QUANTIFYING PHYSICAL ACTIVITY LEVELS IN OLDER, OBESE PATIENTS WITH HEART FAILURE

BY

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DEDICATION

I would like to dedicate this research to my family: to my mother who did the job of two parents and taught me to never give up, and to my sister whose support kept me going through the most challenging times. I love you both and could not have accomplished this feat without you. I would also like to dedicate this to my father, who will have passed 20 years ago this year, whose presence has been felt throughout this entire journey, and whom I know I have made proud.

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TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

1-RM	One-repetition maximum
ACSM	American College of Sports Medicine
ADL	Activity of daily living
AHA	American Heart Association
AT	Aerobic exercise training
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CO	Cardiac output
CPET	Cardiopulmonary exercise test
CR	Caloric restriction/calorically restricted diet
CRF	Cardiorespiratory fitness
CV	Cardiovascular
CVD	Cardiovascular disease
DEXA	Dual x-ray absorptiometry
DLW	Doubly labeled water
DM	Diabetes mellitus
EE	Energy expenditure
EF	Ejection fraction
EKG	Electrocardiogram
ET	Exercise training
HF	Heart failure
HFmEF	Heart failure with a mid-range ejection fraction
HFpEF	Heart failure with a preserved ejection fraction
HFrEF	Heart failure with a reduced ejection fraction
(HR ___)	Hazard ratio
HR	Heart rate
HRR	Heart rate reserve
HTN	Hypertension
Kcals	Kilocalories
LV	Left ventricle/left ventricular
MET	Metabolic equivalent
Mins	Minutes
MRI	Magnetic resonance imaging
MVPA	Moderate-to-vigorous physical activity
NHANES	National Health and Nutrition Examination Survey
PA	Physical activity
PAEE	Physical activity energy expenditure
PAR	Population attributable risk
QOL	Quality of life
RAAS	Renin-angiotensin-aldosterone system
RER	Respiratory exchange ratio
RMR	Resting metabolic rate

RPE	Rating of perceived exertion
RT	Resistance exercise training
SECRET II	Study Examining Caloric Restriction and Exercise Training
SES	Center-based, structured exercise session
SNS	Sympathetic nervous system
SVR	Systemic vascular resistance
VM	Vector magnitude
VO_2peak	Peak volume of oxygen consumption
WHI	Women's Health Initiative

ABSTRACT

Interventions utilizing caloric restriction and exercise training have been shown to improve exercise capacity and weight loss in patients with heart failure with a preserved ejection fraction (HFpEF). These interventions are particularly important in this population as the majority are overweight or obese and proven pharmacotherapy is lacking. While accelerometers allow for objective measurement of physical activity (PA), few studies have examined their use in older, obese patients with HFpEF. Furthermore, cut-points establishing light-intensity and moderate-to-vigorous intensity (MVPA) have not been validated in older, clinical populations, including patients with HFpEF. For this study, wrist-worn, tri-axial accelerometers were used to record free-living PA data in subjects (n=9) during one week of the *SECRET II* exercise training intervention. Cut-points based on accelerometry and indirect calorimetry were calculated using linear regression. Steps/day (9,424$\pm$860) as well as minutes/day of light (365$\pm$39) and MVPA (36$\pm$6) were measured and found to be higher than reported in prior studies of patients with HF. In fact, the older, obese patients with HFpEF in this study appeared to meet national guideline PA recommendations for healthy adults (7,000-8,000 steps/day, 150 minutes/week MVPA). In contrast to previous reports, no significant differences were found when comparing PA levels on days the subjects performed a center-based, structured exercise session (SES) versus "non-SES" days, including weekdays and weekends. Lack of significant differences may have been due to the small sample size, as effect sizes suggest there may be differences in PA levels across the week. Physical activity energy expenditure (PAEE) predicted by the wrist-worn device was found to significantly underestimate PAEE measured using indirect calorimetry (-0.020[-0.025-

-0.014] kcals/kg/min), but this finding may be due to the lack of wrist-based algorithms for predicting PAEE. To our knowledge, this was the first study to quantify PA levels of older, obese patients with HFpEF undergoing an exercise training intervention and to identify wrist-based cut-points for determining PAEE in this population. A larger study is needed to confirm these findings.

REVIEW OF LITERATURE

Overview

Heart Failure (HF) is a clinical syndrome caused by structural and functional changes of the heart that impede the ventricles' ability to fill with or eject blood (1, 2). Heart failure is commonly divided into two distinct phenotypes based on left ventricular (LV) ejection fraction (EF). An inability for the LV to properly fill with blood is caused by diastolic dysfunction and is associated with HF with a preserved ejection fraction (HFpEF); individuals with HFpEF typically have an EF $\geq$50%. An inability for the LV to properly eject blood is caused by systolic dysfunction and is associated with HF with a reduced ejection fraction (HFrEF); individuals with HFrEF typically have an EF $\leq$40%. More recently, HF with a mid-range EF (HFmEF) has been characterized as an EF between 41-49% (3, 4). About 50% of patients presenting with HF signs and symptoms have HFpEF (3, 5). The heart failure syndrome generally results in dyspnea, fatigue, edema, and exercise intolerance (2, 4). These chronic changes are the result of a complex interplay of comorbidities such as coronary artery disease (CAD), hypertension (HTN), obesity, and diabetes mellitus (DM) (1, 3–9) that can be exacerbated by aging. Structural changes include LV hypertrophy (HFpEF) or dilation (HFrEF) and result in functional changes that produce hemodynamic and metabolic alterations. An impaired functional capacity results which further exacerbates the structural and functional abnormalities of the heart, trapping patients in a vicious cycle of HF (2).

Epidemiology of Heart Failure

Heart failure is estimated to afflict approximately 1-3% of U.S. adults, similar to the 2% worldwide (3, 4). In 2012, approximately 5.8 million people had HF (2.4%), a number expected to increase to more than 8 million by 2030 (3.0%) (3, 10). The American Heart Association's (AHA) 2020 update found HF prevalence had already increased to an estimated 6.2 million as of 2016, a 7-9% increase from 2012. The prevalence of HFpEF is increasing at a faster rate than HFrEF (11). The increase is largely driven by the aging of the population, though improved treatment for and survival of acute cardiovascular (CV) events and increased prevalence of comorbidities have also been cited as reasons (1, 3, 4, 11). The presence of multiple comorbidities has been observed in HF, and especially in HFpEF with approximately 50% of patients having 5 or more comorbidities (1, 3). In a subset of the Women's Health Initiative (WHI) cohort (n=42,170), the population attributable risk for HTN in HF was 41%, and 26% for obesity (7). Diabetes is estimated to afflict approximately 45% of patients with HFpEF (12). Despite the increased prevalence of HF, the incidence for this condition has remained relatively unchanged in individuals over the age of 65 (651 per 100,000 in 2006-2008 to 639 per 100,000 in 2016-2018) due to the aging "baby boomer" generation. However, this relationship, where the increase in prevalence surpasses the change in incidence, is weaker in HFpEF (1, 3, 13). Approximately 50% of incident HF hospitalizations are due to HFpEF (11). Total direct medical costs of HF are also projected to more than double to $53 billion between 2012 and 2030 and to $70 billion when including indirect costs. More than 80% of these costs can be attributed to hospitalizations, and costs related to comorbid conditions are not included (4, 10).

Heart Failure Phenotypes

Despite having different etiologies, HFpEF and HFrEF have largely the same pathophysiological detriments and resulting symptoms (2). In HFpEF, comorbidities including DM, HTN, obesity, and aging are thought to cause a state of systemic inflammation and to increase collagen deposition, leading to concentric LV hypertrophy. In HFrEF, a state of volume overload and myocardial injury are the cause of LV dilation (3, 4, 14). While both phenotypes have similar though excessively high mortality rates, HFrEF has greater responsiveness to drug and other therapies while effective therapies for HFpEF remain elusive and instead rely largely on symptom management (1, 3, 4, 6). Overall, epidemiological studies tend to observe lower survival rates compared to clinical trials of patients with HFpEF (15). In the Rotterdam prospective cohort study (n=7,734), which completed follow-up in 2000, 5-year survival after HF diagnosis was just 35% in 725 incident cases (16). However, in the I-PRESERVE pharmacologic study of exclusively patients with HFpEF (n=4,128), which completed follow-up in 2008, 5-year mortality after initiation of the trial was approximately 25%, with 881 deaths. Sixty percent of deaths were attributed to CV causes, 30% to non-CV causes, and 10% to unknown causes (17). More recently, a study evaluating mortality across the entire HF spectrum (n=2,791), which completed follow-up in 2018, observed significantly lower 5-year mortality rates for HFmEF (20%) and HFpEF (17%) than for HFrEF (31%). Death due to cardiovascular causes was significantly more prevalent in HFrEF, accounting for 65% of deaths, while deaths due to non-CV causes of death were significantly more prevalent in HFpEF (62%) and HFmEF (54%) (18). It has been demonstrated that an individual's survival of HFpEF decreases with increasing comorbidity burden (3). Since

the high mortality associated HFpEF is largely due non-CV mortality, it appears lifestyle changes to manage these comorbidities are valuable targets for future research. While both phenotypes of HF result in significant morbidity and mortality, the focus of this thesis will be on the HFpEF phenotype.

Pathophysiology of Heart Failure with a Preserved Ejection Fraction

The pathophysiology of HFpEF is not as well understood as HFrEF, but several studies over the past two decades have elucidated some of the similarities and differences between the two phenotypes. Kitzman and colleagues (2002) identified four pathophysiological domains of HF: LV structure and function, exercise tolerance, neuroendocrine function, and quality of life (19). As for LV structure and function, HFpEF is characterized by hypertrophy in the form of thickened LV walls resulting in a decreased chamber size (19). Although LV filling is reduced, contractility is maintained and thus EF is preserved at or increased above normal. In contrast, HFrEF is marked by LV dilation and increased LV end-diastolic volume due to fluid retention that increases preload (2, 19). Acute cardiac events, like myocardial infarction, diminish contractility and result in functional impairment that decreases the proportion of blood ejected from the LV (2, 4). Despite the differences in LV structure, exercise tolerance is reduced by approximately 40% compared to age-matched controls in both HFpEF and HFrEF (4, 19). The small cavity size in HFpEF and the reduced efficacy of systolic contraction in HFrEF result in decreased cardiac output (CO) (2). While individuals without HF meet the demands of exercise by increasing both heart rate (HR) and stroke volume, central changes in heart failure adversely affect the patients' ability to increase stroke volume and therefore lower tolerance to exercise (6). In both HFrEF and HFpEF, the sympathetic

(SNS) and renin-angiotensin-aldosterone (RAAS) neuroendocrine systems are overactivated, impairing exercise recovery, inducing peripheral vasoconstriction and fluid retention, and potentially leading to chronotropic incompetence. These effects, in turn, augment afterload which further increases the work of the heart (20). Performing activities of daily living (ADLs, e.g., bathing, dressing, feeding oneself) become difficult since patients with HF become dyspneic with minimal exertion. Individuals without HF have adequate parasympathetic tone and neuroendocrine balance to rise to and recover from the demands of exercise (2). Lastly, quality of life (QOL), and particularly physical and health related QOL, is reduced across the heart failure spectrum due to limiting dyspnea and fatigue (21).

Mounting evidence suggests that multiple comorbidities, commonly seen in older patients with HFpEF, can induce a state of systemic inflammation and overactivation of the SNS and RAAS (8, 12, 14). This inflammation, evidenced by elevated levels of circulating proinflammatory cytokines, contributes to inflammation of the coronary vasculature, reducing nitric oxide availability, decreasing enzymatic activity, and promoting collagen deposition and interstitial fibrosis. This pathophysiology can have major effects on myocardial structure and function (11, 15). The SNS and RAAS neurohormonal systems induce peripheral vasoconstriction in an attempt to increase stroke volume and maintain CO, heightening afterload (2). This high-pressure state induces LV concentric remodeling in order to adequately deliver blood to the periphery by thickening myocytes in ventricular walls and further promoting collagen deposition and interstitial fibrosis, thereby decreasing ventricular compliance (4–6, 14). Impaired relaxation due to increased ventricular stiffness requires increasingly higher filling

pressures to adequately fill with blood, inducing a cyclic effect on the already high-pressure state. This process further augments sympathetic stimulation by overstimulating baroreceptors in the ventricles (2, 6, 20). These baroreceptors can be eventually desensitized, contributing to the development of chronotropic incompetence, expressed as abnormal HR recovery, decreased peak HR, and HR instability during exercise, which exacerbates exercise intolerance and reduces QOL (6, 20). These hemodynamic and neurohormonal processes trap the patient in a vicious cycle, making it increasingly difficult to maintain CO. This generally leads patients with HFpEF to have an increased LV mass to volume ratio, decreased oxidative fibers in skeletal muscle, and decreased peak oxygen consumption (VO_2peak) (6, 14, 19). Effects of the condition are especially evident during exertion, as individuals with HFpEF have a lower peak workload and exercise time, higher levels of norepinephrine, and lower anaerobic threshold than individuals without HFpEF (19).

Risk Factors for Developing Heart Failure with a Preserved Ejection Fraction

Heart failure research is relatively robust for patients with HFrEF but is more limited for patients with HFpEF. In HFrEF, the etiology is generally well-known, whereby acute CV events damage the myocardium, reducing contractility and EF. In contrast, HFpEF does not always have a specific cause. Instead, the interplay of one or more risk factors acts to decrease LV compliance, elevate LV filling pressures and afterload, and reduce CO. The risk factors for HFpEF include advanced age, characteristics associated with the female sex, race and ethnicity, and the presence of comorbidities like HTN, diabetes, and obesity. The signs and symptoms associated with these risk factors present clinically in patients with the HFpEF phenotype.

Age

Heart failure, particularly HFpEF, has been referred to as a "disease of old age" (11). This is due to increased prevalence being strongly driven by increasing age (1, 3, 4). Age-related processes have detrimental effects on CV hemodynamics, even in the absence of comorbidities. For example, LV stiffness tends to independently increase with age, as does inflammation and fibrosis of the systemic vasculature. Aging also reduces the heart's ability to increase HR and CO during exercise due to reduced responsiveness to stress, resulting in decreased VO_2peak (1, 6). These age-related changes increase systemic vascular resistance (SVR) and afterload, subjecting the LV to higher filling pressures from increased wall stiffness.

Sex

A large proportion of patients with HFpEF are female, but this is largely attributed to the older age at onset of HF due to the longer lifespan of females. In contrast, male sex is considered a stronger risk factor for HFrEF (3, 9). Adult HF prevalence between 2013-2016 was approximately 5% for females and 7% for males in the 60-79 age group. However, for the oldest age group (>80 years), prevalence for females increased 150% to 12% prevalence, but only increased 86% to 13% prevalence for males (11). In the aforementioned Rotterdam study, the lifetime risk of HF was 33% for men and 29% for women with the mean age of HF diagnosis being higher for women than men. The study did not find any significant differences in mortality rates between sexes (16). In the Atherosclerosis Risk in Communities study, 47% incident HF hospitalizations between 2005-2009 were attributed to HFpEF. The combination of race

and sex that generated the highest rate of incident hospitalization was white women at 59%, but mortality rates were not found to differ by race or sex (22). Another study found similar mortality rates between sexes, but only for the short-term; after approximately six months, survival improved more in women than men (15). In the I-PRESERVE trial, patients with HFpEF who died during the course of the trial were more likely to be male (17). Thus far, evidence supports that the longer female lifespan is a stronger risk factor for HFpEF rather than physiological differences by sex. Research on differences in HFpEF survival by sex is also equivocal at this point. However, some evidence suggests that the increased number of females with HFpEF could be attributed to their longer average lifespan.

Race and Ethnicity

Race and ethnicity also represent significant risk factors in the development of HF. Data on racial and ethnic disparities in HF shows conflicting findings in the HFpEF subset, but overall has been understudied (3). According to the National Vital Statistics System, HF hospitalization incidence among Black Medicare beneficiaries increased 75% between 2015 and 2017, twice that of white beneficiaries (13). In the MESA study, incident HF over 11 years in middle and older adults was highest for Black individuals, followed by Hispanic, white, and Chinese individuals (1). However, when a subset of the same cohort (n=6,781) was analyzed for incident HFpEF cases (n=111), no significant differences were found across race and ethnicity strata. However, these analyses were underpowered due to a small number of cases (9). In the aforementioned WHI cohort, Black women had a lower risk for HFpEF, and Hispanic women had a lower risk for both HFpEF and HFrEF compared to white women. Despite low incidence, risk factors for

HFpEF were particularly numerous in the Black participants. The highest baseline rates of DM were observed in Black women (12%), followed by Hispanic women (8%), and lastly by white women (4%). The presence of HTN also increased the risk of developing HFpEF over the course of the study in both white and Black women (7). This affirms AHA data indicating Black individuals with HF are more likely to have a greater number of significant risk factors than non-Hispanic white individuals (10). This is particularly true for obesity as approximately 50% of non-Hispanic Black individuals in 2017-2018 were obese compared to the national obesity prevalence of approximately 31% (23, 24). The overall mortality of HF does not appear to significantly differ between Black and white individuals, though mortality rates for both are significantly higher than observed in other races and ethnicities (22). Race and ethnicity are risk factors that may be difficult to modify or non-modifiable, given the influence of both sociocultural and biological factors on health outcomes. Age and sex also constitute non-modifiable risk factors for HFpEF. However, being non-modifiable does not lessen the importance of these risk factors in the study of HF prevention, management, and treatment. Increased recruitment of subjects in these strata is needed in future research to further evaluate any racial or ethnic influence on HF expression.

Hypertension and Diabetes Mellitus

Approximately 46% of Americans have HTN, which is a significant risk factor for the development of LV hypertrophy and HF (4, 11, 14, 25). Hypertension, often the product of lifestyle factors like physical inactivity, poor diet, and smoking, promotes inflammation of systemic vasculature (8, 25). Over time, this chronic inflammation increases vascular resistance, preload, and afterload and the elevated LV stress promotes

hypertrophy (6, 8, 14). Some studies have observed the population attributable risk (PAR) for HTN in HF to be approximately 20%, and can hold an even greater weight in HFpEF (7, 11). Hypertension was by far the greatest comorbidity that contributed to the development of HFpEF in the WHI cohort (PAR 41%), and was significantly predictive of incident HFpEF over 11 years in the MESA study (7, 9).

Type II Diabetes Mellitus also represents a significant risk factor in the development of total HF and of HFpEF (25). Of the pathophysiological mechanisms discussed, DM can contribute to cardiac dysfunction via RAAS activation, ventricular fibrosis and collagen deposition, and oxidative stress resulting from chronic hyperglycemia. Moreover, these changes can occur even in the absence of other risk factors (8, 12). The prevalence of HF in individuals with DM is approximately four times higher than in the general population. Interestingly, not only has DM been shown to be a risk factor for HF, but HF has also been shown to increase the risk of developing concomitant DM (26). In the WHI cohort, women with DM were significantly more likely to develop HFpEF over the course of the study compared to women without DM (7). Heart failure patients with diabetes also tend to have poorer disease outcomes (25). The expression of HF and DM together has observed lower functional status and higher all-cause mortality than non-diabetic patients with HF (17, 26). In the I-PRESERVE trial, the prevalence of diabetes was significantly higher in the mortality group (36%) than in the survival group (25%) (17).

Obesity

Since approximately 80% of patients with HFpEF are overweight or obese, bodyweight is one of the most important modifiable risk factors in the development of HFpEF (27). Obesity contributes to systemic inflammation and adversely alters central and peripheral hemodynamics. Excessive body fat contributes to inflammation through increased production of proinflammatory cytokines and continuous fat cell turnover and fibrosis (28). Increased lean mass is likely an important contributor to the increase in central and total blood volume that occurs with obesity, a development that results in increased CO. Interestingly, obesity is associated with decreased SVR, which may be one mechanism that helps explain the protective effect of the obesity paradox, which will be discussed later (14, 28). Elagizi and colleagues (2018) suggest the sustained increase in preload is responsible for an initial LV dilation that promotes a compensatory hypertrophic response (28). However, there are a number of processes contributing to heightened afterload that also play a role in the development of concentric hypertrophy in HFpEF. Fat cells express an abundance of angiotensin I, which additively increases vasoconstriction and LV afterload. The SNS is also overactive in obesity, impairing cardiac reserve and contributing to the development of chronotropic incompetence (6, 14, 28). Increased preload and afterload results in remodeling and a progressive reduction in CO (28). The relationship between body mass index (BMI) and risk for HF appears to be dose-dependent (27). Obesity may be considered a hallmark risk factor of HFpEF due to exceedingly high rates in this particular patient population. Fortunately, obesity is modifiable through diet and exercise and represents a significant area for future research.

As mentioned above, an "obesity paradox" has been observed in HF patients where mortality rates have a U-shaped relationship with body weight. In this "paradox", HF patients with the lowest and highest BMI categories have increased mortality rates relative to HF patients that are overweight and mildly (class I) obese (5, 27, 28). Proposed mechanisms for the obesity paradox in HF include: the obesity-associated reduction in SVR lowering afterload, the protection of moderate amounts of extra body fat against cachexia associated with late-stage HF, and the obesity-related increases in lean mass supporting improvements in cardiorespiratory fitness (CRF). However, while class I obesity (BMI of 30-35 kg/m^2) appears protective for HFrEF, it has been shown to be detrimental for HFpEF. For this reason, HFrEF patients may not benefit from intentional weight loss in the way those with HFpEF may (27). Furthermore, it appears that mortality increases in both HFrEF and HFpEF with class II (BMI of 35-40 kg/m^2) obesity. Interestingly, CRF especially has been shown to improve hospitalization and mortality rates from HF and associated risk factors, regardless of BMI (27, 28). Weight loss deserves adequative study as a therapeutic regimen for HF, as does weight loss that concomitantly improves CRF.

Medical Management for Patients with Heart Failure

The medical management of HF differs according to phenotype. While numerous drug and device therapies have shown promising results in HFrEF, none of these medical therapies have been shown to improve morbidity and mortality in HFpEF (5). Current HFpEF treatment includes a combination of drugs to improve symptoms and manage comorbid conditions including HTN and DM (4). A handful of studies have demonstrated that exercise therapy can improve several of the important HF domains described earlier,

especially exercise tolerance (via CRF) and QOL (4). Most exercise training studies have demonstrated minimal effects on central hemodynamics; instead, most of the benefit is related to changes in peripheral physiology (6). While the benefit of improved CRF is undeniable, no clear guidelines exist for weight loss in HFpEF except for individuals with severe obesity (27, 28). However, body fat has been shown to be an independent determinant of exercise intolerance in HF and HFpEF, suggesting weight loss may be an important contributor to improved CRF (28). Horwich and colleagues (2018) further argue a differentiation between fat mass and lean mass may be more important to understanding the role of overall body composition in HF management (27).

Exercise in the Management of Heart Failure

Patients with HF have been observed to engage in high levels of sedentary behavior (~12 hours) with the majority of active time spent in a light-intensity and achieved periodically throughout the day through ADLs (29). Participating in bouts of exercise training (ET) may increase active time and activity intensity in patients with HF, which can improve health outcomes. Numerous trials have demonstrated the safety and efficacy of ET in the management of HFrEF (30). Less data exist for HFpEF. In the large, multi-center HF-ACTION trial, approximately 2 years of home-based, aerobic exercise training (AT) had modest reductions in all-cause mortality (11%) and HF hospitalization (15%) in 2,331 patients with HFrEF. However, the results were only significant after adjusting for certain baseline characteristics. Adverse events were similar between exercise and usual care groups, demonstrating the safety of ET in this population (31). A sub-analysis of the TOPCAT trial of 1,751 HF patients demonstrated that patients with the AHA's classifications of "poor" and "intermediate" PA levels were both

approximately twice as likely to have HF-related hospitalization, CV death, or aborted cardiac arrest over a 2-year follow-up, compared to those with "ideal" PA levels (32). A 1998 Piepoli and colleagues review of 34 ET in HF studies, largely with reduced EF, found consistent evidence supporting increased VO_2peak, exercise tolerance, ventilatory anaerobic threshold, parasympathetic tone and heart rate variability, and endothelial vasodilation with exercise. Little to no evidence was found supporting changes in various measures of LV function (33). This supports the notion that ET has beneficial effects on the physiology of patients with HF, regardless of EF, and thus should also benefit patients with a preserved EF.

Randomized controlled trials examining the effects of ET in individuals with HFpEF are scarce, but not absent, in the literature. A randomized, single-blind trial by Kitzman and colleagues (2010) used a progressive ET training regime of walking and Airdyne cycling to examine changes in VO_2peak and health-related QOL compared to an attention-control group. Of the 53 older, stable patients with HFpEF enrolled, VO_2peak increased by an average of 2.3 ml/kg/min in the ET group over a 16-week period (34). Despite not reaching between-group significance, a quarter of the ET group had clinically meaningful improvements in VO_2peak on an individual level. Exercise time, peak power output, and serum aldosterone were the only variables to significantly improve compared to the control group. Between-group comparisons for LV Doppler and QOL measures did not reach significance despite within-group improvements being found with ET (35). A similar study by the same researchers used flow-mediated dilation of the brachial artery and measures of stiffness of the carotid artery and found these measures were not significantly different between the ET and control group. Subsequently, Kitzman et al.

hypothesized the changes in VO_2peak may instead be due to improved oxygen perfusion of skeletal muscle (36). Edelmann and colleagues (2011) significantly improved VO_2peak by an average of 3.3 ml/kg/min in an ET + usual care group (n=44), consisting of 12 weeks of AT and resistance training (RT), compared to a usual care alone-control group (n=20) in the Ex-DHF Pilot Study. The secondary outcomes were cardiac structure, diastolic function, and QOL. Echocardiographic E/e', left atrial volume index, and some physical QOL measures were significantly improved in the ET group compared to usual care alone. However, LV mass index and EF did not change. These changes were independent of BMI as there was no significant weight loss (37). This was one of the few studies that found significant improvements in LV diastolic function with ET in patients with HFpEF. Gary and colleagues (2004) were able to significantly improve exercise capacity measured by six-minute-walk distance, QOL, and depressive symptoms using a 12-week, home-based walking + education program (n=16) compared to an education-only control (n=16) in obese, female patients with HFpEF (38). All of these studies reported no adverse events related to exercise and concluded exercise is safe for this population (34, 37, 38).

Diet and Weight loss in the Management of Heart Failure with a Preserved Ejection Fraction

In contrast to patients with HFrEF, the majority of patients with HFpEF are overweight or obese. Thus, diet and weight loss interventions may be beneficial to patients with HFpEF but have received little attention to date. In the first study to examine the effects of a calorically restricted diet (CR) with and without AT in this population, Kitzman and colleagues (2016) conducted a randomized clinical trial of 100

older, overweight and obese patients with HFpEF. This study, coined *SECRET I*, randomized participants into four groups (CR, AT, CR+AT, and attention-control) for a 20-week intervention. The CR-alone group received prepared meals according to a 400 kilocalorie (kcals)/day deficit from an estimated resting metabolic rate. The AT-alone group performed thrice weekly supervised aerobic exercise consisting of track walking and Airdyne cycling. Training intensity began at 40-50% heart rate reserve (HRR) based on results from a baseline cardiopulmonary exercise test (CPET). After approximately 2 weeks, intensity was gradually increased to 60-70% HRR and duration was increased to 15-20 minutes (mins) based on individual exercise and symptom responses. Duration continued to increase thereafter until patients were exercising for one hour per session. The CR+AT group received both interventions but with a 350 kcals/day deficit to account for the difference in EE with exercise. The attention-control group received biweekly phone calls. For the primary outcome of VO_2peak, the CR group significantly increased VO_2peak by 1.3 ml/kg/min, the AT group by 1.2 ml/kg/min, and the CR+AT group by 2.5 ml/kg/min, compared to the unchanged control group. There were no significant influences on QOL except for some measures in the CR group. The combination of CR+AT had a clear additive effect, and there were significant statistical interactions between the two. While the CR group found significant reductions in LV mass and significantly improved echocardiographic mitral E/A velocities, these findings are not consistent with the literature. It is difficult to separate the positive outcomes of the intervention from weight loss as the CR+AT group lost 10% body weight, CR group 7%, the AT group 3%, and the control group 1%, as weight loss has been suggested to independently contribute to improved CRF (28, 34, 39).

Overall, despite lack of consistent improvement in measures of diastolic function in patients with HFpEF, current literature supports ET as a safe and feasible method for improving exercise tolerance and physical QOL in this population. Exercise in combination with a calorically restricted diet has shown positive, additive benefit to exercise capacity with attenuated detriments to lean body mass, which is relevant to the implications of the obesity paradox in HF. The benefits of combined caloric restriction and ET in HFpEF has been understudied and necessitates further exploration as a treatment paradigm.

While multiple measures of body composition were significantly improved in the CR and CR+AT groups in SECRET I, lean mass significantly decreased, despite an increase in protein intake. No significant interactions were found between CR and AT, and AT alone was unable to significantly alter body composition variables in this study (39). Several studies have demonstrated that there is a strong positive relationship between lean muscle mass and physical function in individuals with HFpEF. The importance of lean muscle mass was demonstrated by Haykowsky and colleagues (2013) who compared patients with HFpEF to age-matched controls without HFpEF (n=100) and that found percent lean body mass and percent lean leg mass strongly correlated with VO_2peak (r=0.51, 0.52 respectively). Consistent with HF and obesity literature, this analysis also found total lean mass was not significantly different between groups, but lean mass as a percent of total body mass was lower in the patients with HFpEF (40).

Haykowsky and colleagues (2018) used dual-energy x-ray absorptiometry (DEXA) in individuals with HFpEF and age-matched controls without HFpEF (n=161) to examine the role of fat mass. Total and percent fat mass, abdominal subcutaneous and

intra-abdominal fat, and thigh intermuscular fat were significantly higher in the individuals with HFpEF than in the controls. Total percent lean mass was significantly lower in those with HFpEF, though total lean mass was only modestly different (41). These observations are consistent with the expected pathophysiology of obesity, in which absolute lean mass increases with bodyweight but is reduced relative to total body mass. Peak oxygen consumption, six-minute-walk distance, short physical performance battery, and leg press power were all inversely associated with abdominal subcutaneous fat, and intra-abdominal fat was the strongest predictor of the first two measures in a multiple regression model (41). Together, these data suggest body fat reduction via weight loss may be a viable method of improving exercise capacity in the HFpEF population, particularly if lean mass can be retained. This is particularly important to the obesity paradox. In a secondary analysis of the aforementioned I-PRESERVE trial, individuals with BMIs below 23.5 kg/m^2 and above 35 kg/m^2 were equally more likely (HR 1.27) than individuals with a moderately overweight BMI (26.5-30.9 kg/m^2) to succumb to CV-related hospitalization or death in a sample of 4,109 older, mostly female, patients with HFpEF. A severe obesity classification presented an even higher risk of HF-related hospitalization (HR 1.52). Clearly, overall body composition, not just BMI, needs to be considered in the context of HFpEF, especially when considering weight loss as a treatment.

Measuring Energy Expenditure

Weight loss is based on the concept of energy balance. When an individual is in energy balance, energy intake (e.g., kcals) is equal to energy expenditure (EE) or metabolic rate, resulting in body weight maintenance. An energy surplus occurs when

caloric intake surpasses metabolic rate, resulting in increased body weight. When an energy deficit is present, caloric intake is lower than metabolic rate, resulting in body weight loss. An overweight or obese patient can achieve weight loss by decreasing energy intake, increasing EE, or both. Decreasing energy intake may be achieved through calculated diet strategies, while increasing EE may be achieved through increases in physical activity (PA). Increasing PA can be accomplished through increases in duration at either a light or moderate-to-vigorous intensity, which may or may not include structured exercise. To achieve a one-pound-per-week weight loss, diet and exercise EE must yield a 3,500 kcals/week deficit, or 500 kcals/day.

Several methods have been developed to measure EE. The gold standard technique for determining total daily EE is direct calorimetry, and, for physical activity-related energy expenditure (PAEE) or free-living EE, is the doubly labeled water technique (DLW) (42–44). Direct calorimetry involves the subject living in a controlled chamber so that EE may be measured as body heat released into the chamber environment (45). The DLW technique involves ingesting water containing an isotope and collecting urine samples repeatedly until the molecular structure of the urine has been completely labeled with the isotope (44, 45). Both direct calorimetry and DLW are complicated techniques that involve specialized equipment and personnel, but they are the most accurate methods for assessing EE. Indirect calorimetry, where respiratory oxygen consumption and carbon dioxide production at the mouth is commonly measured with a metabolic cart, provides a relatively accurate estimation of EE and more feasible than DLW (44). However, this method still requires specialized equipment and limits assessment of EE in a free-living environment. Most recently, predicting EE using

algorithms developed for activity monitors, specifically accelerometers, has become widely used (46). Using accelerometers is less accurate than direct and indirect calorimetry, but it allows researchers to estimate EE in a free-living setting, without the need for highly technical equipment, specialized personnel, and financial burden (42). The practicality of accelerometry has accelerated its use in research, and algorithms are continually improving estimates of EE as research advances. Thus far, accelerometry tends to accurately predict EE during low intensity PA and decreases in accuracy as intensity increases, but the trade-off is greater ease of use (46).

The use of accelerometry to objectively measure steps and minutes of light, moderate, and vigorous intensity PA has experienced rapid growth in recent years, evolving from subjective and less accurate self-report questionnaires (47–49). ActiGraph accelerometers are the most widely used and detect changes in velocity over time in different planes, measuring these units of acceleration as "counts". For example, a triaxial accelerometer measures activity counts in three planes of motion (i.e. anteroposterior, mediolateral, and longitudinal/vertical) (47, 50). These counts, typically summed over a specified epoch (e.g. one minute), can be used to assess patterns of active and sedentary behavior throughout the day according to pre-defined intensity intervals (i.e. count "cut-points") (47). Various equations have been developed to convert counts into estimations of PAEE in terms of kcals and metabolic equivalents (METs). Vector magnitudes (VM), which are the average of vector length in the longitudinal, anteroposterior, and/or medio-lateral axes, may also be summed and calculated to estimate PAEE. Vector magnitudes have been shown to have greater sensitivity to movement than vertical counts alone and may provide more accurate estimations of PAEE (51, 52). Furthermore, VMs are a

required unit of measurement for wrist-worn accelerometers due to naturally higher acceleration of limbs during locomotion. Using VMs to estimate PA has been observed to be valid and reliable in older adults, and may be applicable to other clinical populations, including patients with HFpEF (51).

The typical use of accelerometry is for estimating time and intensity of PA, rather than PAEE. However, estimating weekly PAEE has been shown to be valuable in certain clinical populations, like those with cardiovascular disease (48). Estimating PAEE using accelerometry allows researchers to assess PA levels in a free-living setting without being burdened by the gas exchange equipment required for indirect calorimetry. Accelerometers may be worn on the hip or wrist, on the dominant or non-dominant side. There are advantages and disadvantages to each and so the wear location varies among studies. Hip-worn accelerometers tend to result in lower adherence but can overestimate sedentary time, while wrist-worn accelerometers tend to have greater adherence but can overestimate active time (47, 48, 53, 54). Monitors are typically removed during water-based activities like showering, as well as during sleep. Data are usually analyzed as long as an individual obtains a pre-specified, minimum wear time (e.g., 10 hours) (55). Biological sex does not seem to influence device-reported activity and thus men and women are often analyzed as a single group (47, 56).

Accelerometry Use in Clinical Populations

Count and VM "cut-points" have been established for different populations to define a level of counts per minute that appropriately exemplifies moderate-to-vigorous PA (MVPA) for that population. Establishing a cut-point for older adults is difficult, as

this age group has a wide range of exercise capacities and mobility capabilities (49, 56). Gait and balance alone can account for 16% of the variability in PA levels in older adults (49). Using a right-hip, uniaxial ActiGraph accelerometer combined with gas exchange spirometry, healthy older adults (n=38, avg. age 70 years) walked at various speeds on a treadmill to examine a commonly used cut-point of 1,041 counts/min. A VO_2 of 13 ml/kg/min was established as the correlating MVPA threshold based on the MET value for the assigned walking speed, a moderate intensity level that the authors cite is associated with reduced morbidity and mortality in older adults. Subjects were then followed for 7 days in free-living conditions. At this cut point, subjects engaged in an average of 68 mins per day of intermittent MVPA (56). In a large study of healthy middle and older adults (n=1,391, avg. age 65 years) by Bonn and colleagues (2018), count thresholds were established using hip-worn, triaxial ActiGraph accelerometers and combined with the DLW technique for assessing EE. In this study, a threshold of 2,690 units of VM/min established MVPA which has also been used in other studies (57, 58). At this level, women in the highest quartile of MVPA completed approximately 54 mins/day, as compared to 30 min/day in the lowest quartile. Men in the highest quartile completed approximately 66 mins/day, whereas those in the lowest completed approximately 42 mins/day. Results were significantly different across quartiles (57). This count cut-point was significantly more conservative than the prior study, and yet even the lowest quartile of individuals in both sexes achieved the recommended 30 mins/day of MVPA (56, 57). A study of healthy adults (n=54, avg. age 43 years) used free-living accelerometry data from both the right hip and non-dominant wrist, cross-referenced with limited periods of observed activity for accuracy. The wrist-worn MVPA

cut-point established in these younger participants was 3,941 VM counts/min (54). To our knowledge, these are the only wrist-based, VM cut-points developed, as wrist- and hip-worn cut-points are not interchangeable. The MVPA cut-point in this sample was approximately 47% higher than that used for the older adults in the previous study's sample. This finding validates the importance of determining appropriate cut-points for young vs. older adults, using VM vs. vertical counts, and using wrist- vs. hip-worn cut-points. Also, the results often look quite different in studies that have used older individuals and/or those in poor health. In a sub-analysis (n=140, avg. age 79 years) of the LIFE study (n=1,448), older adults with significant physical limitations underwent a 40-minute walking intervention wearing a hip-worn, ActiGraph accelerometer to identify an appropriate MVPA cut-point. "Moderate intensity" was prescribed according to the Borg RPE scale. The median cut-point for MVPA was 1,220 counts/min, though the researchers note there was large variability in the sample. Using these data, the researchers formed an equation for predicting "individually tailored cut-points" to be used when more widely used cut-points (i.e., 1,041 counts/min) are inappropriate. This approach allowed the oldest individuals in the study to reach 204 mins of weekly MVPA at their individually tailored cut-points, contrasting the 114 mins reached at the 1,041-count cut-point. The difference in cut-points equates to a difference in activity time of 44% (59). Thus, it is unlikely that older adults with any significant chronic disease or obesity would have the aerobic capacity necessary to obtain levels of MVPA achieved by non-diseased individuals (49). It has become increasingly clear that more research needs to be done to establish appropriate cut-points for clinical populations. Ultimately, cut-points should correspond to an average of 3 METs in any particular sample, which will

vary depending on the "count" metric (e.g. VMs, vertical counts), wear location (e.g. hip, wrist), brand of the accelerometry device, and characteristics of the population. Differences in functional capacity and resting metabolic rate vary widely among young, middle, and older adults, and especially among clinical populations. To our knowledge, no wrist-worn cut-points exist for older adults, nor older adults with HF.

Measuring Physical Activity in Patients with Heart Failure

There have been very few studies using accelerometers to quantify the PA levels of patients with HFrEF and even less in patients with HFpEF. A short-term prospective study by Waring and colleagues (2017) evaluated the relationship between 30-day incidence of hospital readmission after discharge in decompensated HF patients (n=50) and accelerometer-measured PA levels during that time. A wrist-worn ActiGraph device was worn for all 30 days. Activity levels were defined as "lower" (<60 mins) or "higher" (≥60 mins) levels of daily PA at ≥3,000 VM units/min. Twenty-six percent of subjects were hospitalized for all-causes, while 18% had a HF-specific hospitalization. Hospitalized individuals were 5 times more likely to have been in the lower PA group than in the higher PA group. Interestingly, LV EF did not predict readmission, suggesting PA has a similar effect on morbidity across HF phenotypes (65). Two other accelerometry studies demonstrated no significant difference in PA levels by EF phenotype, further supporting the hypothesis that the global effects of HF (e.g., reduced exercise tolerance and PA levels) are similar across the HF spectrum (55, 66).

Energy Expenditure and Weight loss

Energy expenditure is a function of metabolism and is greatly affected by a loss of metabolically active tissue, as often seen in weight loss. Following calorie-restricted weight loss, sedentary, overweight women (n=140) that did AT or RT thrice-weekly were able to maintain total, resting, and non-exercising PAEE compared to those that did no ET by DLW and indirect calorimetry, despite all subjects experiencing a significant decrease in weight, percent fat, fat mass, and fat-free mass (60). This suggests that AT and RT can help mitigate the metabolic adaptation of decreased EE in the presence of reduced energy intake. Another study with a similar design assessed effects of caloric restriction-induced weight loss on EE in overweight, non-diseased men and women (n=48). The subjects were assigned to one of the following groups: a 25% CR, a 12.5% CR + 12.5% increase in EE through AT, a low-calorie diet of 890 total kcals/day until 15% weight reduction was achieved and thereafter followed by maintenance, and a control group following a weight-maintaining diet. The three intervention groups all demonstrated significant weight loss over six months with the low-calorie diet group experiencing the greatest reduction in bodyweight. However, the CR and low-calorie diet groups both experienced a significant decrease in total daily EE with weight loss, a change that was not experienced by the group that also performed ET. This observation persisted after adjusting for sedentary time measured in a respiratory chamber over a 24-hour period, suggesting decreased PA is an additional behavioral compensation for the decreased energy intake (61). Thus, it appears that ET may be able to mitigate the decrease in EE during weight loss with CR. It is worth noting that both studies used DLW and/or indirect calorimetry to measure daily EE.

Other weight loss studies in individuals without HF have used diet and exercise modification and seen significant improvement in other physical parameters. A study of obese, older adults (n=107) with significant physical impairment (assessed by the presence of 2 of 3 criteria: VO_2peak 11-18 ml/kg/min, low score on a physical performance test closely correlated with a high BMI, and difficulty performing 2 instrumental ADLs [e.g. housework, meal preparation, shopping] or 1 ADL) but lack of advanced heart disease presents a sample closely related in exercise capacity and QOL to patients with HF. A year-long intervention involving a comprehensive aerobic, resistance, and flexibility ET intervention group, a 500-750 kcals/day-deficit diet intervention group, a combined ET + diet group, and a control group assessed physical performance test improvement following weight loss. All three intervention groups improved on the physical tests and in VO_2peak compared to the control group, with the ET + diet group demonstrating the greatest improvement. In contrast, both the ET + diet and the diet-alone group demonstrated statistically significant weight loss. The ET-alone group demonstrated significant improvements in body composition, specifically a decrease in fat mass and increase lean body mass that was slightly attenuated in the ET + diet group. In contrast, lean body mass decreased significantly in the diet-alone group (62).

Caloric restriction-induced weight loss can also result in improvements in measures of diastolic function such as LV mass, end-diastolic volume, LV stroke volume, and peak diastolic filling rate in obese but CV disease-free subjects when compared to normal weight subjects (63). Exercise training studies have shown greater volumes of exercise are positively associated with improved LV filling. Weight loss in obese

individuals has resulted in improvements in concentric LV remodeling. There is also evidence that ET may decrease LV stiffness and improve LV filling, but this response may be limited by age-related changes in cardiac plasticity. To date, no study has examined the effect of weight loss and/or exercise on cardiac function in older patients with HFpEF (64).

Estimating Energy Expenditure from Accelerometry

Algorithms for predicting PAEE from wrist accelerometry have not been developed or validated in any population thus far. Numerous algorithms have been developed using hip-worn accelerometers, but studies have reported low reliability of these estimates (67, 68). The ActiLife software (Pensacola, FL) uses an internal algorithm to scale-down PAEE estimations from algorithms designed for the hip when wrist devices have been worn for data collection. However, ActiLife states that results should be interpreted with caution (69). As mentioned, the advantage to wrist-worn devices is the opportunity to increase wear compliance from participants, which can be lower when using hip-worn devices (47). The disadvantage to wrist accelerometry is an overestimation of activity levels via counts compared to hip-worn devices (53). Despite differences in reported counts between wear locations, current algorithms for predicting PAEE from accelerometer output have, in general, been unable to reliably predict PAEE when compared to criterion measures like indirect calorimetry (67, 68, 70). Furthermore, studies thus far have focused on young and middle adults with limited study of older adults and/or individuals with chronic disease (50, 71).

Research evaluating PAEE predicted by accelerometers is limited in the HF population. Non-cachexic patients with HFrEF have observed significantly lower PAEE but similar total daily EE to non-HF controls suggesting that PA is a critical deficit in this population (72). Furthermore, increasing PA may be important to improving the energy balance in obese patients with HFpEF to support weight loss. German and colleagues (73) used a uniaxial, hip-worn accelerometer to evaluate baseline PA levels for patients with HFpEF (n=58) entering the SECRET I ET intervention. Subjects participated in approximately 33 mins of light-intensity PA, ~10 mins of MVPA, and expended approximately 147 kcals of PAEE daily. In one week, this results in approximately 1,029 kcals PAEE and 70 mins MVPA, which meets the minimum recommendation for PAEE of ≥1,000 kcals but not for MVPA of ≥150 mins (73). The low levels of MVPA observed in these patients with HFpEF was also shown in an arm-worn accelerometry study by Yavari and colleagues (2017) using a sample of older individuals (n=151) that either had HFpEF or HFrEF, were "at-risk" for HF, or were healthy. Time spent in light PA comprised the bulk of active time for all four groups, with HFpEF achieving the lowest amount (~2.2 hours/day) and healthy controls achieving the most (~4.5 hours/day). For MVPA, activity time dropped significantly with healthy older adults engaging in approximately 1.1 hours/day, individuals "at-risk" for HF ~0.7 hours, patients with HFrEF ~0.6 hours, and patients with HFpEF patients just ~0.2 hrs/day. Accordingly, while patients with HFrEF expended approximately 235 kcals/day in MVPA, those with HFpEF only expended 56 kcals/day in MVPA (29). Thus, the patients with HFrEF met the 1,000 kcal threshold recommended for the minimal levels of MVPA as well as the 1,500-2,200 kcal threshold associated with improved CV outcomes (48). Unfortunately,

this study suggests that patients with HFpEF only expended ~395 weekly kcals of MVPA PAEE which does not meet minimal PA recommendations for maintaining CVD (29).

Only one study by Pozehl and colleagues (2018) reported that patients with HF performed an "adequate" amount of PAEE based on data obtained from 7 days of free-living with a hip-worn ActiGraph accelerometer. The subjects with HF in this investigation expended an estimated 304 kcals/day of PAEE. However, only ~10 mins of daily activity were spent in MVPA and thus the majority of PAEE was expended through light-intensity activity (55). Interestingly, the approximately 2,100 kcals/week PAEE achieved by these subjects exceeds the 1,000 kcals/week quota suggested for healthy persons and even meets the criteria suggested for slowing or regressing coronary artery disease at 1,500-2,200 kcals/week (48). The findings of this study also indicated that approximately 13% of these patients with HF met the recommendation of 150 mins of MVPA per week. The authors of this study note that while the absolute percentage of patients meeting recommendations is low, it is abnormally high relative to the literature which indicates that less than 2% of patients with HF typically reach the recommended level of PA (55). While these findings are atypical of most PA literature, they suggest that accumulating light-intensity PA may be a viable way for older HF patients to increase PAEE (48). Older adults without HF have been observed to spend approximately 90% of their active time in a light-intensity, and thus light-intensity PA may be easier to modify as a strategy for increasing PAEE than MVPA in an older population (56). Increasing the proportion of time spent in MVPA compared to light-intensity PA may be particularly important for increasing PAEE in the HFpEF population, but increasing the proportion of time spent in light-intensity PA compared to being sedentary also increases

PAEE and holds value independent of MVPA (48). Replacing one hour of sedentary time with light-intensity PA is significantly associated with an increase in PAEE, a decrease in BMI, and a smaller waist circumference in healthy older adults (57). Unfortunately, only 61% of stable HF patients (n=68) in one study noted receiving PA recommendations from their doctors. Furthermore, 89% of these were limited to generalizations about PA being "good" without specific exercise recommendations, despite 44% of patients not obtaining at least 30 mins of daily MVPA and 50% taking fewer than 5,000 steps/day (74). The lack of holistic recommendations by medical providers for a condition like HFpEF that has only marginally effective drug therapies is concerning. Targeting an integrative approach, merging the concept of cardiac rehabilitation with general health maintenance, for patients with HFpEF needs further investigation.

Quantifying Step Counts

Counting steps using an accelerometer or pedometer is a relatively universal concept that is usually easy for individuals to understand. Accelerometry has been found to have higher sensitivity to step counts compared to pedometers and tends to report significantly higher steps/day totals, especially when using wrist-worn accelerometers (75, 76). Ayabe and colleagues (2008) observed steps/day obtained using a hip-worn, uniaxial accelerometer to strongly correlate with daily PAEE (r=0.92) and mins of MVPA (r=0.85) in cardiac rehabilitation patients (n=77). Further analysis estimated ~6,500-8,500 steps/day would result in the recommended 1,500-2,200 kcals/week of PAEE (77). Step counts may be particularly useful in cardiac rehabilitation when patients are not able to achieve prescribed intensity levels, and because they can be easily measured (48). Using daily steps to assess activity levels has been suggested as the most

"robust" metric for the HF population (29). The aforementioned study by Yavari and colleagues (2017) found that subjects with either HFpEF or HFrEF, as well as those "at-risk" for HF, averaged <5000 steps/day. This was significantly less than the healthy controls who accumulated ~6,281 steps/day. Patients with HFpEF took the fewest daily steps at ~2,121 per day (29). Importantly, Izawa and colleagues (2013) observed taking fewer than 4,889 steps/day to be a significant, independent predictor of mortality in patients with HF (78). Another HF study found median steps/day to be 4,950 among patients (n=68), with approximately 50% of the sample engaging in fewer than 5,000 steps/day. Unlike previous metrics of PA data, steps/day were found to significantly differ by phenotype, suggesting steps/day may be a more sensitive measure for detecting functional differences by phenotype. Patients with HFpEF were, again, more sedentary than patients with HFrEF (median 3,246 steps/day) (74). The aforementioned German and colleagues study (73) observed steps/day consistent with the HFpEF literature (mean 3,785 steps/day) (73).

Taking fewer than 5,000 steps/day generally categorizes a healthy adult as "sedentary" (55, 74). For patients with HFpEF, taking fewer than 5,000 steps/day appears to be associated with increased morbidity and mortality (78). Future research should consider involving steps/day as a metric for assessing PA levels, particularly in populations that are more often sedentary like HFpEF. Additionally, establishing steps/day "cut-points", like the 6,500-8,500 steps/day suggested by Ayabe and colleagues (2008), may be a viable way to objectively assess PA and potentially estimate PAEE.

The Effect of Structured Exercise Programs on Physical Activity Patterns

Studies using structured exercise programs have observed substantially lower PA levels in participants following the structured exercise sessions (SES) as well as on the following "non-SES" days. This "compensation" for the increased PAEE associated with SES was demonstrated in older, obese women (n=36) undergoing a CR and ET intervention using triaxial hip accelerometry. For the group that performed moderate-intensity ET only, daily PAEE on SES days (~578 kcals/day) was significantly higher than on non-SES days (~451 kcals/day). Notably, the difference (127 kcals) was less than the energy cost of the SES (~325 kcals/session), and PAEE on SES days did not significantly differ from baseline. For the group that performed vigorous-intensity ET only, daily PAEE on SES days (~451 kcals/day) was actually significantly lower than non-SES days (~519 kcals/day). The difference (69 kcals), again, was less than the energy cost of the structured exercise (~297 kcals/session), and the SES days actually observed significantly lower PAEE compared to baseline, while PAEE on non-SES days did not differ. Together, this evidence suggests that participants performed lower amounts of PA following their exercise sessions on SES days to compensate for the increase in PAEE, a relationship that was exaggerated with increased intensity in the vigorous group (79). This behavioral compensation to the increased PAEE associated with SES was also demonstrated by Ayabe and colleagues (2004). In this study, a single cardiac rehab participant was observed over the course of 24 hours and found that the time in cardiac rehab was virtually the only PA of moderate-to-vigorous intensity achieved that day. Furthermore, PA levels for all subjects outside of cardiac rehab hours were not significantly different between cardiac rehab days and non-cardiac rehab days

(80). A separate analysis of the same study revealed very pronounced, significant differences in average steps/day between cardiac rehab days (~8,500) and non-cardiac rehab days (~5,500) (77).

To date, PA levels of patients with HF during an exercise program have not been objectively quantified. While low levels of PA have been consistently observed in patients with HF, little is known about the impact of a structured, center-based exercise program (SES) on levels of PA in this patient population. Patients with HFpEF, specifically, tend to be obese and have multiple comorbidities. Understanding PA levels and patterns in this population will be critical to designing effective exercise programs in older, obese patients with HFpEF. While PAEE can be estimated from accelerometry, PA cannot be measured because validated cut-points for older patients with HFpEF do not exist. Moreover, wrist-worn accelerometers, which may improve participant adherence over hip-worn accelerometers, also lack established PA cut-points and algorithms for predicting PAEE in older, obese patients with HFpEF.

Given the gaps in the existing literature, the purpose of this study is to quantify levels and assess patterns of PA over the course of one week in older, obese patients with HFpEF participating in an exercise intervention program. Using wrist-worn accelerometry and indirect calorimetry during walking exercise, customized cut-points using VMs will be calculated and used to measure levels of light-intensity PA and MVPA throughout the week. Physical activity patterns will also be assessed by steps/day. Lastly, walking PAEE predicted using an ActiGraph accelerometer will be compared to PAEE measured through indirect calorimetry. We hypothesize that PA levels expressed in steps/day, light-intensity PA, and MVPA in these older, obese patients with HFpEF will

be higher on SES days versus non-SES days as well as higher on weekdays versus weekends. We also hypothesize that PAEE predicted by the wrist-worn accelerometer will overestimate PAEE compared to indirect calorimetry.

METHODS

Overview

Older, obese patients with HFpEF were recruited to the controlled, single-blind, SECRET II randomized clinical trial, and were randomly assigned to one of two groups: aerobic exercise + caloric restriction (AT+CR), or aerobic exercise + resistance exercise + caloric restriction (AT+RT+CR). Near the end of the SECRET II study (summer and fall of 2019), a subset of participants (n=10) participated in a sub-study with the goal of quantifying PAEE by wearing a COSMED K5 portable metabolic system during one ET session and wearing an ActiGraph wGT3X-BT accelerometer for approximately seven days. Physical activity EE in METs and kcals during a single bout of exercise was determined using the K5 and estimated from the ActiGraph using the Freedson VM (2011) algorithm and then converted into kcals/kg of bodyweight and kcals/kg/min of the exercise session. Individualized VM cut-points for MVPA were created using collected accelerometer data and were used to provide objective measures of steps/day and minutes of light-intensity and MVPA for the seven days of wear. All study tests and procedures were conducted at the Wake Forest School of Medicine and the Wake Forest Clinical Research Center.

Participants

Participants of the SECRET II study (n=84) had chronic, stable HFpEF (EF $\geq$50%, LV diastolic dysfunction grade $\geq$1, and HF signs and symptoms present by cardiologist review using NHANES HF score $\geq$3 or Rich et al. criteria for HF), were aged $\geq$60 years, and had a BMI $\geq$28 kg/m^2. Exclusion criteria included: HF with a primary

etiology of valvular disease, changes in medications, symptoms, or hospitalization during ≤6 weeks prior to enrollment, uncontrolled HTN, uncontrolled DM, evidence of significant chronic obstructive pulmonary disease, recent stroke, cancer or other conditions with life expectancy <2 years, anemia with hemoglobin <10 g/dL, renal insufficiency with glomerular filtration rate <30 mL/min/1.73m^2, pregnancy or the possibility of becoming pregnant, uncontrolled psychiatric disease, plans to move out of the study area prior to study completion, and refusal to sign the informed consent (81). Final decisions on eligibility were decided by a board-certified cardiologist with experience in HFpEF following baseline assessments.

SECRET II Baseline and Follow-up Testing

Participants underwent a CPET at baseline and 20-week follow-up to assess VO_2peak. This primary outcome measure was obtained as the average of the final three, 15-second VO_2 values. Ventilatory threshold was defined by the Wasserman method. The test was administered via motorized treadmill using a modified Naughton protocol and according to standards established by the AHA. A MedGraphics Ultima metabolic system was properly calibrated and then used for measurement of gas exchange. Patients were encouraged to give a maximal, exhaustive effort which was evaluated by the presence of an RER >1.05, age-predicted maximal HR >90%, and RPE >16 on a 20-point scale. Concurrent BP, HR, and EKG monitoring was employed throughout the test. Tests were overseen by a certified exercise physiologist and board-certified cardiologist. Other assessments included, but were not limited to: height, weight, skeletal muscle mass and quality by DEXA and MRI, muscle strength by Biodex isokinetic dynamometer, and quality of life by the Kansas City Cardiomyopathy Questionnaire and SF-36.

SECRET II Exercise Training Interventions

Following testing, subjects were randomized to one of two groups: AT+CR or AT+RT+CR. Both exercise interventions were individualized based on exercise capacity data obtained from CPET results. Both groups met three times per week for a duration of 20 weeks. The AT-alone group met separately from the AT+RT-group to protect against contamination. Thirty minutes of aerobic exercise and 20 minutes of resistance exercise constituted a total of 50 minutes for the AT+RT-group; 20 minutes of chair-based stretching exercises were implemented in the AT-alone group to substitute the RT duration. The exercise programs were designed to be progressive, slowly increasing difficulty after surpassing pre-specified milestones.

Aerobic Training

An exercise prescription was determined for each participant HRR, VO_2peak, and RPE achieved during CPETs. Initial intensity was established between 40-50% HRR calculated by a standard formula. Exercise intensity progressed over the first 6-8 weeks until 60-70% HRR could be maintained for at least 20 minutes. Following this time period, exercise intensity was re-evaluated every $\leq$3 weeks according to submaximal heart rate response. If safe and well-tolerated, duration gradually increased to 30 minutes. Exercise was performed either continuously or in intermittent bouts. If or when the subject could complete 30 minutes of continuous aerobic training, the exercise intensity was increased up to 70-80% HRR. Aerobic training was comprised of walking on an indoor track and/or riding a stationary, recumbent bicycle. Notably, PA during stationary cycling is not captured by an accelerometer. Blood pressure was measured pre- and post-

exercise, and HR and oxygen saturation were assessed pre-, mid-, and post-exercise to assess adherence to individual exercise prescriptions. Aerobic training was the first activity performed by either group.

Resistance Training

Following the aerobic exercise, participants in the AT+RT group were allowed to rest until HR and BP returned to baseline values. Like the AT intervention, the RT intervention was designed to be individualized and progressive. An orientation session was required of all participants to become familiar with the exercise equipment. The orientation included machine demonstrations to improve safety and soreness outcomes. Subjects underwent one-repetition-maximum (1-RM) testing to guide intensity. Recommendations from the AHA and the American College of Sports Medicine (ACSM) guided RT protocol, including intensity which started low for all participants and progressed on an individual basis. During the first 3 weeks, subjects completed RT exercises at 20-30% 1-RM. Beginning week 4, the first set of RT exercise was increased to 40-50% 1-RM and a second set was added with an exhaustive repetition scheme. For weeks 5-24, intensity was increased if subjects could complete >12 repetitions for two consecutive intervention days. Every four weeks, 1-RM testing was repeated to ensure subjects were receiving an optimal stimulus for progressive strength gains. A 70-80% 1-RM intensity was the objective for the final 8 weeks of the study. Participants rotated between Nautilus (Vancouver, WA) machines targeting the large muscle groups of the upper body (chest press and compound row) and of the lower body (leg curl, leg extension, leg press, and calf raise). Nautilus equipment was chosen based on its ability to accommodate a large range of body sizes and more minute changes in resistance.

Notably, like stationary cycling, accelerometers do not capture PA during seated resistance training. Vitals including HR, BP, and oxygen saturation were assessed pre- and post-exercise.

SECRET II Caloric Restricted Diet Component

Participants' diets were reduced by 300 kcals/day to produce a weekly 2,100 kcals deficit, a level thought to reduce bodyweight by ~0.5-1.0 pounds/week. Indirect calorimetry was used to assess RMR and guide total individual caloric needs. Breakfast was prepared by participants but was guided by a thirty-six-item menu. Participants were also instructed to keep a written log of all breakfast choices. Lunch, dinner, and snacks were prepared by the Wake Forest Baptist Medical Center's Metabolic Kitchen in the Clinical Research Unit. Meals were picked up from the Kitchen thrice weekly. Weigh-ins and progress reviews were conducted weekly.

Energy Expenditure Sub-study

A subset of participants (n=10) was asked to participate in a sub-study approximately 2-3 weeks after they started the SECRET II intervention. Subjects wore a COSMED K5 (Rome, Italy) portable metabolic system to analyze gas exchange for PAEE analysis. Thirty minutes prior to exercise, the K5 was calibrated. Subjects were weighed while holding the K5 to account for the extra approximately 2.5 pounds. A polar HR monitor was worn around the chest and the ActiGraph wGT3X-BT accelerometer was placed on their non-dominant wrist. Participants were instructed to sit at rest for approximately 5 min to obtain resting values of EE and HR. The K5 was worn for the entire 50-minute session of AT-only (n=5) or AT+RT (n=5). The VO_2 was collected

every minute, HR every 10 seconds via the K5, and RPE every 10 minutes. Physical activity EE for the session was calculated by the metabolic system, kcals/min was calculated by hand using exact session duration, and bodyweight in kilograms was included to ensure relativity in PAEE units (kcals/kg/min). For the group that completed both AT and RT, components were separated for comparability to the group that completed only AT.

Accelerometry

Prior to the exercise bout, each participant had an initialized, triaxial ActiGraph wGT3X-BT accelerometer (Pensacola, FL) placed on their non-dominant wrist which was worn throughout the entire exercise session. After completing the exercise session, participants continued to wear the same accelerometer for no less than seven days. After returning the accelerometer, the data were downloaded to a PC and processed using ActiLife v6.13.4 software. Wear time was validated using the Choi (2011) algorithm, customized to use VMs, have a minimum daily wear time of 600 minutes or 10 hours, and require a minimum of 4 valid days of wear time to be included in the dataset. The algorithm defines a non-wear period as a minimum length of 90 minutes with 0-99 consecutive VM counts detected each minute. Up to 2 consecutive minutes of more than 100 counts were accepted as artifact. Data were scored using the Freedson VM3 (2011) algorithm for PAEE and Freedson Adult (1998) for METs. When EE data were imported into ActiLife, the "Worn on wrist?" box was checked to scale down PAEE from hip-based VMs based on an internal algorithm since no equations for predicting PAEE from wrist accelerometry have been developed and validated thus far (69). A customized cut-point establishing MVPA was created specific to this sample based on combined

ActiGraph and COSMED exercise session data. Raw GTX3 data were downloaded into a resolution of 10-second epochs. The MET rates recorded by the accelerometer were extracted from each 10-second epoch and aligned graphically with the COSMED MET data to identify matching session times. Only track walking was included due to the underestimation bias associated with wrist devices during seated exercise. Participant data logs were used to record start and finish times for each exercise segment. If hand-recorded session time and accelerometry start time did not match, the exercise duration in the logbook was added to the beginning of the accelerometer start time. Rest breaks were excluded from the cut-point analysis. Customized cut-points were identified to estimate total time spent in light and MVPA for this sample of older, obese patients with HFpEF. These cut-points were calculated based on raw VM volume during each available session. After time-matching VM data with the COSMED data, a linear regression approach was used to predict VM counts from the COSMED MET values across all participants. The resulting regression equation was used to estimate 3 METs and served as the MVPA transition. The yield was then multiplied by 6 to transform the 10-second epoch values into 60-second interval cut-points. The resulting cut-points designated light-intensity activity as equal to 1,853-4,039 VM counts/min and MVPA as equal to $\geq$4,040 VM counts/min. Sedentary activity was defined as 0-1,852 VM counts/min per the findings of Koster and colleagues (2016) (82). The data was summarized as averages of PA metrics (e.g. steps/day, minutes of light PA, minutes of MVPA) across individual days of the week, as well as day categories (e.g. SES, non-SES, weekday, weekend).

Analytic Plan

Data were checked for normality and inspected for outliers. Paired t-tests were used to analyze differences in PA variables between SES days (Monday/Wednesday/Friday) and non-SES days (Tuesday/Thursday/Saturday/Sunday), and weekdays (Monday-Friday) and weekends (Saturday/Sunday). The PA variables analyzed were steps/day, minutes of light-intensity PA, and minutes of MVPA. Effect size was analyzed using Cohen's d. Relationships between steps/day and intensity of PA were explored using Pearson correlation analysis. A paired t-test was used to analyze PAEE by the ActiGraph compared to the COSMED by each participant ID number. A follow-up one-sample t-test was run to explore the direction of bias for the accelerometer when compared to the mean PAEE of the COSMED. Sensitivity analyses were not performed due to the limited number of outliers. Data were analyzed using IBM SPSS Statistics software v.26.

RESULTS

Paired t-tests were used to analyze differences between day categories (SES versus non-SES days, weekdays versus weekends) for PA variables (steps/day, minutes of light-intensity PA, and minutes of MVPA). Effect size was analyzed using Cohen's d. Pearson correlation analysis was then used to explore relationships between steps/day and intensity of PA. Lastly, a paired t-test was used to analyze PAEE predicted by the ActiGraph and COSMED, followed by a one-sample t-test with the COSMED's PAEE prediction as the test value to assess the presence of bias.

Participant Characteristics

Participants (n=9) were recruited from the *SECRET II* study. Participants were older with an average age of 68 years, classified as obese, and mostly female (Table 1). Data were considered normal by the Shapiro-Wilk test for normality and confirmed by Q-Q plots.

Table 1. Baseline characteristics

ID	All (n=9)
Age (yrs.)	68.2 + 7.1
Female No. (%)	7 (78)
Black No. (%)	3 (33)
Body weight (kg)	101.9 $\pm$ 19.7
BMI (kg/m^2)	37.9 $\pm$ 4.8

Age, body weight, and body mass index (BMI) are expressed in terms of mean $\pm$ standard deviation (SD).

The Effect of Day Category on Metrics of Physical Activity

Figures 1-3 show comparisons of PA variables by day category: SES days (M/W/F), non-SES days (T/Th/S/S), weekdays (M-F), and weekends (S/S). Figure 1

shows mean steps/day on SES days (mean±SE: 9,618±1,099 steps) was not significantly different from mean steps/day on non-SES days (9,361±1,152 steps; p=0.697). Average daily steps were higher on weekdays (9,835±1,066 steps) compared to weekends (8,585±1,220 steps), but this difference was also non-significant (p=0.122).

Figure 1. Average steps/day by day category

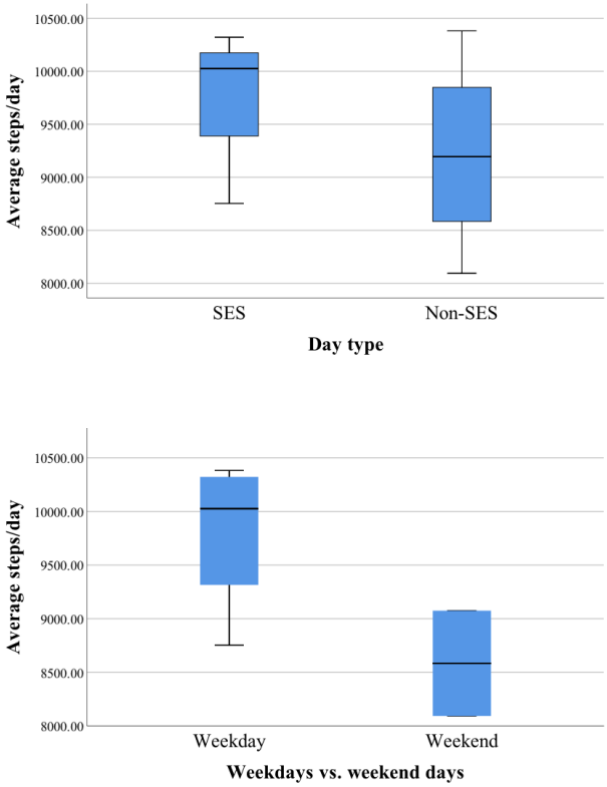
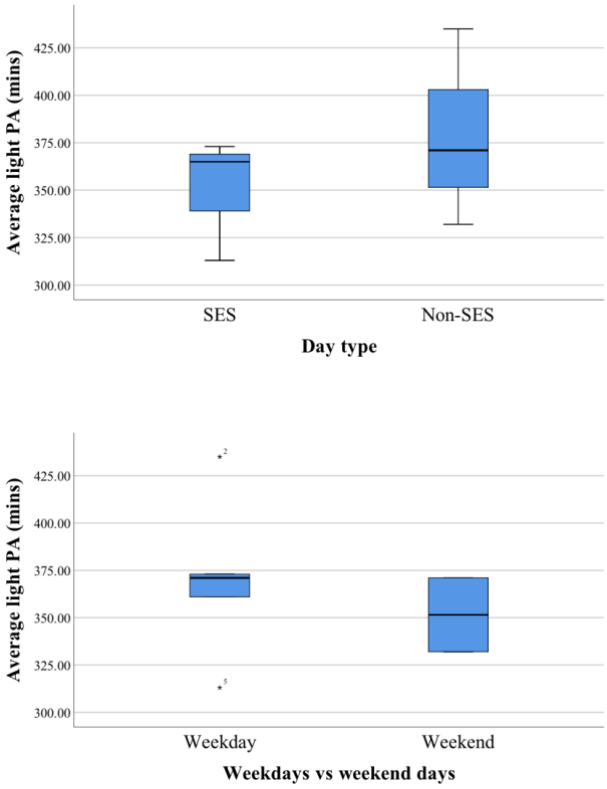


Figure 2 shows minutes spent in light-intensity PA was approximately 5.8 hours (mean±SE: 347±25 mins) on SES days and approximately 6.1 hours (367±21 mins) on non-SES days. Average minutes spent in light-intensity PA on weekdays was 362±21 minutes and on weekends was 352±33 minutes. Neither of these comparisons were found to be statistically significant (p=0.299, p=0.743, respectively).

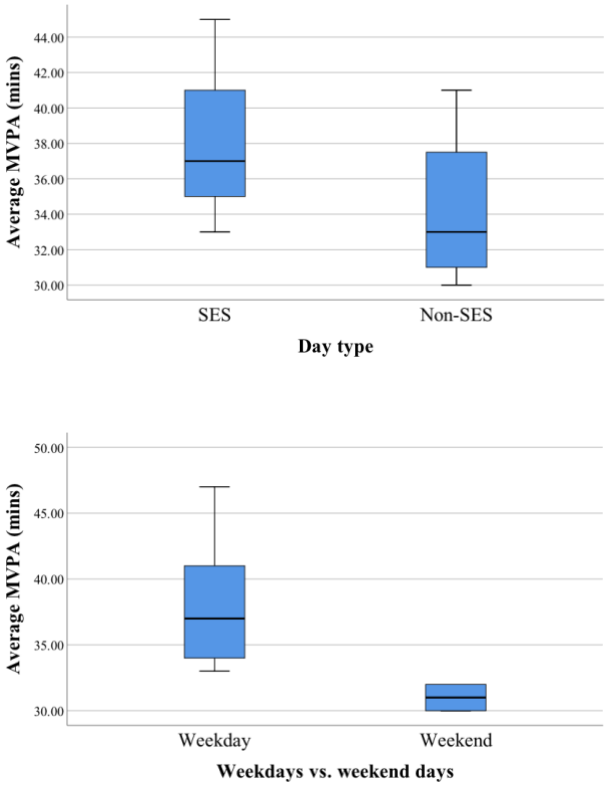
Figure 2. Average minutes of light-intensity physical activity by day category



**Denotes extreme outliers in participant data.*

Time spent in MVPA on SES days averaged 38±12 minutes compared to non-SES days which averaged 33±10 minutes. Minutes of MVPA averaged 37±12 minutes on weekdays compared to 31±10 minutes on weekends, but differences were not significant for either comparison (p=0.085, p=0.185, respectively; Figure 3). The outliers were ignored but acknowledged as a limitation to continuing with the test.

Figure 3. Average minutes of moderate-to-vigorous physical activity by day category



Very large effect sizes were noted for daily steps taken and daily minutes spent engaging in MVPA on weekdays when compared to weekends. A large effect was noted for daily minutes of MVPA on SES days when compared to non-SES days, but a large, negative effect was revealed for daily minutes of light PA on SES days comparatively. Moderate effect sizes were found for steps/day on SES days compared to non-SES days, and for light PA minutes on weekdays compared to weekends (Table 2).

Table 2. Cohen's d effect size analysis for metrics of physical activity by day category

	Steps/day	Daily light PA[a]	Daily MVPA
SES days	0.54	-0.71	0.74
Non-SES days			
Weekdays	1.68	0.52	1.77
Weekends			

For effect size, 0.2 denotes a small effect size, 0.5 denotes a moderate effect size, 0.8 denotes a large effect size, and >0.8 denotes a very large effect size. [a]Light PA and MVPA are expressed in minutes.

Pearson correlation analysis revealed strongly significant, positive correlations between minutes of MVPA acquired on SES days and steps/day on both SES and non-SES days as well as total weekdays. Minutes of MVPA on non-SES days was strongly associated with average steps/day on SES days as well as total weekday steps. Weekday minutes of MVPA was strongly, significantly associated with steps/day on SES days and total weekdays. Minutes of MVPA completed on weekends had strong, significant correlations with every steps/day category. Together, this data suggest completed minutes of MVPA were significantly correlated with overall activity levels throughout the week, including both SES and non-SES days (Table 3).

Table 3. Pearson correlation analysis for minutes of physical activity by average steps/day category

	SES steps/day	Non-SES steps/day	Weekday steps/day	Weekend steps/day
SES light PA[1]	0.776*	0.696*	0.792*	0.566
SES MVPA	0.909**	0.811**	0.888**	0.779*
Non-SES light PA	0.536	0.652	0.579	0.650
Non-SES MVPA	0.851**	0.775*	0.830**	0.760*
Weekday light PA	0.707*	0.549	0.704*	0.415
Weekday MVPA	0.882**	0.756*	0.850**	0.727*
Weekend light PA	0.417	0.734*	0.494	0.806**
Weekend MVPA	0.798**	0.851**	0.811**	0.855**

*[1]All metrics of PA are in minutes. SES and non-SES are in days. *p<0.05. **p<0.01.*

Comparison Between Energy Expenditure Predicted by Accelerometry vs. Indirect Calorimetry

Table 4 depicts a series of statistical analyses that were completed comparing PAEE predicted by the ActiGraph accelerometers to PAEE determined by the COSMED k5 portable metabolic system. The sample size was reduced to n=6 based on accelerometry and COSMED data that could be matched for time overlap. The PAEE algorithm used to analyze accelerometry data was the Freedson VM3 (2011) algorithm in ActiLife, which incorporates VM counts/min and body mass in kg. A paired t-test was run by participant ID number for PAEE in kcal/kg of body weight/min and triaxial acceleration collected simultaneously, which found a statistically significant difference between the two values. A one-sample t-test was run as a follow-up with the mean of the COSMED dataset as the test value. This exploratory analysis identified a strongly

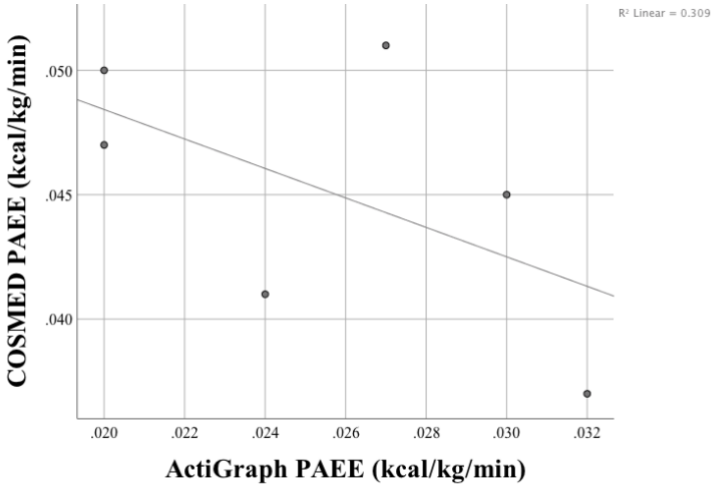
significant underestimation of PAEE by the ActiGraph device compared to the COSMED measurement. This agrees with the moderate, negative association between the two variables identified by Pearson correlation. Figure 4 depicts this heterogeneity.

Table 4. Relationships between physical activity energy expenditure (PAEE) estimated by the ActiGraph accelerometer and measured by the COSMED portable metabolic system during a bout of track walking

	Mean ± SD kcal/kg/min	**Paired t-test[1] Mean[95% CI[a]]**	**One-sample t-test[2] Mean[95% CI]**	**Pearson correlation**
ActiGraph	0.026 ± 0.005	-0.020[-0.029-0.010]**	-0.020[-0.025-0.014]***	-0.556
COSMED	0.045 ± 0.005			

*Sample size was n=6 due to missing data. [1]A paired samples t-test was run by participant ID. [2]A follow-up one-sample t-test was run with ActiGraph as the dependent variable and the test value set as the mean of the COSMED dataset. [a]CI = confidence interval. *p<0.05. **p<0.01. ***p<0.001.*

Figure 4. Relationship between physical activity energy expenditure predicted by the ActiGraph accelerometer and measured by the COSMED portable metabolic system



PAEE = physical activity energy expenditure. PAEE is expressed in terms of kilocalories (kcals) expended per kilogram (kg) of body weight per minute (min).

DISCUSSION

The results of the present investigation suggest that older, obese patients with HFpEF participating in an exercise intervention accumulated similar levels of PA on SES and other non-SES days, which included weekends. However, the large effect sizes suggest that significant differences between days may have been found with a larger sample size. Another finding of the present investigation is that current algorithms for predicting PAEE from accelerometry during a single bout of exercise in older, obese subjects with HFpEF provide estimations that are significantly different from actual PAEE levels measured using indirect calorimetry. Further study is warranted to improve the validity of estimating PAEE in older, obese patients with HFpEF.

Baseline Characteristics

Ten participants of the final eighty-five subjects participating in the SECRET II study were recruited to participate in the COSMED EE investigation. Nine of these subjects participated in the accelerometry study, and six of these were included in the accelerometry and COSMED comparison. These participants were randomly assigned to either the AT+CR (n=5) or AT+RT+CR (n=4) groups. The demographics of this sample are fairly representative of HFpEF populations and what is reported in the literature (4, 27, 83) as they were predominantly females (78%), older (avg. 68.2$\pm$7.1 years), obese (avg. BMI 37.9 kg/m^2), and mostly white (67%).

Activity Levels of Study Participants

The average daily step count achieved by this sample of older, obese patients with HFpEF was >9,000, though there was moderate variability (SE ~1,000 steps). Still,

average steps/day in this sample were well over the minimum recommendation for healthy adults (≥5,000 steps) (84). The national guideline-recommended amount is ≥7,000-8,000 steps/day for healthy older adults and ≥6,500 in older adults with chronic disease (76, 77). A step count of fewer than 5,000 daily steps is considered sedentary, which has been reported as the average for patients with HF (76, 85). One review of ten PA studies found that individuals living with chronic heart disease performed, on average, 4,684 steps/day. Heart failure patients, specifically, averaged 4,342 steps/day (86). Another study found that only 35% of patients with HF achieved 5,000-10,000 steps/day and just 15% achieved >10,000 steps. Thus, it appears the older, obese HFpEF participants in this study accumulated more steps/day than has been commonly reported for the HF population (74). Patients with the HFpEF phenotype have been consistently observed to achieve some of the lowest levels of PA, quantified by steps/day, compared to patients with HFrEF and individuals without HF. This difference between HF phenotypes has not been observed when assessing PA by minutes accrued or PAEE, suggesting that step counts may be a more robust measure of PA in this population (29, 74, 85). In fact, one study found significant differences in steps/day, time spent in light PA and MVPA, and PAEE during MVPA across the HF spectrum (non-HF controls, individuals at-risk for HF, patients with HFrEF, and patients with HFpEF) in unadjusted models, but only steps/day remained statistically significant after adjusting for covariates (29). Notably, a higher step count may be expected in the sample in the present investigation due to active enrollment in an exercise program and the use of a wrist-worn device.

The average amount of light-intensity PA accumulated by the older, obese patients with HFpEF in this study was approximately 6 hours (~365 mins) daily. No national guidelines exist for a recommended amount of weekly light-intensity PA, but reducing sedentary time with any intensity of PA, including light-intensity, is beneficial in older adults independent of MVPA, and is recommended (48, 84). Although there is limited guidance on the amount of light aerobic activity that should be acquired, the subjects of the present study accumulated more light-intensity activity than what has been reported in the literature for patients with HF. Subjects in the study by German and colleagues (73) study averaged ~33 mins/day of light PA, compared to the ~365 mins by the subjects in this study. However, PA data were collected at baseline rather than during the ET intervention. Furthermore, light-intensity PA was quantified using a uniaxial, hip-worn accelerometer and without population-specific cut-points (73). Consequently, the light PA that was quantified in the present investigation mid-ET intervention and using a triaxial, wrist-worn accelerometer will naturally be higher, which limits this comparison. The amount of daily light-intensity PA accumulated by the subjects in this study was similar to the amount of light-intensity PA, approximately 376 mins, accumulated over the course of a week by the cardiac rehab participants in the study by Ayabe and colleagues (2004) (80). Data from NHANES revealed patients with congestive HF accumulated an average of ~3.5 hours/day light-intensity PA, significantly less than the average ~4 hours/day achieved by individuals without any CV disease (CVD) (87). Though the older, obese subjects with HFpEF in this study achieved greater amounts of light-intensity PA than other patients with HF and CVD, they still achieved less than the approximately 14 hours/day that has been observed in healthy, active older adults (56).

The older, obese patients with HFpEF in this study achieved approximately 36 mins/day of MVPA which meets the guidelines for healthy adults (84). The level of MVPA in these HF subjects is much higher than the average approximately 10 mins/day observed in two separate studies of patients with HFpEF (29, 73). Patients with CVD have observed significantly lower levels of MVPA than individuals without CVD according to NHANES data, and patients with congestive HF observed the lowest levels of all CVD categories. The patients with congestive HF averaged ~9 mins/day of MVPA, while the individuals without CVD averaged ~15 mins/day of MVPA (87). Ayabe and colleagues (2004) observed slightly greater levels of MVPA with approximately 18 mins/day, on average, in their sample of cardiac rehabilitation participants (80). Only one study observed similar PA levels to the patients in the present study, with 56% of the subjects with HF participating in ≥30 mins/day of MVPA, though they were only monitored for 2 days (74). Patients with the HFpEF phenotype have observed lower levels of both light-intensity PA and MVPA than the HFrEF phenotype (29, 74). Thus, it appears that the subjects of the present investigation accumulated higher levels of daily MVPA than is commonly observed in the literature for patients with HFpEF.

The high levels of PA observed in the older, obese patients with HFpEF in this investigation should not be surprising since these subjects were participating in a randomized clinical trial with aerobic exercise prescribed according to ACSM guidelines. According to ACSM's *Guidelines for Exercise Testing and Prescription*, the aerobic exercise prescription for patients with HF is 3-5 days/week for ≥30-60 mins/day at 60-80% HRR or a Borg RPE of 11-14 (moderate-to-vigorous intensity). The recommendation type of exercise is walking and stationary cycling. The prescription for

the participants of SECRET II was based on the ACSM guidelines. Over the first 6-8 weeks of the intervention, aerobic exercise intensity and duration gradually increased up to 60-70% HRR for 20 minutes based on individual responses. Thereafter, duration was gradually increased up to 30 minutes and, once that goal was met, intensity was gradually increased up to 70-80% HRR. Exercise was completed thrice weekly and consisted of track walking and/or stationary bicycling. Thus, the cohesiveness of the exercise prescription in the present study with the current, gold standard, aerobic exercise recommendations for HF effectively increased steps/day, mins/day of light-intensity PA, and mins/day of MVPA in older, obese patients with HFpEF to levels similar to what is achieved by healthy adults and older adults. Previous studies that have reported lower levels of PA in patients with HF have only reported PA data at baseline, rather than during the intervention (73, 85). Other studies have collected PA data only cross-sectionally in HF patients (29, 74). Additionally, customized cut-points were implemented which accounted for the low absolute movement intensity of these patients. Thus, the patients with HFpEF in the present study observed higher levels of PA than in the rest of the HF literature because they were currently participating in a structured exercise program, following an individualized exercise prescription designed according to well-established ACSM guidelines for HF, data were collected mid-intervention rather than at baseline, and customized, population-specific cut-points were implemented.

The strongest correlation of PA measure in the present study was observed between SES steps/day and SES MVPA ($r=0.91$, $p<0.01$), which supports reports in the literature indicating that, in general, steps per day is an indicator of MVPA (74, 84). The aforementioned Ayabe and colleagues (2008) study observed a significant, positive, dose-

dependent relationship between daily step count and minutes of MVPA ($r=0.85$, $p<0.01$) (77). Non-SES light-intensity PA was not significantly correlated with steps/day in the present study, and light-intensity PA, in general, had weaker correlations with steps/day than MVPA did. The data obtained in the present study indicate that steps/day and minutes of MVPA may be more strongly associated with overall PA levels than minutes of light-intensity PA in older, obese patients with HFpEF. Furthermore, steps/day and minutes of MVPA may provide more information, compared to light PA, about the effectiveness of the exercise prescription for increasing PA levels in patients with HF due to comparison against established PA recommendations for healthy adults.

The Effect of a Structured Exercise Program on Daily Physical Activity Levels

Previous studies involving structured exercise programs have demonstrated behavioral compensation in participants to the increased PA levels on SES days. However, study participants, in general, have lower PA levels on the other days of the week. Wang and Nicklas (2011) observed a compensation effect to acute exercise in older, obese women undergoing an exercise intervention. Following an acute bout of moderate-intensity, structured exercise, the women decreased their PAEE for the remainder of the day, evidenced by PAEE on SES days that did not differ from baseline. For the women in the vigorous-intensity exercise group, the effect was more pronounced. Following vigorous exercise, women reduced PAEE for the remainder of the day to the degree that PAEE on SES days was significantly lower than baseline levels, while PAEE on non-SES days remained similar (79). This effect was also present in participants undergoing cardiac rehabilitation thrice weekly in the Ayabe and colleagues study (2004). The intensity of daily PA peaked during the hours of cardiac rehab, which was

significantly different from the same period on non-cardiac rehab days. However, the PA levels during remaining blocks of both days were not significantly different from each other. Thus, the significant increase in MVPA accumulated on cardiac rehab days supports the increased PAEE and steps/day observed on cardiac rehab days which was followed by a compensatory reduction in PA levels over the remainder of the day and the following day (77, 80).

The present study observed no significant difference in steps/day between SES days (~9,700) and non-SES days (~9,200) in older, obese patients with HFpEF undergoing an ET intervention. Additionally, no significant difference in steps/day was observed when analyzed by weekdays (~9,800) versus weekends (8,600), though overall step counts were high. This is in contrast to the aforementioned Ayabe and colleagues (2009) study that observed a significant and very pronounced difference in steps/day between cardiac rehab (~8,500) and non-cardiac rehab (~5,500) days in a larger sample of patients (n=77). As mentioned, the strongest correlation for SES steps/day was with SES MVPA ($r=0.92$, $p<0.01$). The strongest correlation for weekday steps/day was also with SES MVPA ($r=0.89$, $p<0.01$). Together, this emphasizes that participating in greater steps/day can increase daily levels of MVPA in these patients with HFpEF who generally have low exercise tolerance. This has implications for reaching the 6,500-8,500 step count that has been suggested to correspond to the 1,500-2,200 kcals/week PAEE important for improved CVD health outcomes (48, 77). Effect size analysis revealed a moderate effect (0.54) of SES exercise days on daily steps compared to non-SES days which suggests a greater difference in steps/day may have been observed with a larger sample size. Effect size analysis also revealed a very large effect (1.68) of weekdays on

daily steps compared to weekends. The lower activity levels observed on weekends suggest the ET intervention may have increased total activity levels during the week, but this investigation may not have been adequately powered for detecting a true effect of steps/day on weekly PA as result of the intervention.

The present investigation indicated that there were non-significant differences in light-intensity PA and MVPA between SES and non-SES days. On SES days, participants tended to perform lower levels of light PA (~ 5.8 hours/day) but higher levels of MVPA (~38 mins/day). In contrast, on non-SES days, participants tended to spend more time in light PA (~6.3 hours) and less time in MVPA (~34 mins). While these differences in daily PA levels were not statistically significant because of the small sample size and low power, effect size analysis indicates there is a large negative effect (Cohen's d=-0.71) for minutes of light PA on SES days versus non-SES days, and a large positive effect (Cohen's d=0.74) for minutes of MVPA on SES days versus non-SES days. Based on these findings, it appears that with a larger sample size, it is likely that there would have been differences in these metrics of PA. Moderate-to-vigorous PA was significantly correlated with daily steps, but light PA was not. This suggests that MVPA can be effectively increased by increasing steps/day. Performing an adequate amount of MVPA has important implications as it can increase PAEE which may be beneficial for weight management and cardiovascular disease outcomes (48).

While it appears there were no significant differences in measures of PA between SES days and non-SES days as well as weekdays and weekends, there are very few subjects in the present study so statistical power is limited. Effect size analyses suggest there may be differences that might be observed with a larger sample size. A greater

amount of steps/day and minutes of MVPA was observed in the present sample on SES days than on non-SES days. This is expected considering the subjects in this study are participating in a supervised, center-based ET intervention involving HF-specific, prescribed exercise. Interestingly, a greater amount of light-intensity PA was observed on non-SES days than on SES days. This may suggest the participants were compensating for the increased PAEE on SES days by lowering energy output for the remainder of the structured day after center-based exercise and increasing the proportion of PA spent in light-intensity on the following non-SES day, which has been observed in other studies (79, 80).

The Use of Vector Magnitude Cut-Points

To our knowledge, this is the first study to develop VM cut-points in older, obese patients with HFpEF and the first study to develop wrist-based VM cut-points in older adults (54). Creating valid cut-points for older adults has proved challenging due to the large variability in physical limitations that occurs with advancing age (49, 71). The VM cut-point developed in the present sample for light PA (1,853-4,039 VM counts/min) and MVPA (≥4,040 VM counts/min) based on free-living data in older adults is similar to the VM cut-points established by Montoye and colleagues (2020). Using a combined lab-based and free-living approach with young and middle adults, the cut-points developed for light PA (2,860-3,940 VM counts/min) and MVPA (≥3,941 VM counts/min) using wrist-worn accelerometers were able to predict free-living activity levels that were not significantly different from directly observed activity (54). The congruence of cut-points in this study with the present investigation increases the validity of our findings and holds promise for future development of wrist accelerometry. The cut-points developed in the

current investigation were high, knowing the demographics of typical patients with HF and given the comparison to Montoye and colleagues' (2020) younger, non-diseased sample. Furthermore, the sample in the current investigation achieved approximately 250 minutes of weekly MVPA which meets national guidelines for PA (84). Therefore, given that the PA levels of the present sample are similar to that of a younger, healthier age group and the aforementioned cut-points appear to have accurately quantified guideline-based levels of weekly MVPA during an ET trial suggested by the congruence between the exercise prescription and the achieved levels of PA, the use of these cut-points may be limited to patients engaging in ET and not applicable to the typical patient with HF (85). Rosenberg and colleagues (2020) recorded an average of 4.5 hours of daily light PA and ~1 hour of MVPA in a large sample of older adults (n=954) using a hip-worn ActiGraph device (88). Compared to the sample in the current investigation that accrued approximately 6.1 hours of daily light PA and ~0.6 hours of MVPA, wrist accelerometry was able to predict similar levels of activity. Furthermore, the Rosenberg and colleagues (2020) study also found that daily time spent in MVPA significantly decreased in a dose-response manner with increased age. Daily MVPA also significantly decreased by approximately 15 minutes when comorbidities or obesity were present. These findings increase the validity and comparability of the PA levels in the present sample of older, obese patients with HFpEF (88).

Only one study thus far has established a sedentary VM cut-point (<1,853) for the non-dominant wrist in older adults, which underestimated daily sedentary time by just 23 minutes compared to the activPAL, a thigh accelerometer that has repeatedly demonstrated a high degree of accuracy measuring sedentary behavior (82). For this

reason, 1,853 VMs were used to establish a sedentary cut-point in our sample. This is supported by another study that found the mean difference between hip and wrist accelerometry was minimized when estimating sedentary time (<2,000 VM counts) in free-living older women (75).

Comparison Between Energy Expenditure Predicted by Accelerometry and Indirect Calorimetry

No wrist-based accelerometry algorithms have been developed or validated to predict PAEE thus far. The ActiLife software contains a "Worn on wrist?" feature that can be selected when scoring data to scale-down PAEE from hip-based VMs based on an unspecified, internal algorithm (69). This feature allowed for a better comparison between PAEE predicted by wrist accelerometry and PAEE assessed by indirect calorimetry in the present investigation, compared to if the hip-based algorithm had been used alone. Using VMs also improved the comparison because this unit has observed greater accuracy in predicting PAEE than using counts/min (71). The present study found that wrist-worn accelerometry significantly underestimated PAEE during track walking in a small sample of older, obese patients with HFpEF compared to indirect calorimetry.

As mentioned, accelerometry research for estimating PAEE in older adults is lacking. One study found a hip accelerometer was unable to predict PAEE that was statistically similar to indirect calorimetry during rest, aerobic MVPA, or a functional task in an older adult sample, but was able to do so in two younger samples (71). Another study was also able to predict PAEE up to 6 METs using wrist accelerometry compared to indirect calorimetry, but only young, healthy participants were used (50). Both studies

employed laboratory approaches which limits applicability to free-living settings. The significant underestimation of PAEE in the present study agrees with available evidence from younger populations, emphasizing that further study is warranted to establish valid methods for predicting EE by wrist accelerometry. Predicting PAEE using wrist accelerometry and the Freedson VM3 (2011) algorithm in ActiLife has observed only moderate correlation with indirect calorimetry and low reliability, but both hip- and wrist-worn devices can significantly underestimate PAEE (70). This result has not been consistently found, however, and both wrist and hip locations have demonstrated high reliability using VMs elsewhere (89). A review of 19 accelerometry and DLW-predicted PAEE studies in free-living adults, 5 of which used wrist devices, concluded that all accelerometry-predicted PAEE should be interpreted with caution due to large heterogeneity for explained variance in PAEE among studies (R^2=0.04-0.80). Interestingly, the variance did not significantly differ by wear location and sample size was the only factor to significantly correlate with R^2 (67). This may suggest that, despite a greater breadth of literature on PAEE predictions using hip accelerometry compared to the wrist, accelerometry in general struggles to accurately and reliably predict PAEE. Furthermore, estimating PAEE requires more specificity in prediction than estimating minutes of PA due to the calculations required for conversion of counts to units of PAEE, which increases the difficulty of quantifying PAEE accurately. Additionally, studies thus far have focused on young and middle adults with little to no study on older adults or individuals with chronic disease. Only one study was found to compare five PAEE prediction equations using hip accelerometry in older adults in a home-based setting intended to replicate free-living. When compared to indirect calorimetry, each equation

was found to over- or underestimate PAEE (68). This is important to the study of HF because patients with HF have observed significantly lower PAEE compared to non-HF controls. Increasing PAEE via ET may improve disease management and weight loss outcomes (72). The high variability among accelerometry and PAEE studies emphasizes the need for further research. The results of the current investigation support the evidence in the literature demonstrating wrist-worn accelerometers underestimate true PAEE. These data are strengthened by the novel use of wrist accelerometry in an older adult sample with HF. However, due to the inherent nature of the present ET intervention, the data obtained may not be applicable to individuals not participating in ET.

Limitations

There are a number of limitations in the present study. The data related to step counts should be interpreted with caution. Evidence has shown that wrist-worn accelerometers tend to overestimate step counts compared to hip accelerometers in free-living settings. Accelerometry in general also overestimates steps compared to pedometers, which are the instruments that comprise the bulk of step count studies (75, 76). The VM cut-points for MVPA developed in the present investigation used data from older patients with HFpEF participating in an ET intervention and therefore may not be generalizable to inactive older adults or the typical patient with HF. Despite ActiLife's internal algorithm for scaling down wrist-predicted PAEE from an equation designed using hip accelerometry, no algorithms for wrist accelerometry have been developed and validated using randomized controlled trials thus far. Additionally, the Freedson VM (2011) equation used in the present analysis was developed using young adults which do not have comparable physical capabilities or metabolic rates to older adults. Therefore,

the PAEE results in the present study must be interpreted cautiously and viewed as purely exploratory. Lastly, power calculations were not performed, and sample sizes were small for PA metrics (n=9) and the PAEE comparison (n=6). Therefore, whether statistical analyses were powered adequately to find significant results is unknown.

Strengths

The present study also had many strengths. To our knowledge, this was the first study to develop wrist-worn accelerometry cut-points in older adults as well as patients with HF and only the second study to formulate wrist cut-points for any population. Our results agree with the other developed cut-points, increasing the validity of our light PA and MVPA findings. Validity was also improved due to the use of indirect calorimetry as the criterion measure rather than subjective observation or self-report, as well as the implementation of triaxial VMs. Accelerometers were worn while free-living which increases external validity. The PA levels of our sample were high for both light PA and MVPA which suggests that the SECRET II ET intervention may have been effective at improving global levels of PA in a typically sedentary population, though differences in PA metrics between SES and non-SES days did not reach statistical significance.

Future Directions

Further study is needed to develop valid and reliable cut-points using wrist accelerometry in all populations. Developing more customized cut-points using existing datasets may improve methods for quantifying PA levels in other populations. Numerous studies have explored the validity of PAEE equations using hip-worn accelerometers but without consistent results, and no studies have developed algorithms for predicting PAEE

using wrist-worn accelerometry. Daily step counts may be the most robust measure for assessing PA in individuals with chronic conditions like HFpEF at this point in time and should be considered as the primary outcome for ET studies seeking to improve active behavior in these populations. A trial comparing patients with HF participating in ET and patients with HF not participating in ET would be needed to further explore this hypothesis.

Conclusion

In conclusion, daily steps, minutes of light PA, and minutes of MVPA did not differ significantly on a daily basis in a small sample of older, obese patients with HFpEF participating a thrice weekly ET intervention. Evidence collected by accelerometry demonstrated that this sample was more active than the typical patient with HF in the literature, with PA metrics equal to those observed in healthy adults. Finally, wrist-worn accelerometry significantly underestimated EE measured by indirect calorimetry during track walking in patients with HFpEF. The intervention may have improved total levels of weekly physical activity, but further study using a larger sample size and a non-ET control group would be needed to explore this observation.

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CURRICULUM VITAE

Education

Wake Forest University

Master of Science Candidate, Health and Exercise Science, expected May 2021

California Polytechnic State University, San Luis Obispo

Bachelor of Science, Kinesiology, June 2019

Concentration: Exercise Science

Clinical Experience

Healthy Exercise & Lifestyle ProgramS (HELPS), *Cardiovascular Lab Coordinator* May '20-Present

Healthy Exercise & Lifestyle ProgramS (HELPS), *Graduate Student Staff* Aug '19-May '20

Research Experience

Master's thesis: *Quantifying physical activity levels in older, obese patients with heart failure*

ExTra-MATCH III: Meta-analysis of exercise training in HFpEF, *Data Assistant* Jan '21-Present

Study Examining Caloric Restriction and Exercise Training (SECRET) II Study, *Volunteer*

Oct '19-Feb '20

Other Exercise Experience

Wake Forest Wellbeing Center, *Graduate Assistant* Aug '19-Present

Cal Poly Recreation Center, *Certified Personal Trainer* Mar '17-Jun '19

Certifications & Membership

American College of Sports Medicine, Clinical Exercise Physiologist Mar '21-Present

American Heart Association, Basic Life Support Aug '19-Present

National Academy of Sports Medicine, Personal Trainer Oct '16-Oct '20