14%), 8.5 (6%), 55.5 (48%), and 109.6 (68%) kcals, respectively.

Figure 7: Unadjusted Mean Physical Activity Energy Expenditure (PAEE) at Baseline and Follow-Up for the Groups

* Indicates a statistically significant difference at follow-up based on adjusted means (from ANCOVA) compared to Attention Control group (P < 0.05)
‡ Indicates a statistically significant difference at follow-up based on adjusted means (from ANCOVA) compared to Diet Only group (P < 0.05)

Comparison of Exercise and Non-Exercise Days

In order to further investigate the changes observed in the PA variables, additional analyses were conducted to compare days that patients attended a cardiac rehab program exercise session (exercise day) compared to days they did not attend an exercise session
(non-exercise day) during the final week of the intervention. Since not all of the groups received exercise treatment, this analysis was only conducted on those in the Ex and E+D groups.

Paired sample t-tests indicated there was a significant difference in steps per day between non-exercise days and exercise days at follow-up in both the Ex (3433.57 ± 540.63 to 6808.86 ± 1094.35, respectively) and E+D (4627.44 ± 557.61 to 9037.89 ± 1168.36, respectively) groups (Figure 8). Only the E+D had significantly greater minutes of LPA on exercise days than non-exercise days (48.66 ± 5.32 vs. 40.71 ± 5.02, respectively) as well as minutes of MVPA (52.96 ± 7.12 vs. 15.85 ± 2.15, respectively) (Figures 9 and 10). Furthermore, the Ex and E+D groups had significantly higher PAEE on exercise days than non-exercise days (262.00 ± 52.85 vs. 119.71 ± 20.47 and 378.84 ± 56.88 vs. 172.64 ± 26.75, respectively) (Figure 11). However, no significant differences were observed between the Ex and E+D groups for steps/day, minutes of LPA or MVPA, or PAEE on either exercise or non-exercise days.
Figure 8: Unadjusted Mean Steps/day at 20 Weeks During Non-Exercise Days vs. Exercise Days

No significant differences were observed between groups for non-exercise and exercise days.

Figure 9: Unadjusted Mean LPA at 20 Weeks During Non-Exercise Days vs. Exercise Days

No significant differences were observed between groups for non-exercise and exercise days.
Figure 10: Unadjusted Mean MVPA at 20 Weeks During Non-Exercise Days vs. Exercise Days

No significant differences were observed between groups for non-exercise and exercise days.

Figure 11: Unadjusted Mean Physical Activity Energy Expenditure (PAEE) at 20 Weeks During Non-Exercise Days vs. Exercise Days

No significant differences were observed between groups for non-exercise and exercise days.
Physical Activity Measures Versus Primary Outcomes: Body Weight and VO$_2$peak

The relationship between the change in accelerometer-derived PA measures (steps/day, PAEE, minutes of LPA and MVPA) from baseline to follow-up and change in primary outcomes (VO$_2$peak and body weight) were determined using the Pearson Product Moment Correlations. The calculated r-values are shown in Table II. The increase in minutes spent in MVPA from baseline to follow-up was significantly correlated, albeit weakly, with both primary outcome measures, VO$_2$peak and body weight. No other PA variables were significantly correlated with the primary outcome measures. There was a significant correlation between change in body weight and VO$_2$peak ($r = 0.684$).

Table II: Correlations Between Changes in PA Levels and Primary Outcomes

<table>
<thead>
<tr>
<th>Variables</th>
<th>Steps/day</th>
<th>PAEE</th>
<th>LPA</th>
<th>MVPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO$_2$ peak</td>
<td>.053</td>
<td>.039</td>
<td>-.260</td>
<td>.329*</td>
</tr>
<tr>
<td>Body Weight</td>
<td>.212</td>
<td>.236</td>
<td>-.133</td>
<td>.387*</td>
</tr>
</tbody>
</table>

*Significant correlation with a P-value < 0.05
DISCUSSION

Numerous studies have evaluated, either subjectively and/or objectively with accelerometers, the physical activity (PA) levels of healthy subjects, those with cardiovascular disease, as well as patients with heart failure and a reduced ejection fraction (HFrEF), as well as patients with heart failure and a preserved ejection fraction (HFpEF). However, no studies to date have evaluated the PA levels of subjects with heart failure and a preserved ejection fraction (HFpEF).

Additionally, no studies to date have studied the effects of a randomized controlled trial of an exercise intervention, with and without weight loss, in either type of heart failure patient. Therefore, the primary aim of this thesis was to objectively measure PA levels in those with HFpEF and evaluate the changes in PA variables between patients in the four intervention groups: exercise only (Ex), diet only (Diet), exercise plus diet (E+D), and attention control (AC). The secondary objective of this thesis was to explore the relationship between the changes in PA levels and changes the primary outcomes of the study, VO2peak and body weight.

Participant Demographics

As shown in Figure 1, 80 HFpEF patients were recruited for the SECRET study at the Wake Forest University Baptist Medical Center. However due to either lack of adequate data and/or lack of accelerometer wear, at either baseline or follow-up, 37 patients were excluded from this sub-study. Most of these exclusions were because subjects did not meet the criteria for sufficient wear-time of ≥ 10 hours of data for ≥ 3 days. Ultimately, 43 HFpEF patients were included in this study. Patients had an EF% of approximately 61%, which is consistent with the definition used to diagnose HFpEF in
which patients present with symptoms but have a normal EF% (≥ 50%). The participants in this sample were elderly (mean: 68 ± 5.7 years), mostly female (74%), and predominantly white (62.8%). Additionally, participants in this study were overweight/obese with a mean weight of 103 ± 17.5 kg, a BMI of 38.8 ± 5.7 kg/m², and a % body fat of 44.5 ± 6.4%. There was a significant difference in age (6 years) between the Ex and E+D groups, but no other significant demographic differences were observed between the groups.

This SECRET trial consisted of a greater proportion of females than males, which is to be expected in the HFpEF population and widely reported in the literature. The exact reason for the increased prevalence of HFpEF in women is unclear, but it has been speculated that the “protective” role of estrogen is absent in elderly women after menopause. Additionally, women have been shown to demonstrate a greater amount of LV hypertrophy and less LV dilation in response to the pressure overload associated with high blood pressure than men.

To date, four randomized controlled trials of exercise training in the HFpEF population have been reported. Overall, the participants in the present study were similar to the participants of the previous studies in regards to age, gender, EF%, and NYHA class. The main differences between the four previous RCTs and this study is the higher body weight and body fat of the participants of the present investigation. However, SECRET was designed with the goal of weight loss through diet and/or exercise and therefore the inclusion criteria included obese HFpEF patients with a BMI > 30 kg/m² compared to the lower BMI criteria (>25) for the previous RCTs.
Changes in Primary Outcomes: Body Weight and VO$_2$peak

Both the Diet and E+D groups had significantly lower body weight at follow-up (94.0 ± 1.27 and 93.5 ± 1.30 kg, respectively) compared to the AC group (102.9 ± 1.47 kg). As discussed earlier, no studies to date have examined the effects of exercise, with or without a dietary component, in either HFpEF or HFrEF patients. However, the changes in body weight observed in the present study are consistent with other weight loss programs reported in the literature. Ross et al.\textsuperscript{135} reported a 10% weight reduction in 16 weeks in obese individuals undergoing diet, both with and without an exercise training program. Ades et al.\textsuperscript{163} examined body composition changes in overweight cardiac rehabilitation participants undergoing a 16 week high-caloric expenditure exercise training program and dietary changes. Despite a combination of high-caloric expenditure exercise and dietary changes, there was a slightly smaller reduction in body weight (-8.2 kg) in the study by Ades et al. than in the E+D group in the present study (-10.3 kg). This could be attributed to the higher body weight (104 vs. 95 kg) of the participants in this particular study compared to the cardiac rehabilitation participants of Ades et al., respectively. Individuals with a higher body mass expend a greater number of calories at the same level of exercise as individuals with a lower body mass.

Although the Ex group did lose weight from baseline to follow-up (-4.3 kg, 4%), the body weight at follow-up was not found to be statistically different than the other three groups. This was not totally unexpected, since several studies\textsuperscript{164–166} have shown that 3 day/week of exercise training within a traditional cardiac rehabilitation (CR) programs does not produce significant weight loss. One study found a weight reduction of 5% after 12 weeks of CR\textsuperscript{165}, while another\textsuperscript{166} observed a weight loss of -4.5
kg after 12 weeks. It is generally well accepted that ≥180 minutes/week of exercise are necessary for significant weight loss without significant dietary changes. The Ex group in the present investigation participated in an exercise program consisting of 30-40 minutes of aerobic exercise 3 times/week. Consequently, patients in the Ex only group only accumulated ~90-120 minutes per week of moderate intensity PA, an amount apparently insufficient for weight loss.

Patients in the Diet and E+D groups had a significantly higher VO₂peak at follow-up (16.2 ± 0.36 and 16.8 ± 0.37 ml·kg·min⁻¹, respectively) compared to the AC group (13.9 ± 0.41 ml·kg·min⁻¹). The Ex group was not found to be statistically different at follow-up than the other groups (15.5 ± 0.45 ml·kg·min⁻¹). The Diet and E+D groups increased their VO₂peak by 9 and 13%, respectively; whereas the Ex group only increased their VO₂peak by 7%. Multiple studies have examined the effects of exercise training in the HFrEF population and generally report improvements of 18-25% in VO₂peak. However, Brubaker et al. reported a similar non-significant increase in VO₂peak in older HFrEF patients participating in a 16 week exercise only intervention results after exercise training in HFrEF patients. Further analysis of this data indicated that after 16 weeks of aerobic training, 26% of patients had a clinically significant increase of ≥10% and another 39% had an improvement of 0-9.9%.

Comparable results were found in the Ex group of the present study in which 22% had a clinically significant increase in VO₂peak (≥ 10%) and the remaining 78% increased their VO₂peak by 0-9.9%. It appears that exercise training alone produces variable responses in the change in VO₂peak, despite similar training programs in older HFrEF and HpEF
patients. Further studies are warranted to determine why some older HF patients respond more favorably to exercise training than others.

Five studies to date have examined the effects of exercise training in the HFrEF population\textsuperscript{106–110}; however, only two studies\textsuperscript{108,110} were similar to the present investigation in regards to design (RCT) as well as the frequency, duration and intensity of the exercise program. Both Kitzman et al.\textsuperscript{110} and Edelmann et al.\textsuperscript{108} reported similar increases in VO$_2$peak of 16%, despite differences in training duration (16 and 12 weeks, respectively). The main difference between the present investigation and the previous reports mostly relate to the patient populations. Although the patients studied by Kitzman et al.\textsuperscript{110} were similar in age (70 vs. 68 years, respectively) to the patients in the present investigation, they had significantly lower body weight (79 vs. 104 kg, respectively). The HFrEF patients studied by Edelmann et al.\textsuperscript{108} were slightly younger than those in the present study (65 vs. 68 years, respectively) and also had a lower BMI (31 vs. 38 kg/m$^2$, respectively). The combination of older age and higher body weight of the participants may explain the lower VO$_2$peak changes observed in the present study.

In contrast to the Ex group, patients in the Diet and E+D significantly improved their VO$_2$peak after 20 weeks. The significant increase in VO$_2$peak in the Diet group was unexpected since these patients were not assigned to an exercise group. However, the Diet group lost a significant amount of body weight, whereas the Ex group did not lose any weight. Since VO$_2$peak is expressed in ml·kg·min$^{-1}$, losing weight, even without exercise, will increase an individual’s VO$_2$peak. In fact, after adjusting for body weight by expressing VO$_2$peak in ml·min$^{-1}$, there was no significant difference between the Diet and AC groups at follow-up. Furthermore, in this investigation there was a significant
correlation (r = 0.68) between change in body weight and change in VO₂peak. This indicates that the weight loss observed in this trial explains 46% of the variance in the change in VO₂peak. Other factors such as medication, disease severity, and genetics may contribute to the remainder of change in functional capacity. Furthermore the possibility that the Diet group may have begun exercising on their own cannot be ignored as patients will often “drop-in” to interventions they did not receive.

The E+D group demonstrated the greatest increase (13%) in VO₂peak as well decrease in body weight (9%). This further demonstrates the important relationship between changes in body weight and VO₂peak in this population. Annesi ¹⁶⁸ found controlled eating self-efficacy has a mediating role between exercise and weight loss, which explains why the Diet and E+D groups lost a significant amount of weight but the Ex group did not. Annesi also observed a significant relationship between controlled eating self-efficacy and exercise self-efficacy. It is possible that as individuals experienced weight loss, they felt better physically and gained confidence about exercise, allowing more PA both during and outside the exercise program. Moreover, as weight loss was the goal of this group, it is likely that patients in the E+D group were more motivated to increase their PA levels in order to reach their weight loss goals.

Changes in Physical Activity Measures

A uniaxial accelerometer was used in this investigation to objectively measure physical activity (PA) and quantify steps/day, minutes of light (LPA), moderate-vigorous (MVPA), and PA energy expenditure (PAEE). At baseline, this sample of HFpEF patients averaged 3,679 steps/day with a range of 1,354-6,514 steps/day. Based on the
classification system of Tudor-Locke and Bassett, these HFpEF patients used in this investigation would be classified as “sedentary” (< 5,000 steps/day). Although this is the first study to examine PA levels in the HFpEF population, Shedd objectively quantified PA levels of HFrEF patients participating in the HF-ACTION trial. The HFrEF patients averaged more steps/day (4,858 ± 1,895 steps/day) than the HFpEF participants in the present study. The 32% higher step counts found by Shedd could be related to the younger (58 vs. 68 years), lower BMI levels (30 vs. 38 kg/m²), and a higher functional capacity (VO₂peak = 15.8 vs. 14.7 ml·kg·min⁻¹) of the HF ACTION patients compared to participants in the present study.

Ayabe et al. examined the relationship between step counts and PAEE in cardiac patients involved in a CR program. The investigators found patients should accumulate at least 6,500 steps/day in order to achieve the 1,500 kcal of PAEE, the generally recommended for the secondary prevention of CVD. After the 20 weeks of the present intervention, all four groups increased their steps/day, but the E+D group was significantly greater than the other groups at the 20 week follow-up. At follow-up, the E+D group averaged 6,629 steps/day which changed their initial activity classification from “sedentary” to “low-active” and close to the target level established by Ayabe et al. All other groups remained in the “sedentary” category. It is interesting to note that the AC and Diet groups increased their steps from baseline to follow-up by (~500 steps/day, ~15%). These findings suggest that patients participating in a lifestyle intervention study, regardless of group assignment, do often “drop-in” and increase their PA levels. The Ex group also increased their steps/day, to a greater extent (+ 1349 steps/day, 46%) than the AC and Diet groups; however, at follow-up the steps/day
achieved by the Ex group was not significantly different than the other groups. Thus, it appears that participating in the exercise intervention 3 times per week did have a greater impact (2-3 fold) on steps/day than the non-exercise Diet and AC groups.

The number of minutes/day of light (LPA) and moderate-vigorous (MVPA) PA were also quantified in order to assess the levels of PA in these HFpEF patients. At baseline, the patients in this particular study accumulated approximately 32 minutes/day of LPA. There are no specific recommendations for the recommended amount of LPA, but it is generally believed that “more is better”. There were no significant differences between the groups in minutes of LPA at follow-up. This would be expected as patients undergoing exercise training (Ex and E+D) would likely exercise at an intensity that would be expected to be within the moderate-vigorous range.

At baseline, the patients in this study accumulated approximately 9.5 minutes/day of MVPA. Although there are no specific recommendations for the amount of LPA, the CDC recommends that individuals accumulate at least 30 minutes/day of MVPA most days of the week to improve health. All four groups increased minutes of MVPA from baseline to follow-up, but the E+D group was significantly higher than the other groups at 20 weeks. Patients in the E+D group increased their MVPA by over 200% to 30.1 minutes/day, more than double observed in the Ex group (12.4 minutes/day) at follow-up. Consequently, patients in the E+D group meet the CDC recommendation of ≥ 30 minutes/day of MVPA whereas the Ex group did not. Minutes of MVPA has been shown to have the greatest relationship to a variety of health outcomes 38.

Physical activity energy expenditure (PAEE) was also used in this investigation to quantify PA levels in HFpEF patients. The amount of PAEE generally recommended by
the CDC-ACSM and Surgeon General is ≥ 150 kcals/day or 1,000 kcals/week. However, weight loss and coronary artery disease regression are more likely to occur at ≥ 2,000 kcals/week (≥300 kcals/day)\textsuperscript{170}. At baseline, the HFpEF patients in this investigation averaged 142 kcals/day. While this appears to be close to the recommended levels, there was a wide range of PAEE observed among the participants in this investigation (38 – 226 kcals/day). The high levels of body weight of these HFpEF patients would make it easier to expend more calories and thus may explain the relatively high baseline levels of PAEE. Despite increases in PAEE from baseline to follow-up in all four groups, only the E+D group was significantly higher than the other groups at follow-up. At follow-up, patients in the E+D group expended an average of 1,834 kcals/week which approaches the recommended PAEE level associated with CAD regression and/or weight loss (> 2,000 kcals/week)\textsuperscript{91}. When this caloric expenditure of 1,834 kcals/week is extrapolated over the course of the 20 week intervention it would be expected that patients would lose ~10.5 kg. In fact, on average, the E+D group lost on average,10.3 kg. In contrast, the Ex group did not significantly increase their PAEE from baseline to follow-up.

Using similar methods, Childress\textsuperscript{171} objectively quantified the PA levels of overweight older adults randomized to a physical activity (PA) group, physical activity and weight loss (PA + WL) group, or control. Physical activity levels were measured using a Kenz-Lifecorder accelerometer, the same device used in this present investigation. In contrast to the present investigation of HFpEF, Childress observed significant increases in PAEE levels in both the PA and PA + WL at 6 months, but there were no differences between the two PA groups. While the HFpEF patients used in the present investigation were older and heavier, the primary difference was the exercise
intervention. Whereas the present investigation involved center-based exercise training only, the intervention employed by Childress was a community-based intervention that focused on increasing lifestyle PA at a community center and at home. This approach appears to result in greater amounts of PAEE compared to a “traditional” exercise program.

Comparison of Exercise and Non-Exercise Days

The E+D group increased their steps/day by approximately twice as much as the Ex group, which was somewhat surprising since both groups were prescribed the same exercise intervention of 3 times per week for 40-60 minutes. One potential explanation for these differences could be that participants in the E+D group might have been more physically active on non-exercise days than the Ex group. Figure 8 indicates that the E+D group did accumulate more steps (1,193) on non-exercise days than the Ex group (4,627 vs. 3,434 steps/day, respectively). Moreover, the E+D group took 2,230 more steps than the Ex group on exercise program days. This suggests that the E+D patients did more PA during the exercise sessions or additional PA outside of the structured program. In either case, this additional PA in the E+D patients likely contributed to the greater weight loss and improvement in VO$_2$peak observed in the E+D group.

The E+D group also demonstrated non-significantly higher levels of LPA, MVPA, and PAEE on non-exercise and exercise days compared to the Ex group. This is unexpected as both groups participated in the same exercise intervention. Figure 10 shows minimal difference in MVPA between the Ex and E+D groups on non-exercise days (9.1 vs. 15.9 minutes, respectively). Although not statistically different, the E+D
group had 23.3 more minutes of MVPA on exercise days than the Ex group. Furthermore, the E+D group expended nearly 100 more kcal than the Ex group on the three exercise days. Higher levels of MVPA and PAEE in the E+D group, compared to the Ex group, may be explained by the impact of weight loss on physical activity. The decreased body weight in the E+D group may have increased exercise tolerance allowing them to exercise for a longer duration during exercise sessions. These benefits could have potentially extended to non-exercise days as well, thus resulting in more minutes of LPA on non-exercise days in the E+D group than the Ex group (40.7 vs. 29.9 minutes, respectively). It was also interesting to observe that the Ex group appeared to decrease their PAEE on non-exercise days compared to the AC group. This compensation of decreased PA levels the day after a structured bout of exercise has been observed in previous studies in the elderly population\textsuperscript{172,173}. Patients either are fatigued from the previous bout of PA or believe that the structured bouts of activity (2-3 times/week) are sufficient.

Relationship Between Physical Activity Measures and Primary Outcomes

The change in minutes of MVPA per day was the only PA measure found to be correlated with both primary outcomes (\( \text{VO}_2\text{peak} \) and body weight). Since the major difference in treatments between the Diet and E+D groups is the moderate intensity PA obtained in the center-based exercise program, this finding does not come as a surprise. Childress et al.\textsuperscript{171} reported a similar correlation between minutes of MVPA and change in body weight in overweight older adults during a weight loss intervention. In contrast to the present study, Childress et al.\textsuperscript{171} also found significant correlations between
changes in body weight and changes in steps/day ($r = .42$) and PAEE ($r = .37$). The higher BMI and disease severity of the HFpEF patients in the present study may have prevented them from reaching the same PA levels as the older overweight adults studied by Childress et al. The lower range of PA and primary outcome measures observed in the present study may have reduced the correlations between these measures.

Limitations

There were several limitations to the present study. This study did have a high exclusion rate. It could be argued that the participants who were excluded were less compliant and more physically inactive which could have biased the results. Secondly, while dietary data has been collected for this study, it has not yet been analyzed and thus could not be included in this thesis. Consequently, the impact of diet changes on the primary outcomes and PA measures could not be determined. Another limitation is that PA levels were assessed at both baseline and follow-up by wearing an accelerometer for ~10 days. It is possible that participants in any of the groups could have temporarily modified their PA levels and thus altered the accelerometry results. Finally, as the case with any RCT, the impact of “drop-outs” and “drop-ins” cannot be controlled and may have affected the results of the study.

Conclusions

This is the first study to evaluate a randomized controlled trial of an exercise and diet intervention in HFpEF patients. Results of this 20 week study suggest that exercise and diet is the most effective short-term combination for weight loss and for increasing
VO₂peak in this population. Another unique finding of this study was that diet alone compared to exercise alone was superior for producing improvements in VO₂peak and weight loss. This is also the first study to evaluate PA levels before and during an RCT of diet and exercise in HFpEF patients. Results of this trial suggest that the E+D group demonstrated the largest increase in PA measures and that changes in PA levels only modestly correlate with changes in VO₂peak, suggesting other factors, particularly diet changes, also play an important role in the weight loss in HFpEF patients.
New York Heart Association Functional Classification

Class I: Patient that has heart disease and symptoms are exacerbated at physical activity levels that would inhibit normal individuals

Class II: Symptoms are exacerbated at levels of ordinary exertion

Class III: Symptoms are exacerbated at exertion levels that are less than ordinary

Class IV: Symptoms are exacerbated at rest
APPENDIX B

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

Stage A: Patients who have no structural disease or disorder of the heart, but are at high risk of developing heart failure

Stage B: Patients who have structural disease or disorder of the heart, but have not yet developed symptoms of heart failure

Stage C: Patient who has underlying heart disease, which is associated with past or present heart failure symptoms

Stage D: Patient in end-stage heart failure which requires a specialized treatment regimen such as mechanical circulatory support, cardiac transplantation, continuous inotropic infusions, or hospice care
APPENDIX C
SECRET Study Hypotheses

Primary Hypothesis: The Exercise plus Diet group will have a greater increase in VO$_2$peak and lose more body weight than the other intervention groups.

Secondary Hypothesis: Patients participating in the exercise interventions (Exercise Only and Exercise plus Diet) will demonstrate significant increases in objectively measured physical activity levels compared to the non-exercise groups (Diet Only and Attention Control).

Tertiary Hypothesis: A significant correlation will be observed between increased physical activity levels and increased VO$_2$peak but there will not be a significant relationship observed between changes in physical activity levels and weight loss.
APPENDIX D

SECRET Inclusion and Exclusion Criteria

Inclusion Criteria:

HF Clinical Score (>3)

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea/difficulty breathing</td>
<td></td>
</tr>
<tr>
<td>Trouble with breathing (SOB)</td>
<td>1</td>
</tr>
<tr>
<td>Hurrying on the level or up slight hill</td>
<td>1</td>
</tr>
<tr>
<td>At ordinary pace on the level?</td>
<td>2</td>
</tr>
<tr>
<td>Do you stop for breath when walking at own pace?</td>
<td>2</td>
</tr>
<tr>
<td>Do you stop for breath after 100 yds on the level?</td>
<td>2</td>
</tr>
</tbody>
</table>

Physical Examination

<table>
<thead>
<tr>
<th>Heart Rate (bpm)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>91 to 110</td>
<td>1</td>
</tr>
<tr>
<td>111+</td>
<td>2</td>
</tr>
</tbody>
</table>

Rales/Crackles

| Either lower lung field                                 | 1     |
| Either lower and either upper lung field                | 2     |

Jugulovenous Distention

| Alone                                                   | 1     |
| Plus Edema                                              | 2     |
| Plus Hepatomegaly                                       | 2     |
Chest X-Ray Film

Cephalization of pulmonary vessels 1
Interstitial edema 2
Alveolar Fluid plus Pleural Fluid 3
Interstitial Edema plus Pleural Fluid 3

Normal EF (>50%)

>60 years of age
BMI >30 kg/m²

Exclusion Criteria:

Medical

Valvular heart disease as the primary etiology of CHF
Significant change in cardiac medication <4 weeks
Uncontrolled hypertension as defined according to current JNC guidelines
Uncontrolled diabetes
Evidence of significant COPD; assessment may be made by pulmonary function test
Recent or debilitating stroke
Cancer or other non-cardiovascular conditions with life expectancy less than 2 years
Anemia (<11 grams Hgb) determined by CBC
Significant renal insufficiency (creatinine >2.5mg/dl) determined by CMP

Pregnancy—women of child bearing potential are excluded from
participation

Psychiatric disease- uncontrolled major psychoses, depressions, dementia, or personality disorder

Other

Plans to leave area within 1 year

Refuses informed consent

Screening Echocardiogram

Left ventricular ejection fraction < 50%

Significant valvular heart disease

Familiarization/Screening Exercise Test

Evidence of significant ischemia

ECG: 1mm flat ST depression (confirm with echocardiogram wall motion)

Echo: Wall motion abnormality or decrease in global contractility

Stopped exercising due to chest or leg pain or any reason other than exhaustion/fatigue/dyspnea

Exercise SBP > 240 mmHg, DBP > 110 mmHg

Unstable hemodynamics or rhythm

Unwilling or unable to complete adequate exercise test

Magnetic resonance imaging

Indwelling metal-containing prosthesis (orthopedic, valvular, other)

Pacemaker or defibrillator

History of welding occupation (ocular metal debris)

Uncontrollable claustrophobia

77
Any other contra-indication to MRI

Thigh muscle biopsy

History of bleeding disorder

Current anticoagulation

Contraindication to stopping aspirin for 1 week

Allergy to topical anesthetic
REFERENCES


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171. Childress KS. Assessments of physical activity before and after an exercise intervention in overweight/obese older adults with CVD or the metabolic syndrome. 2009.


SCHOLASTIC VITA

DANIEL CLEVENGER

PERSONAL INFORMATION

Birthplace: Muncie, Indiana
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UNDERGRADUATE STUDY

2005-2010 Ball State University
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PROFESSIONAL EXPERIENCE

2010-2011 Laboratory Coordinator
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2005  Adult Physical Fitness Program Intern
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PRESENTATIONS

2012  Effects of a Randomized Controlled Trial of Diet and/or
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2010  Pitching Biomechanics and Injuries of the Elbow in Youth
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