Dyspnea in Heart Failure with a Preserved Ejection Fraction

BY

KAREN M. VUCKOVIC

B.S., University of Illinois, Champaign-Urbana, 1979

B.S.N., Creighton University, Omaha, Nebraska, 1981

M.S., Northern Illinois University, DeKalb, 1995

THESIS

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Defense Committee:

Mariann R. Piano, RN, PhD, Chair and Advisor
Eileen Collins, RN PhD
Lauretta Quinn, RN, PhD
Catherine Ryan, RN, PhD
Dorie W. Schwertz, RN, PhD
Shane Phillips, PT, PhD, Department of Applied Health Sciences

This dissertation is dedicated to my husband, Victor.

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LIST OF ABBREVIATIONS

6MW	Six-minute walk
6MWT	Six-minute walk test
ACE	Angiotensin-Converting Enzyme Inhibitor
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
ARB	Angiotensin Receptor Blocker
ATS	American Thoracic Society
a-vO_2	Arteriovenous difference
BA	Brachial artery
BART	Brachial Artery Ultrasound
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood pressure
Bpm[a]	Beats per minute
Bpm[b]	Breaths per minute
Cm	Centimeter
CCB	Calcium channel blocker
CRC	Clinical Resource Center
CO	Cardiac output
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease

EF	Ejection fraction
FEV_1	Forced expiratory volume in 1 second
FMD	Flow-mediated dilation
GFR	Glomerular filtration rate
HDL	High density lipoprotein
HF	Heart failure
HFPEF	Heart failure with preserved ejection fraction
HFREF	Heart failure with reduced ejection fraction
HR	Heart rate
HRR	Heart rate recovery
HTN	Hypertension
K	Potassium
kg	Kilograms
LA	Left atrium
LV	Left ventricle
MCID	Minimally important clinical difference
MHz	Mega Herz
mL	Milliliter
mm	Millimeter
mmHg	Millimeters of mercury
MRC	Medical Respiratory Council Dyspnea Scale
NO	Nitric oxide
NYHA	New York Heart Association

O_2	Oxygen
PCO_2	Partial pressure of carbon dioxide
pH	Hydrogen ion concentration
PO_2	Partial pressure of oxygen
Peak VO_2	Peak oxygen consumption
PI	Primary Investigator
PP	Pulse pressure
RARS	Rapidly adapting receptors
RR	Respiratory rate
SARS	Slowly adapting receptors
SD	Standard deviation
SEM	Standard error of the mean
SpO_2	Oxygenation saturation
TNF	Tissue necrosis factor
VAS	Visual analogue scale
VO_2	Oxygen consumption

SUMMARY

Dyspnea is the cardinal symptom of heart failure (HF) and the leading reason patients seek medical care, but its pathophysiological mechanisms and correlates are incompletely understood. The purpose of this study was to describe and compare the level of dyspnea in African American patients > 50 years of age with preserved vs. reduced ejection fraction heart failure (HFPEF vs. HFREF) before and after the 6-minute walk (6MW) test. Self-reported dyspnea scores (Borg, Visual Analogue [VAS], and Likert Scales) were correlated to selected physiologic factors (blood pressure, oxygenation saturation) associated with dyspnea. In a subset of patients flow-mediated dilation (FMD) was measured to determine if there was an association between dyspnea and endothelial function. We enrolled a convenience sample from an established HF clinic. Baseline characteristics did not significantly differ between HF groups other than ejection fraction ($p < .001$) and the use of angiotensin-converting enzymes (ACE) inhibitors ($p < .001$). Compared to HFREF, more patients with HFPEF consistently reported dyspnea (vs. no dyspnea) at baseline using the Borg and VAS scales. However, the occurrence of dyspnea was equivocal for the HFREF group and differed based upon the tool used (Borg 34% vs. VAS 81%). Using Borg scores, both groups experienced significant increases in dyspnea of a similar magnitude during the 6MW test ($p < .001$). Both groups were still significantly dyspneic after 3 minutes of recovery compared to baseline scores ($p < .001$). Again decreases were of a similar magnitude. There were no significant correlations between dyspnea scores and physiologic variables. Lastly, FMD was impaired in both HF groups at baseline. However, in the HFREF group, the 6MW test was associated with further impairments ($p < .02$) and FMD correlated with dyspnea scores during recovery.

In summary, the 6MW test was an effective strategy to examine dyspnea in patients with HF. Patients with HFPEF reported more dyspnea at baseline but results varied with the tool used. Therefore, we recommend using two dyspnea tools at rest and with activity to evaluate dyspnea in chronic HF. Our study was the first to examine dyspnea scores between African Americans with HFPEF vs. HFREF before and after the 6MW test.

I. INTRODUCTION

A. Foreword

Anyone may experience dyspnea or shortness of breath at high altitudes or following exhaustive exercise, but for patients with heart failure (HF) dyspnea is a burdensome symptom which may occur even at rest. Dyspnea, the most common symptom of HF, limits the individual's ability to perform simple daily activities. Despite dyspnea being the primary reason that patients with HF seek health care (Adams et al., 2005; Pang et al., 2008; Patel, Shafazand, Schaufelberger, & Ekman, 2007), our understanding about its characteristics and physiological mechanisms is incomplete. Current HF treatment guidelines do not directly address the management of dyspnea aside from administering diuretics (Hunt et al., 2009; Lindenfeld et al., 2010).

Heart failure can be divided into two clinical phenotypes *reduced* and *preserved* ejection fraction (formerly known as systolic and diastolic HF respectively). In heart failure with reduced ejection fraction (HFREF), myocardial contractility is impaired resulting in inadequate stroke volume; whereas heart failure with a *preserved* ejection fraction (HFPEF) is associated with impaired relaxation, stiffening of the left ventricle and increased filling pressures. To date, the majority of clinical HF trials have enrolled patients with HFREF, which has led to evidence based treatment guidelines specific to this phenotype. In contrast, few randomized controlled trials have included patients with HFPEF (Ahmed et al., 2006; Kitzman, Brubaker, Morgan, Stewart, & Little, 2010; Massie, Carson, McMurray, 2008; Yusuf, Pfeffer, Swedberg, Granger & Held, 2003). More than 50% of patients with HF have HFPEF and the estimated prevalence of HFPEF within the general population is approximately, 1.1-5.5% (Bibbins-Domingo et al., 2009;

Go et al., 2012). Despite this rising prevalence, our understanding about the pathophysiology and management of HFPEF is incomplete. And there are no specific treatment guidelines for patients with HFPEF in the U.S.

Heart failure occurs in all ethnicities; however, African Americans are disproportionately affected by HF (Go et al., 2013). The reasons for this disparity are unclear. African Americans develop HF at an earlier age, have the highest risk of developing HF (4.6 per 1000 person-years), and the highest rate (75%) of incident HF not attributable to myocardial infarction (Bahrami et al., 2008). Data from epidemiological studies and HF registries have found HFPEF patients to be older, hypertensive and to have a history of atrial fibrillation (Shah, 2012). However, in terms of HFPEF, African Americans have been underrepresented in nearly all the HFPEF trials. Therefore it is not clear if the same risk factors (e.g., hypertension, atrial fibrillation), symptoms such as dyspnea, and other pathophysiologic features (endothelial dysfunction) are also prominent in African Americans.

B. Study Purpose, Hypothesis, and Aims

The **purpose** of this prospective study was *to describe and compare the level of dyspnea in African American patients with HFPEF vs. African American patients with HFREF before and after a single bout of physical activity (i.e., 6-minute walk test).* In addition, physiologic factors associated with dyspnea such as heart rate (HR), blood pressure (BP), and oxygenation saturation (SpO_2) were also evaluated before and after the 6-minute walk (6MW) test to determine if there was an association between these factors and the severity of dyspnea. Finally in a subset of patients flow-mediated dilation (FMD) was measured to determine if there was an association between dyspnea and endothelial function. The specific aims and hypotheses were as follows:

Aim #1: To determine the occurrence of dyspnea experienced at rest, during, and after physical activity (6MW test) in patients with HFPEF compared to patients with HFREF using four questionnaires: Medical Research Council (MRC) dyspnea scale, modified Visual Analogue Scale (VAS), 7-point Likert (Likert) scale, and Modified Borg (Borg) scale.

Hypothesis #1: Both HF patient groups will report an increase in dyspnea following the 6 MW test. The HFPEF group will report higher dyspnea scores compared to the HFREF group following the 6MW test.

Aim #2: To describe the physiologic alterations that may occur during and after the 6MW test (i.e., respiratory rate [RR], oxygen saturation [SpO_2], blood pressure [BP], pulse pressure [PP], heart rate [HR], heart rate recovery [HRR] and 6MW distance) and to determine how these parameters correlate with self-reported dyspnea in patients with HFPEF and HFREF.

Hypothesis #2: There will be an increase in RR, BP, and HR in both groups. Increased dyspnea will be associated with a decreased ability of physiologic/hemodynamic parameters to return to baseline following the 6MW test and the 6MW test will cover a shorter distance.

Aim #3: To characterize peripheral vascular endothelial function in patients with HFPEF and HFREF by measuring flow-mediated dilation (FMD) assessed by non-invasive ultrasound and determine the association between vasoreactivity and self-reported dyspnea.

Hypothesis #3: Endothelial function will be impaired in both groups and will be positively correlated with dyspnea scores.

Most patients with HF experience dyspnea (85-96%; Ziles & Brutsaert, 2002) but it is not clear whether all patients with HF (HFPEF vs. HFREF) experience the same level of dyspnea at rest and with activity/exercise. Nor has it been established whether underlying physiologic factors, such as SpO_2 influence dyspnea experienced with activity such as walking (Borlaug & Paulus, 2011; Borlaug et al., 2006). Therefore, in addition to measuring patient reported dyspnea,

we measured physiologic factors associated with dyspnea such as heart rate (HR), blood pressure (BP), and oxygenation saturation (SpO_2) at rest, during the 6-minute walk (6MW) test and during a 3-minute recovery phase.

It is known that impaired endothelial function (or endothelial dysfunction) is associated with reduced exercise tolerance, impaired functional capacity (Katz, Krum, Khan, & Knecht, 1996; Nakamura et al., 1994) and increased mortality (Katz et al., 2005). It is also well known that endothelial function is impaired in the peripheral (Katz et al., 1992), coronary (Treasure et al., 1990) and pulmonary (Porter et al., 1993) circulations in patients with HF. Clark, Poole-Wilson, and Coats (1996) hypothesized that peripheral rather than central mechanisms may play the lead role in adaptations to exercise in HF patients. As noted in more detail below, changes in blood flow in the periphery may initiate and influence the onset of dyspnea in HF patients. However, the association between endothelial dysfunction, which is a key mediator of vascular reactivity and therefore blood flow, and dyspnea in HF patients has not been examined. For this study, we examined peripheral vascular endothelial function using brachial artery ultrasound to measure FMD.

Often, patients with HF experience dyspnea with physical activity and may unknowingly limit their activity level to avoid symptoms (Pina & Daoud, 2004). This is especially important in HFPEF because these patients are more sensitive to variations in HR and may experience dyspnea predominantly with activity, meaning that activity-associated changes in HR may precipitate symptoms (Borlaug et al., 2010). Consequently, we will study patients' reports of dyspnea as related to physiologic measures of HF at rest *and* after a standardized 6MW test. The concern is that untreated or unrecognized dyspnea will lead to avoiding activity, and in turn lead to inactivity and physical deconditioning. The implications of this study are particularly

important for African Americans with HF since they have greater functional decline and doubled mortality rates compared with their Caucasian counterparts.

C. Novelty of the Study

Heart failure-REF and HFPEF are two different phenotypes of the syndrome of HF. To date, the majority of studies enrolling patients with HF have included patients with ejection fraction (EF) < 40% and used improved mortality as a primary outcome. To our knowledge there are no data which examined the relationship among dyspnea scores, 6MW test results (distance), and HRR in African American patients over 50 years of age with HFPEF. In addition, the association between dyspnea scores and endothelial function using high resolution ultrasound in patients with HFPEF before and after activity has not yet been investigated.

II. OVERVIEW OF THE LITERATURE

A. Introduction

Over the last 20 years, therapeutic advances have decreased the morbidity and mortality rates associated with HFREF. However, the prognosis remains unchanged for patients with HFPEF (Kitzman, 2011; Unzek & Francis, 2008). In the past, HF researchers excluded patients with HFPEF from clinical trials. As a result, evidence-based treatment and symptom management for HFPEF is limited, as demonstrated by a review of the current HF guidelines (Hunt et al., 2009; Lindenfeld et al., 2010). Importantly, HFPEF is now recognized as the fastest growing form of HF in the United States; approximately 50% of the 5 million Americans who have HF have a *preserved* or normal ejection fraction (Roger et al., 2011). Despite its significance and a growing body of research, gaps remain in our understanding of the pathophysiology of HFPEF and its related symptomatology; specifically, dyspnea. Also, among HF patients, dyspnea continues to be the leading cause for why patients seek medical care. This chapter provides an overview of the literature related to dyspnea and HFPEF, in order to provide a better understanding of the variables measured in this study.

B. Definition and Language of Dyspnea

Although there is no universally accepted definition of dyspnea, it is commonly defined as a "subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity" (American Thoracic Society [ATS], 1999; 2012). In other words, "dyspnea" implies that the individual is *aware* of their own difficulty in breathing. The terms shortness of breath and breathlessness are used interchangeably with dyspnea. Yet, many disagree that dyspnea and breathlessness are synonymous since the intensity and quality of

breathlessness are measureable and occur with exertion, whereas dyspnea may occur unexpectedly, such as during rest (Ambrosino & Serradori, 2006). Mahler (2005) and other suggest that breathlessness is not the same as dyspnea, but rather a component of dyspnea; that is, breathlessness is one of many uncomfortable sensations that can be experienced during dyspnea. In fact, a variety of specific sensations such as "chest tightness" or "effort in breathing" may contribute to the overall sensation of "dyspnea." Experts agree that dyspnea does not arise from an exclusive sensory pathway and is not a single sensation (ATS, 2012). Instead dyspnea comprises multiple pathways and sensations that can, in some cases, be measured as distinct sensations and linked to a specific physiological process (Sheel, Foster, & Romer, 2011). In this paper, dyspnea as defined by the American Thoracic Society (2012) will be used to describe uncomfortable breathing with both activity and at rest. Breathlessness will used to describe one of the sensations experienced during dyspnea.

Early research conducted by Simon and colleagues (1989; 1990) investigated whether different neurophysiological stimuli mediated distinct breathing sensations in healthy adults and cardiopulmonary patients. Simon et al. (1989) investigated whether dyspnea-related sensations could be induced in healthy subjects (N = 30) using different stimuli. Following each stimulus, subjects were asked to choose a descriptor of their breathing sensation. The investigators concluded that subjects selected certain descriptors in response to specific stimuli. This association provided the initial evidence that dyspnea may encompass several sensations and not be explained by a single physiologic mechanism. In a subsequent study with cardiopulmonary patients of various etiologies (N = 53), Simon et al. (1990) used cluster analysis to determine if there was an association between descriptors of dyspnea and the subject's pathophysiological conditions. Again investigators found that patients chose qualitative descriptors relative to a specific condition. For example, the descriptors related to the exhalation cluster were chosen by

patients with asthma. Congruent findings from studies in other cardiopulmonary patients led researchers to propose that the patients choice of descriptors is disease specific and reliable (*N* = 169; Elliot et al., 1991; *N* = 218; percent agreement 68%; *r* = 0.69; *p* = 0.004; Mahler et al., 1996). In particular, Mahler et al. (1996) found that the descriptor "suffocating" was used more frequently by patients with HF (*n* = 17 [5 females]; EF < 50%).

Other investigators have found that in addition to the individual's pathological condition, the patients' choice of descriptors may vary by gender. Ekman, Boman, Olofsson, Aires & Swedberg (2005) compared descriptors between men (*n* = 47) and women (*n* = 40) with HF. The descriptor ("I feel that I am suffocating") was selected by both men and women, with more males choosing "suffocating" (*p* = 0.01). Caroci and Lareau (2004) compared descriptors between male patients with COPD (*n* = 30) and male HF patients (*n* = 30) and found that the descriptor "suffocating" was endorsed equally by both groups. Notably, both groups experienced dyspnea with similar intensity and frequency (COPD [chronic obstructive pulmonary disease] subjects reported experiencing *severe to very severe* dyspnea 13.1 ± 10.8 times per month, whereas HF subjects reported a frequency of 12.1 ±11.9 times per month: *p = 0* .79). On the other hand, Ekam and colleagues (2005) found that women tended to describe their symptoms with greater variability than men. For example, of the 11 descriptors presented to the subjects, no descriptor was scored significantly higher by women.

Collectively these findings highlight the challenges in characterizing dyspnea. It is likely that different sensations of dyspnea may be influenced by age and gender as well as underlying pathological processes. Currently the best characterized physiological processes which have been linked to corresponding sensory descriptors are: (a) work/effort with diseases that impair respiratory muscle performance; and (b) tightness with bronchoconstriction, such as the

sensation commonly experienced with asthma (ATS, 2012). The majority of physiological-based dyspnea research has been conducted with pulmonary patients.

The descriptor, air hunger, indicating unsatisfied inspiration has been used by cardiopulmonary patients to describe uncomfortable breathing at rest and during exercise. It is thought to be the result of the imbalance which develops between the neurophysiological mechanisms driving inspiration and the afferent feedback from the mechanical or sensory receptors in the respiratory system. In other words, stimuli (exercise, hypercapnia, or hypoxia) induce inspiratory drive or demand but ventilatory capacity is limited causing uncomfortable breathing. Various terms have been used to describe this imbalance such as efferent-reafferent dissociation (Mahler & O'Donnell, 2005) motor command-afferent mismatch (Nishino, 2011), and neuromechanical uncoupling (Clark et al., 1999). This sensation has been reported by pulmonary patients undergoing symptom-limited stress testing (Scano, Innocenti-Bruni, & Stendardi, 2010) and HF patients treated in an emergency department (Parshall et al., 2001). Ventilatory imbalance or mismatch resulting in uncomfortable breathing at rest and with activity in patients with HF is an underpinning of our study.

In summary, experts agree dyspnea is comprised of various sensations produced by a variety of stimuli and some descriptors are disease specific. Consequently, it is unlikely that the same sensation will be reported by all patients. Common descriptors reported by patients with HF are "suffocating" and descriptors related to unsatisfactory inspiration. Furthermore, patients with HF, in particular, HFPEF, frequently have pulmonary related comorbidities (e.g., asthma) which may influence their description of their respiratory symptoms.

C. Mechanics of Normal Breathing

Breathing is centrally coordinated by the respiratory center located in the medulla oblongata and pons. Neurons in this region of the brainstem respond to various sensory stimuli,

such as the partial pressures of arterial carbon dioxide ($PaCO_2$) and oxygen (PaO_2), and lung stretch, which are transmitted by central and peripheral chemoreceptors and mechanoreceptors respectively. The frequency (rate) of breathing and tidal volume are tightly regulated to maintain PaO_2, pH, and $PaCO_2$ within a normal range under varying conditions, such as exercise. Although the rate and depth of breathing does not require a conscious effort, it can be voluntarily modified (breath-holding or intentional hyperventilation) by commands from the cerebral cortex.

The brainstem controls breathing by processing sensory information from several types of sensory receptors, and in turn sends impulses to activate the respiratory muscles. These sensory receptors include: (1) central chemoreceptors in the medulla sensitive to CO_2; (2) peripheral chemoreceptors in the carotid and aortic bodies predominantly detecting O_2; (3) mechanoreceptors in the lungs, joints, and muscles; (4) pulmonary stretch receptors in the smooth muscle of the upper airways; and (5) J (juxtacapillary) receptors on the end of afferent C-fibers in the alveolar wall adjacent to the capillaries. For some cases certain pathological conditions are known to be associated with the activation of specific receptors types. For example, the engorgement of the pulmonary capillaries that occurs in pulmonary congestion is thought to be sensed by J receptors which in turn, activate C-fibers resulting in rapid, shallow breathing (Nishino, 2011). Thus, under certain pathological conditions activation of C-fibers may mediate a change in breathing pattern that results in an increased rate and smaller tidal volume which patients describe as "uncomfortable" or difficult breathing. Several receptors types, when activated, produce dyspnea; however, we will focus on peripheral receptors that are important during exercise.

D. Breathing During Exercise

In healthy individuals, under normal conditions, the most important factor in the control of breathing is the arterial PCO_2 level but the prevailing mechanism(s) during exercise are not as

clear. Dejours (1963), one of the first investigators to study ventilatory changes during exercise, concluded that the cause of increased ventilation during exercise is likely due to the interrelationship between input from peripheral sensors, that is, local physical and chemical changes in active muscle (peripheral mechanoreceptors) and central command (brainstem). In other words, ventilatory response to exercise is not solely, centrally mediated but is influenced by the metabolic changes in the peripheral tissues, including respiratory and skeletal muscle.

During light to moderate exercise ventilation increases but $PaCO_2$ levels do not rise and PaO_2 levels increase slightly while pH remains constant. None of these factors are likely to account for a large increase in ventilation during exercise (West, 2005). This suggests that during physical activity such as walking peripheral factors may contribute to ventilatory response.

In patients with HF, it has been hypothesized that hypoperfusion and fatigue in the skeletal and respiratory muscle groups may influence the ventilatory response to exercise (Buchanan & Richerson, 2009; Cahalin et al., 2013; Piepoli & Coats, 2013). This hypothesis is the basis of the skeletal muscle hypothesis or model which was developed to explain exercise intolerance in patients with HF. This model is an important underpinning for our study (Piepoli et al., 1996).

E. Pathophysiology of Dyspnea

Dyspnea is the result of the interactions among physiological, psychological, social, and environmental factors and is analogous to the perception of pain (Lansing, Gracely, & Banzett, 2009). Similar cortical-limbic processes appear to underlie both symptoms although less is known about the underlying mechanisms of dyspnea in HF. Experts agree that dyspnea (like pain) consists of sensory (intensity) and affective (unpleasantness) dimensions (Mahler et al., 2010).

1. Neural Pathways

Neuroimaging studies suggest that dyspnea activates several areas of the cortex in particular the insula and amygdala (Banzett et al., 2000; Herigstad, Hayen, Wiech, & Pattison, 2011). Interestingly, the insular cortex is associated with emotion and autonomic homeostatic mechanisms while the amygdala is associated with emotion and memory. Patients often state once they experience dyspnea they become fearful of evoking the symptom again. Consequently, they avoid physical activity becoming further deconditioned. Dyspnea varies between patients and conditions. Dyspnea is weakly correlated with disease severity suggesting that dyspnea is modulated by cognitive and affective factors. Presently the number of neuroimaging studies is few and it is difficult to draw solid conclusions based on the evidence related to the affective factors contributing to dyspnea. Thus it is important to acknowledge that dyspnea has an affective component which may influence someone's level of activity but it was not measured in our study.

2. Sensory Receptors in Heart Failure

Dyspnea can occur when the ventilatory response is disproportionate or mismatched to the level of activity; for example, an individual hyperventilating at rest. Recently, Piepoli and Coats (2013) describe this type of ventilatory response as "overventilation." It is the abnormal ventilatory response characteristic of patients with HF that is of interest in this study.

As previously discussed, the process of ventilation is the response of the interplay among several types of central (brainstem) and peripheral receptors (skeletal muscle and the respiratory system) to various stimuli. Table I summarizes these relationships.

TABLE I

LOCATION OF SENSORY RECEPTORS AND ASSOCIATED STIMULI

Receptor Type	Receptor Location	Stimuli	Quality Descriptor
Central Chemoreceptor	Medulla	Hypercapnia Changes in pH	Air hunger
Peripheral Chemoreceptors	Carotid and aortic bodies	Hypoxia	Air hunger
Peripheral Chemoreceptors	Skeletal muscle Respiratory muscle	Hypoxia	Air hunger
Metaboreceptors	Skeletal muscle	Metabolic by- products (Lactate, pH, K)	
Chest wall Mechanoreceptors	Muscle, joints, and tendons in chest wall	Muscle contraction Muscle fatigue Mechanical loads	Work Increased sense of effort
C fibers or (J receptors)	Bronchial and pulmonary circulation	Bronchoconstriction	Chest tightness Suffocation
Vagal receptors	Smooth muscle airways	Distention of vasculature	

Note: Air hunger is associated with multiple descriptors. Adapted from ATS, 2012; Nishino, 2011; Sheel, Foster, & Romer, 2011; West, 2005; Widdicombe, 2001; K = potassium.

In patients with HF, several types of receptors may contribute to or relieve dyspnea. For example, stretch receptor types located in the upper airways mediated by the vagus nerve may contribute to dyspnea and are activated during pulmonary congestion. In contrast, the slowly adapting stretch receptors (SARS) found in the smooth muscle cells of large airways are important in inhalation and stimulation of these receptors decreases the sensation of dyspnea (Sheel et al., 2011). Other receptor types involved in inhalation and exhalation are the non-myelinated rapidly adapting stretch receptors (RARS). These fibers connect to myelinated vagal

afferent fibers and are activated by mechanical and chemical irritants, inflammatory and immunological mediators, and pathological changes in the airways and lungs (Widdicombe, 2001). It is believed that SARs and RARs are the receptors types that mediate the response to inhaled furosemide to relieve dyspnea (Sudo, Hayashi, & Nishino, 2000; Sheel et al., 2011). Another vagal-mediated receptor in the lung is the juxtaalveolar or J-receptor found in pulmonary and bronchial circulation. These receptors transmit afferent input via unmyelinated vagal C-fibers. J-receptors are of interest in patients with pulmonary congestion and acute dyspnea since these receptors respond to or are activated by increased interstitial fluid outside the capillaries. In this study, patients who are experiencing pulmonary congestion will not be enrolled.

Two peripheral receptors not associated with pulmonary congestion, but important in understanding the potential mechanisms contributing to dyspnea during exercise in HF patients are the metaboreceptors and mechanoreceptors. Together these receptors are referred to as ergoreceptors.

Metaboreceptors are peripheral nerve endings located in skeletal muscle and respond to local changes in the cellular environment such as lactate, potassium (K), and pH (Scott, Davies, Coats, & Piepoli, 2002). Thus these peripheral sensors respond to hypoxia and cellular by products, and as such are influenced by skeletal muscle metabolism.

Mechanoreceptors are peripheral nerve endings which respond to stretch. Afferent signals from mechanoreceptors in the joints, tendons, and muscles of the chest wall project to the brain and may contribute to the sensation dyspnea. For example, in healthy adults, if the respiratory muscle spindles are activated out of phase with the respiratory cycle it can create the sensation of dyspnea. Although studies examining stimulation and activation of the intercostal and phrenic

afferent fibers in human subjects are limited, investigators speculate signals from these fibers probably play a role to generate and modulate dyspnea (Sheel et al., 2011).

F. Dyspnea in Heart Failure: Muscle Hypothesis

Campbell and Howell (1963) proposed that dyspnea is the result of a mismatch between central ventilatory drive and the magnitude of ventilation produced. In other words, dyspnea occurs when there is dissociation between signals to the respiratory muscles and the incoming afferent information from chemoreceptors, mechanoreceptors and metaboreceptors (Nishino, 2011).

The underlying assumption that sensory information causes inappropriate ventilation is a fundamental concept to the skeletal muscle hypothesis (also known as the muscle hypothesis) proposed by Coats, Clark, Piepoli, Volterrani, and Poole-Wilson (1994) to explain HF symptomatology. The muscle hypotheses proposes that skeletal muscle abnormalities in HF result in activation of muscle mechanoreceptors and metaboreceptors (ergoreceptors), leading to an increase in ventilation via myelinated and non-myelinated muscle fibers, producing two common HF symptoms, a sensation of breathlessness and the perception of fatigue. In addition, mechanical and metaboreceptors may drive the increased sympathetic activity seen in HF and in turn, increase peripheral resistance, decrease muscle perfusion and reinforce sympathetic activation (Coats et al., 1994; Francis, Cohan-Solal, & Lageart, 1999).

G. Dyspnea, the Skeletal Muscle Hypothesis, and Endothelial Dysfunction

In well-conditioned healthy adults, skeletal muscle fatigues with exertional exercise. In patients with HF, simple activities (such as walking) may provoke dyspnea and fatigue, and at times be equivalent to exertional fatigue experience by healthy adults. At first, the mechanisms of these HF symptoms seem apparent; namely, skeletal muscle hypoperfusion related to reduced cardiac output and a blunted response to increase cardiac output during exercise. Theoretically,

patients with HF and muscle hypoperfusion/fatigue should improve with inotropic agents (enhance contractility) and vasodilating drugs (decrease peripheral resistance; reduce afterload); however this is not always the case. In fact, hemodynamic function correlates poorly to exercise capacity, thereby pointing toward the periphery as an important determinant of dyspnea and fatigue (Clark, Poole-Wilson, & Coats, 1996). The relationship among hemodynamics, peripheral factors, and exercise capacity is best explained by the Fick equation.

$$VO_2 = CO \times (a\text{-}vO_2) \text{ ml/kg/min}$$

Pulmonary oxygen consumption (VO_2) is determined by cardiac output (CO), arteriovenous oxygen difference ($a\text{-}vO_2$ diff) or a combination of these. Cardiac output represents the central response to while the $a\text{-}vO_2$ diff represents the venous response or peripheral contribution. The peripheral contribution is determined by skeletal muscle perfusion, extraction and metabolism (Kitzman & Haykowsky, 2012).

The "muscle hypothesis" proposed by Clark, Poole-Wilson, and Coats (1996) as explained and illustrated below helps to clarify the incongruity between hemodynamics and exercise capacity. Skeletal muscle becomes fatigued during exercise due to a limited capacity for aerobic metabolism and this leads to activation of metaboreceptors (ergoreceptors). Activation of metaboreceptors results in an increase in ventilation and creates the sensation of breathlessness. In addition, the sympathetic nervous system is activated, increasing vascular resistance and afterload. This causes a further decrease in myocardial performance (left ventricular dysfunction) and reduced blood flow to the periphery (Figure 1).

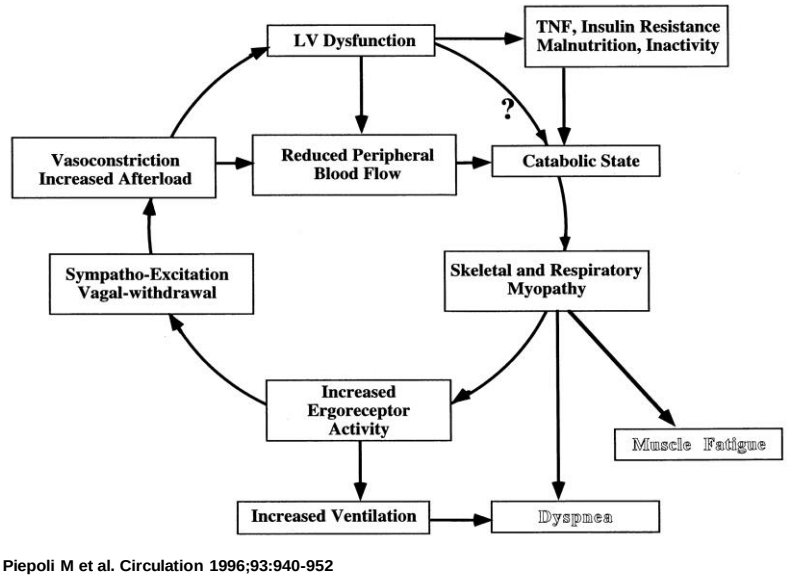

Figure 1. Conceptual model of the muscle hypothesis of HF. An initial reduction in left ventricular causes inactivity resulting in skeletal myopathy. Adapted with permission from Piepoli M et al. *Circulation* 1996;93:940-952 .LV = left ventricle; TNF = tissue necrosis factor.

Piepoli et al. (1996) stated that abnormalities in vasomotor tone may also explain the decreased peripheral blood flow in HF. Furthermore, factors such as insulin resistance, increased peripheral vascular resistance, and increased endothelin levels may contribute to reducing blood flow and augmenting sympathetic activation. Although not stated as such by Piepoli et al. (1996) it is now known that the same factors are closely associated with endothelial dysfunction. Subsequent work by other investigators has supported the contribution of endothelial dysfunction to muscle abnormalities in HF (Fang & Marwick, 2003).

Endothelial dysfunction is characterized by the inability of the endothelium to maintain its regulatory and protective functions with respect to vasoreactivity, inflammation, coagulation,

and cell proliferation (Vanhoutte, 2009) and is associated with diabetes (Arcaro et al., 2002) hypertension (Shimbo et al., 2010), aging (Celermajer, 1994) and HF (Kaye, Ahlers, Autelitano, & Chin-Dusting, 2000). Vasoreactivity is commonly measured in research studies using brachial artery (BA) ultrasound to assess endothelial function in various patient populations. In patients with HF this method has been used to evaluate the response to pharmaceutical, device (implantable defibrillator and cardiac resynchronization) and exercise therapies (Vuckovic, Piano, & Phillips, 2013). The overwhelming majority of these trials have only included patients with EF < 35%. As a result, there is a significant body of evidence which supports the hypothesis that endothelial dysfunction is a factor in HFREF (McKelvie et al., 1995; Tai, Meiniger, & Frazier, 2008) but a limited number of studies have examined that relationship in HFPEF. In addition, findings from several studies and reviews (McKelvie et al., 1995; Tai et al., 2008) indicate that exercise training improves endothelial function, but again the study populations have predominantly HFREF patients (N = 52, EF 31±7%, Belardinelli, Capestro, Misiani, Scipione, & Georgiou, 2006; N = 40, EF 19 ± 9%, Hambrecht et al., 2000; N = 27, EF < 40%, Wisloff et al., 2007).

A modified model of the skeletal muscle hypothesis incorporating endothelial dysfunction as a key factor in the relationship among the variables contributing to HF pathophysiology and symptoms is shown in Figure 2 (Phillips & Vuckovic, 2011). This model is applicable to the development of HFPEF and HFREF; an initial cardiac abnormality (myocardial ischemia or pressure/volume overload due to HTN) is essential, and is represented in the model as left ventricular dysfunction. We believe that endothelial dysfunction may be a central component in the development of dyspnea. The methods used in this study will help to determine the design of future studies which in turn, will examine the potential mechanisms underlying dyspnea and the relationship to endothelial dysfunction ultimately leading to new therapies.

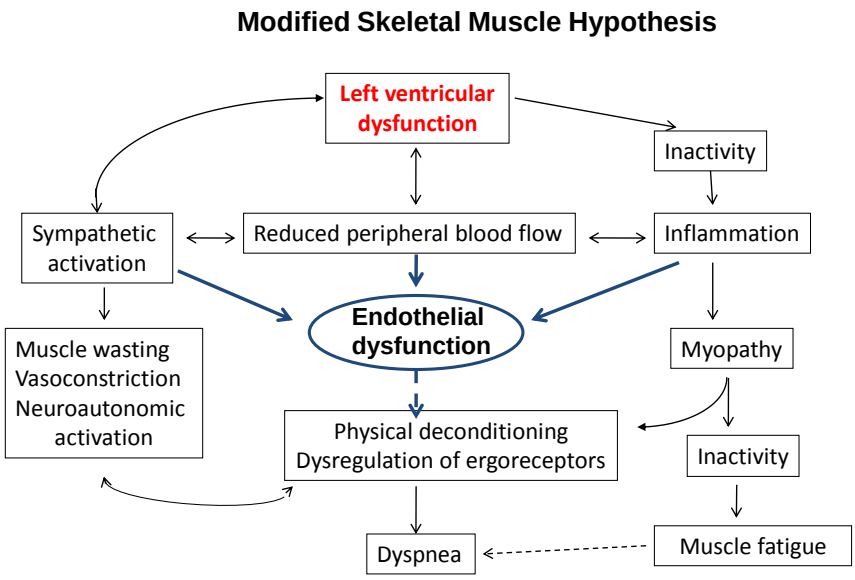

Figure 2. Modified skeletal muscle hypothesis by Phillips & Vuckovic (2011).

H. Heart Failure with Preserved and Reduced Ejection Fraction

Heart failure is a syndrome that can be defined (a) clinically by symptoms (dyspnea, fatigue, exercise intolerance) and signs (edema, pulmonary crackles) as the result of a cardiac condition or (b) hemodynamically by the inability to provide adequate cardiac output at rest or with exertion, or do so only at the expense of elevated cardiac filling pressures (Borlaug & Redfield, 2011). Heart failure is often the end-result from a myriad of myocardial insults which share the same clinical presentation (chest pain) but have different underlying mechanisms of disease and different treatment modalities. For example, patients with coronary ischemia and

valvular disease may have chest pain but are treated differently. Likewise, HFPEF and HFREF may present similarly but have different underlying mechanisms of disease.

Patients with HFPEF (EF ≥ 50%) and patients with HFREF (EF < 40%) share the same clinical presentation but experts propose that the pathogenesis of HFPEF and HFREF differ. Although increased left ventricular (LV) mass is commonly found in most forms of HF, the type of ventricular remodeling as measured by echocardiography in HFPEF and HFREF are distinct (Borlaug & Redfield, 2011; Fukuta & Little, 2007). Left ventricular chamber dilation (eccentric remodeling) is the defining characteristic of HFREF. In contrast, patients with HFPEF have a normal or near normal LV chamber size with increased wall thickness, a greater ratio of wall thickness to chamber dimension, and an increased ratio of ventricular mass to chamber volume (concentric remodeling) compared with HFREF patients and healthy controls (Kitzman et al., 2002). The echocardiographic changes in HFPEF are similar to the findings observed in patients with arterial hypertension and with aging (Lakatta, 1993). Although antecedent HTN is a potential risk for all types of HF it is thought a particularly common cause of HFPEF.

The hallmark pathophysiological findings in HFPEF are prolonged LV relaxation, slow LV filling, and increased LV stiffness (Dickstein, 2008). Prolonged LV relaxation and elevated diastolic LV stiffness are of marked importance during exercise (Borlaug, Nishimura, Soraija, Larn, & Redfield, 2010). In healthy adults during physical activity, CO increases due to increased venous return, contractility, HR, and peripheral vasodilation (Higginbotham et al., 1986). Abnormalities in each of these components have been identified in HFPEF. Thus, HFPEF can be conceptualized as a disorder of cardiovascular reserve function; that is, derangements in the diastolic (blunted preload increase with activity), systolic (limited stroke volume response), chronotropic (impaired HRR) and vascular reserve (endothelial dysfunction; Borlaug & Paulus, 2011) that are unmasked by physical activity (Borlaug et al., 2006).

The pathological changes discussed above highlight two important points relative to our study. First, patients with HFPEF are likely to experience exercise intolerance, thereby limiting their ability to perform simple daily activities; a growing concern as more patients survive and live longer with HF. Second, it is evident that central hemodynamic derangements are important, but do not entirely explain the symptoms and pathology associated with reduced and preserved HF.

With respect to this second point, a small but growing body of literature suggests that although elderly patients with HFPEF have improved exercise performance ($VO_{2\ peak}$) central mechanisms may not play a lead role in the response to exercise. Rather, it is the contribution of the peripheral mechanisms that may determine improvements in exercise performance as discussed below (Fujimoto et al., 2012; Haykowsky et al., 2011).

Bhella et al. (2011) examined whether $VO_{2\ peak}$ decreased in response to exercise in patients with HFPEF (n = 11; age 73 ± 7 years; EF 74.1% ± 7.5) compared to age-matched healthy control subjects (n = 13; EF 68.2% ± 2.7). These investigators observed that cardiac reserve was not different between groups and that the hemodynamic profile of the HFPEF group was similar to patients with impaired skeletal muscle metabolism (mitochondrial myopathies). Furthermore, Bhella and colleagues (2011) suggest that the impairment may be related to skeletal muscle metabolism/fatigue or the inability of a left ventricle to respond to metabolic signals to increase CO. The data from this study were the baseline findings upon enrollment in the year-long endurance exercise training study discussed below (Fujimoto et al., 2012).

Haykowsky et al. (2011) reported that in a study of elderly patients with HFPEF (n = 48; age 69 ± 6 years; mean EF not reported, enrollment criteria EF > 50%; 80% Caucasian with HTN) and control subjects (n = 28; age 68 ± 5 years; 100% Caucasian without HTN) that a-vO_2 difference was significantly reduced during incremental exhaustive upright exercise ($p < .001$).

The a-vO_2 difference was the strongest independent predictor of reduced exercise capacity (partial correlate, 0.61; standardized *B* coefficient, 0.41; $p = 0.005$), whereas the measures of stroke volume were similar to findings for the control group.

Finally, Fujimoto and colleagues (2012) examined whether hemodynamics, LV diastolic function and structure would change following a year-long endurance exercise training program in patient s with HFPEF ($n = 11$ enrolled, 7 completed; age 74.9 ± 6 years; EF 76% ± 8; HTN 100%). Patients with HFPEF walked or cycled three times per week for 25 minutes per session at 70-80% of maximal HR with monthly incremental increases in frequency and duration. After a year of training the average exercise time was approximately 200 minutes per week; however, there were no significant exercise-induced effects on BP or HR ($p = .37$), hemodynamics, LV function or structure ($p = .50$) including arterial stiffness.

Taken together the findings from these studies suggest that abnormalities in peripheral circulation and skeletal muscle play an integral part in the pathology of HF, and in particular, endothelial dysfunction (Kitzman & Haykowsky, 2012; Kokkinos, Choucair, Graves, Papademetriou, & Ellahham, 2000; Maurer & Schulze, 2012). Therefore, in this study we will enroll a subgroup of patients with HFPEF and HFREF and assess endothelial function using non-invasive ultrasound to measure vascular function.

I. Summary

Dyspnea (uncomfortable breathing) with activity is a primary symptom in reduced or preserved ejection fraction HF, but it is not clear if all patients with HF experience dyspnea with the same quality and intensity (Kitzman & Groban, 2008). The sensation of dyspnea does not arise from a single pathway; rather it is a complex interaction among physiologic and psychological interactions. It is important to understand dyspnea because it is the most common reason patients with HF (reduced and preserved ejection fraction) seek medical care but the

mechanisms involved this symptom are not well understood, particularly with respect to HFPEF. Heart failure with a preserved ejection fraction is the fastest growing yet least understood form of HF. Therefore, investigating dyspnea in patients with HFPEF is key to decreasing the morbidity and mortality of HF and in turn, improving the quality of life for patients and reducing the burden on the health care system. In addition, it is concerning that African Americans with HF have been underrepresented in clinical trials despite having higher morbidity and mortality rates than other ethnic groups. For this reason we choose to study dyspnea in African American patients with HF and preserved ejection fraction.

III. METHODS

A. Introduction

In this chapter we provide details related to the study design, sample, dyspnea scales, data collection, and statistical analysis. In addition we discuss the protocols for the 6MW test and FMD measures of the brachial artery (BA) with adaptations for the HF population.

B. Design and Sample

This main study was a prospective repeated measure study using a pre-test/ post-test design wherein the level of dyspnea and related physiological factors were compared between two groups of HF patients (HFPEF vs. HFREF) at rest and following physical activity (6MW test). There was an additional substudy whereby subjects were randomly invited to participate (selected using a random numbers table) in a substudy that measured peripheral vasoreactivity in the BA using FMD. Subjects who declined to participate in the FMD substudy were not excluded from enrolling in the main study. The study was carried out using a convenience sample from the Heart Center Clinic which is located within a large urban academic medical center at the University of Illinois Hospital and Health Systems. Previous investigators from the College of Nursing successfully recruited minority subjects for HF studies (N = 194; 75% African American; 8% Hispanic) from this clinic. The research protocol was approved by the University of Illinois Institutional Review Board. The study design is diagrammed in Figure 3.

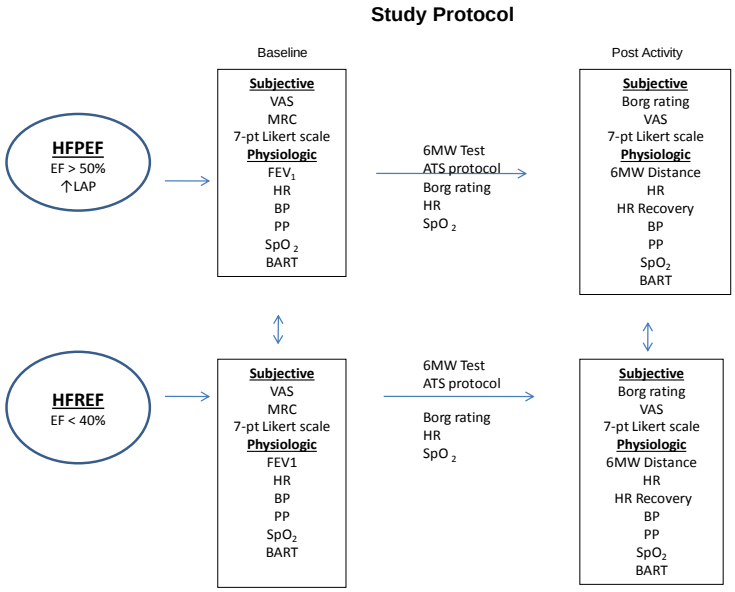

Figure 3. Diagram of study protocol. 6MWT = 6-minute walk test; ATS = American Thoracic Society; BART = brachial artery ultrasound; BP = blood pressure; EF = ejection fraction; FEV_1 = forced expiratory volume; HR = heart rate; LAP = left atrial pressure; VAS = visual analogue scale; MRC = medical respiratory council dyspnea scale; PP = pulse pressure; SpO_2 = pulse oximetry.

1. Sample Size Determination

A power analysis was conducted *a priori* (G-power version 3.1.3, Univeristat Dusseldorf, Germany) to determine the number of subjects needed to detect a significant difference in dyspnea scores between groups, HFPEF vs. HFREF and pre-test vs. post-test scores (mean differences 2–tailed independent T-test, 80% power with statistical significance set at α = 0.05, effect size 0.5). The expected effect size (ES) was derived from a previously published study which measured dyspnea scores using the Borg scale in response to an exercise program in patients with HFREF (*ES* = -0.46; *N* = 40, Oka, 2000). Since no prior published studies of this type had enrolled patients with HFPEF at the time of conception, it was determined that we

needed to enroll 60 subjects (HFPEF, *n* = 30; HFREF, *n* = 30). This sample size was consistent with other studies, which measured dyspnea in response to an exercise program in patients with HFREF (*N* = 29, Beniaminovitz et al., 2002; *N* = 40, Oka et al., 2000; *N* = 23, Poezhl et al., 2008). Since the FMD substudy was a pilot, a power analysis was not conducted to determine sample size (*N* = 20; HFPEF, *n* = 10; HFREF, *n* = 10).

2. Identification of Potential Subjects

A convenience sample of self-identified African American male and female adult patients at least 50 years of age with HFPEF (*n* = 19) and HFREF (*n* = 28) were recruited from the University of Illinois at Chicago Heart Failure Program. The principal investigator (PI) identified potential subjects from the HF clinic appointment list, reviewed demographics, and then screened the medical record of potential subjects to determine eligibility. If the criteria were met, the PI invited potential subjects to participate in the study at the subject's convenience at the time of their clinic appointment. If subjects were selected and interested in the FMD study an appointment was made for another day to complete the study. Subjects who declined or were not selected for the FMD substudy had the option of: (a) completing the study that day or (b) making another appointment for the study at their convenience. Patients with HFREF served as the comparison group for the study, given that current knowledge of HF therapy and pathophysiology is derived from our understanding of HFREF.

3. Inclusion/Exclusion Criteria and Rationale

Heart failure (HF) is the leading discharge diagnosis for patients older than 65 years of age; however, African Americans develop HF symptoms (i.e., dyspnea) at an earlier age. In this study we recruited African American men and women ≥ 50 years of age with HFPEF and HFREF. Preserved and reduced ejection fraction HF share symptoms such as dyspnea and fatigue leading to exercise intolerance. However, the underlying mechanisms of disease are not

identical and hence the treatment should not be the same for the two disorders (Borlaug & Redfield, 2011). To distinguish between the disorders; we used a cutpoint of an EF > 50% as criteria for HFPEF and a cutpoint of an EF < 40% as criteria for HFREF (Paulus et al., 2007) determined by 2-Dimensional echocardiography.

Commonly, echocardiographic findings between individuals with HTN without HFPEF and individuals who develop HFPEF overlap; consequently, it is necessary to distinguish between these two groups using additional criteria such as increased left atrial (LA) size and increased LA volume. Melenovsky et al. (2007) compared the ventricular and atrial abnormalities from urban community-dwelling men and women over 50 years of age with HFPEF (n = 37; 76% African American), asymptomatic LV hypertrophy (n = 40; 73% African American) and a normotensive control group (n = 56; 61% African American) to determine the parameters selective for HFPEF. The authors concluded that LA size was significantly altered only in HFPEF. The current standards and guidelines from the American Society of Echocardiography (Nagueh et al., 2009) state that LA size often reflects the cumulative effects of elevated filling pressures over time and in turn, may indicate chronic dyspnea. In other words, the size of the LA indicates the volume and diameter (remodeling) of the chamber. Other evidence comes from observational studies which collectively indicate that the LA volume ≥ 34 ml/m^2 (determined by echocardiogram) is an independent predictor of HF (n = 1,375, EF > 50%, age ≥ 65 years; Abhayaratna et al., 2006). Left atrial size can be measured by volume or diameter (normal 3.5-4.1 cm) and reflects left atrial pressure (Klein & Garcia, 2008). In this study we will use EF > 50% and increased LA pressure to define preserved ejection fraction HF (Nagueh et al., 2009). Although both parameters (diameter and size) are routinely measured, LA pressure is reported in the medical record. Since echocardiographic data is fundamental to determine eligibility for the study, the test had to be performed within two years of study enrollment.

Current HF treatment guidelines oppose the use of serial echocardiograms to monitor clinical status if patients are clinically stable (Dickstein et al., 2008; Hunt et al., 2005). Consequently, patients in the Heart Center often do not have an annual echocardiogram.

Table II lists the inclusion criteria for both groups. Criteria were the same for each group with the exception of for echocardiographic parameters; specifically, ejection fraction and LA pressure.

TABLE II

INCLUSION CRITERIA FOR EACH GROUP

HF-*Preserved* EF	HF-*Reduced* EF
• Self-identified as African American ≥ 50 years of age	• Self-identified as African American ≥ 50 years of age
• Clinically stable with a diagnosis of HF for at least 3 months.	• Clinically stable with a diagnosis of HF for at least 3 months.
• English-speaking and able to give consent	• English-speaking and able to give consent
• EF > *50%* AND dilated left atrium demonstrated on echographic findings within the past two years	• EF < *40%* demonstrated on echographic findings within the past two years

Patients with potential confounding factors were excluded. For example, patients who could not walk for 6 minutes independently (walker, wheelchair-bound) were excluded. Patients with a diagnosed primary pulmonary disease or valvular disease were excluded since these

conditions are known to be associated with an enlarged LA and as such, are potential confounding factors (Abhayaratna et al., 2006). In addition, patients who were in the process of adjusting medications were not enrolled until the target doses were stabilized for at least 3 months. The exclusion criteria for the study were:

- African Americans patients < 50 or > 90 years of age or non-African American patients with HF of any age
- Use of assistive device (walker, wheelchair) or any condition (e.g. lower extremity weakness) that would interfere with performance of the 6MW test
- Comorbid disease (infiltrative disease restricting movement such as scleroderma) or behavioral limitations that may interfere with performing the 6MW test
- Diagnosed with pulmonary disease requiring continuous oxygen
- Patients who are in the process of having drug doses titrated
- Echocardiographic data are not available within the past two years
- NYHA Class IV (dyspnea at rest)
- Cardiovascular event or procedure within the past month
- Cardioverter defibrillator and/or cardiac resynchronization device implanted within the previous 3 months
- HF secondary to significant uncorrected primary valvular disease, congenital heart disease, or obstructive cardiomyopathy
- Unstable diabetes mellitus (A1C > 9.0)
- BP systolic reading > 180 mm Hg and or diastolic BP readings > 100 mm Hg) for two consecutive readings OR resting HR > 120 bpm
- New onset atrial fibrillation

C. Procedures for Data Collection

Subjects were consented by the PI on the day they performed the study and assigned a unique three digit identification number. Demographic and health information data extracted from the medical record or data collected by the PI during the study was coded with this number. The PI interviewed subjects and extracted health information in order to compare the differences between groups related to age, gender, race, duration/etiology of HF, echocardiographic parameters, EF, medications, comorbid conditions, and laboratory values. New York Heart Association (NYHA) functional classification was determined by the cardiologist or by the HF advanced practice nurse. Vital signs, height (cm), and weight (kg), and were measured on all subjects since anthropometric measures can influence the 6MW test (Vuckovic & Fink, 2011). See Appendix A and B.

Prior to rating their dyspnea, enrolled subjects performed hand-held spirometry (Contec SP10; Qinhuangdao, China) to determine forced expiratory volume in one second (FEV_1). While seated, subjects were instructed to inhale deeply, hold their breath, and then blow hard and fast into the filtered mouthpiece for three seconds. The test was performed for 2-3 times or until two consecutive readings were obtained unless the patient complained of light-headedness.

Next, subjects were asked to complete four scales. Three scales evaluated their level (intensity) of dyspnea at baseline (prior to walking) and a fourth scale, the MRC, described activities likely to evoke dyspnea. The order of the scales was randomized to prevent bias. This process took about 5-15 minutes to complete. The following Table III outlines the timepoints the scales were administered.

TABLE III

Timeline Dyspnea Scales Administered

Scale	Baseline	During the 6WM test (1-minute intervals)	Post 6MW test
MRC	x		
VAS	x		x
Likert	x		x
Borg	x	X	x*

Note. * Dyspnea was measured at 1-minute intervals during recovery using the Borg scale. MRC = Medical Respiratory Council Dyspnea Scale; modified VAS = Visual Analogue Scale

After baseline dyspnea scores were obtained, subjects performed a 6MW test using a standardized protocol (Appendix G). During the 6MW test, the PI recorded HR, RR, and BP at one-minute intervals and three-minutes during recovery. In a subset of subjects, endothelial function was assessed by BA ultrasound (a non-invasive technique to determine blood vessel size/blood flow), before (baseline) and after the 6MW test. The ultrasound took place in the Clinical Research Center (CRC). All other data was collected in the Heart Center which has a designated area for the 6MW test, portable defibrillator/heart monitor with memory, and access to immediate medical care if needed.

D. Scales to Measure Dyspnea

Dyspnea questionnaires and scales have predominantly been validated in patients with pulmonary disease. Despite a growing interest in understanding dyspnea in the HF population, there is no method agreed upon for measuring dyspnea in acute or chronic HF (Johnson, Oxberry, Cleland, & Clark, 2010). In this study, patients with HF were asked to describe and rate their experience of dyspnea using the MRC dyspnea scale, a VAS, Likert and the Borg scale, all of which have previously been used in dyspnea studies with patients with HF (Appendices C-F).

1. Medical Respiratory Council Dyspnea Scale (MRC)

The Medical Research Council Dyspnea Scale (MRC) was designed by Fletcher et al. (1960) to measure the severity of dyspnea with activity reported by coal miners with pulmonary disease. Originally the MRC was developed as a series of five statements describing respiratory discomfort ranging from none (Grade 1) to severe (Grade 5) that was associated with performing everyday activities (Appendix C). The scale can be self-administered by asking subjects to choose the statement that best describes their condition or it can also be used by an interviewer with the statements reframed as questions (Stenton, 2008). Scoring is usually completed in seconds with either method. The scale has been used extensively in pulmonary populations but has had limited use in HF research. In a five year study of survival in patients with HF, Nielsen and colleagues (2003) used the MRC as a screening tool for dyspnea in eligible subjects. An ongoing trial (ClinicalTrials.gov NCT01148719) of exercise intolerance in the frail elderly with HF includes the MRC scale as a screening tool for subject eligibility. Yorke, Moosavi, Shulgham and Jones (2010) used the MRC scale to validate a new dyspnea questionnaire for the cardiopulmonary population and reported a mean MRC score (severity of dyspnea) of 2.6 (*SD* = 1.1) for the patients with chronic HF (*n* = 106; EF = 35% ± 15) in an outpatient clinic setting. In this study we will use the MRC scale to determine the subject's perception of dyspnea related to their everyday activities prior to the 6MW test during an interview with the PI.

2. Visual Analogue Scale (VAS)

The Visual Analogue Scale (VAS) consists of a horizontal or vertical line 100 mm in length with anchors at the extremes (e.g. 'not breathless" to "extremely breathless"; Appendix D). The subject marks the VAS line to represent the intensity of breathlessness, which is scored by measuring the distance from the lower end of the line to the mark (Gift, 1989a;

Mahler, 2005). The vertical VAS was validated to measure clinical dyspnea (Gift, 1989b). The use of VAS in HF research is discussed in detailed below. The VAS score was taken with the subject sitting upright before and after the 6MW test.

3. 7-Point Likert Scale (Likert)

Several variations of Likert items or scales have been used in cardiopulmonary research to evaluate dyspnea. The subject grades the severity of dyspnea by indicating a score on a scale. Previous HF investigators have used 5-point and 7-point scales that are symmetrical with zero as the midpoint and better-worse responses arranged at equidistant intervals.

Large HF trials have used a 7-point Likert scale to measure the resolution of acute dyspnea as a clinical endpoint (Pang et al., 2008), whereas smaller studies in a chronic HF population have used a VAS and Borg scale to measure dyspnea following an exercise intervention (Johnson et al., 2010). In an observational cohort study in acute HF (N = 524), Mebazaa and colleagues (2010) evaluated the utility of a 5-point Likert scale, 7-point Likert scale and a VAS to detect the change in dyspnea (sitting and supine) following conventional treatment. The investigators found that all scales detected change but suggest the VAS was most sensitive to change in the supine position. In a randomized controlled pharmaceutical trial of dyspnea relief in acute HF (N = 232), Metra and colleagues (2010) concluded that a 7-point Likert scale was more sensitive to early changes in dyspnea (hours), whereas the vertical VAS was sensitive to changes in dyspnea over a period of days. Ander et al. (2004) examined the change in dyspnea in a sample of predominantly African American patients with acute HF (N = 74) and found a change in VAS of 21.1 mm (95% confidence interval, 12.3-29.9 mm) corresponded with a patient's perception of a meaningful change in dyspnea. However, the investigators used an uncalibrated 10 cm horizontal line for scoring, and reported that some patients had difficulty performing the task. In this study, we will use a 7-point Likert (referred to

as Likert in this paper) scale and calibrated vertical VAS to measure dyspnea before and after physical activity in a sitting position (Appendix E).

4. Modified Borg Scale

The Borg scale (Borg, 1982) is routinely used in cardiopulmonary medicine and research to measure breathlessness and muscle fatigue during acute exercise (ATS, 2002; Balady et al., 2010). The modified scale is a 12-point rating scale with descriptive anchors ranging from 0 (no dyspnea) to 10 (maximal dyspnea). Several studies have evaluated the validity and reliability of Borg ratings during exercise in cardiopulmonary populations. A rating of 3-5 is considered optimal or the safe zone for exercise training (Balady et al., 2010; Appendix F).

The modified Borg scale has been used to rate dyspnea in response to submaximal exercise and treatment. In a study of African men (n = 26) and women (n = 19) with NYHA class II and III HF, Adedoyin and colleagues (2010) reported a mean Borg score of 2.3 (SD = 3.3) upon completion of the 6MW test. Although the authors did not report EF, 71% of the subjects (n = 25) had "hypertensive heart failure." Boni and colleagues (2005) used the Borg scale to assess the change in dyspnea in a sitting and supine position following vasodilator and diuretic therapy in non-obese patients with HF (n = 9; preserved and reduced EF; mean EF 43± 15%). The investigators found the Borg scale to be sensitive to positional changes (pre-treatment mean dyspnea score 1.5 ± 0.5 supine vs. mean dyspnea score 2.7 ± 0.5 recumbent; $p < 0.01$). Furthermore, the change in Borg score was positively correlated with the change in inspiratory capacity ($r^2 = 0.43$; $p < 0.01$). For this study, the Borg score was obtained at baseline, 1-minute intervals during the walk test (6 time points) and at 1-minute intervals for a total of three minutes during the recovery period. In total Borg scores were sequentially recorded for 9 timepoints.

In a retrospective analysis to determine the minimally clinical important difference (MCID) for three standardized measures of dyspnea in patients with chronic lung disease, Ries

(2005) calculated the ES (change after intervention divided by the standard deviation at baseline) for the selected studies. The author estimated that 1 unit of change in the Borg scale was associated with a moderate ES in pulmonary patients. A consensus statement has suggested a 1 unit change in improvement in the Borg scale and 10 % improvement in the VAS scale reflect the MCID for dyspnea irrespective of the etiology (MRC Clinical Trials Unit & Cicely Report, 2005).

E. Six-Minute Walk Test (6MW Test) and Protocol

After completing the dyspnea scales and spirometry testing enrolled patients performed the 6MW test; a commonly used objective measure of functional capacity in HF research, which indicates the ability to perform daily activities. In this study the 6MW test was used as a surrogate for daily activities. Unlike a cardiopulmonary stress test (the gold standard to measure functional capacity) the 6MW is a valid and reliable test that does not require specialized equipment and can easily be performed in most research and clinical settings. The 6MW test is safe even in severe HF (NYHA Class IV patients) and has been used to monitor disease progression, evaluate treatment effects, and predict mortality and rehospitalization (Vuckovic & Fink, 2010). When conducting the 6MW test, the PI asked the subject to walk back and forth along a flat 100 foot long surface. The subject attempted to walk as far as possible while the investigator measured a six-minute period using a stopwatch (ATS, 2002). The test was self-paced, meaning that the subject stopped to rest and resumed walking or terminated the test when he or she could walk no further. The subject rated dyspnea or perceived exertion before, during, and after the walk using the Borg Scale at 1-minute intervals. The investigator measured the distance walked rounded to the nearest meter (ATS, 2002; Balady et al., 2010; Appendix G).

Normative values for the 6MW distance have not been established, but a review of several studies suggests that in healthy adults 6MW distances range from 386 to 800 meters

(Alameri, Al-Majed, & Al-Howaikan, 2009; Gibbons, Fruchter, Sloan, & Levy, 2001), and in patients with HFREF the reported baseline (pre-intervention) distances range from 169 to 400 meters (Arslan et al., 2007; Boxer et al., 2008), with the shortest distances measured in elderly, frail HF patients (Boxer et al., 2008). All these ranges, however, should be interpreted with caution because variability in 6MW distances can be due to several influencing factors, including gender and race. Importantly, changes in the 6MW distance have been found to correlate with worsening HF and mortality (Alahdab et al., 2009; Bittner, 1993; Rostagno et al., 2008). In African American patients who met the Framingham criteria for the diagnosis of HF (N = 126, mean EF not reported; 68% NYHA class III or IV) Alahdab et al. (2009) found that a 6MW distance of < 200 meters was the strongest independent predictor of all-cause mortality (adjusted *HR* 2.14, 95% *CI* 1.20 to 3.81, p = .01) and hospitalization for HF (adjusted *HR* = 1.62, *CI* = 1.10 to 2.39, p = .015). In contrast, other investigators have reported a 6MW distance < 350 m to be predictive of mortality in predominantly Caucasian patients with HF (Arslan et al., 2007; Bittner et al., 1993).

An important consideration to increase the reliability of the 6MW test is to follow a standardized protocol. In this study the PI performed the 6MW test on all subjects using a standardized protocol based on the ATS recommendations with modifications for the HF population.

The 6MW test followed a standardized scripted protocol (Appendix G) based on the recommendations from the ATS (2002). Baseline data were recorded including electrocardiogram (EKG) strip to verify heart rhythm. The use of encouragement and eye contact were consistent throughout testing and a single observer conducted all testing thereby increasing inter-rater reliability (Vuckovic & Fink, 2011). During the 6MW test, the subject was monitored for changes in HR, rhythm (Zoll M series; Burlington, MA), SpO_2 (Nonin, Model 2500;

Plymouth, MN) and dyspnea using the modified Borg scale (ATS 2002; Balady et al., 2010). Subjects stopped walking at any time if they needed to rest and then could resume walking or terminate the test.

At the end of the six minutes or at the time a subject decided to terminate the test, the distance walked (meters) was measured and the number of laps were recorded. Subjects rated their dyspnea and fatigue (exertion) using the Borg scale. Dyspnea was measured in sitting (90° relative to horizontal) position at 1-minute intervals for three minutes during recovery. The subject also rated their dyspnea using the Likert and VAS scales in addition to the Borg scale.

The subject's heart rhythm was monitored during the 6MW test and for 3 minutes following completion of the 6MW test (recovery). Data (EKG strips) were saved in a de-identified format (3-digit identification code). Calculations for HRR were performed using the formula $HRR = HR_{peak} - HR_{(time)}$. Heart rate at peak (highest HR recorded during the 6MW test) and HR at one minute intervals was verified by calculating the average of three consecutive sinus beats or averaged over one minute if the subjects was in atrial fibrillation (Froelicher & Myers, 2006). Heart rate recovery one minute post-exercise (treadmill) has been found to be an important index of mortality in patients with chronic HF (n = 202; EF = 24 ± 9%; Tang, Dewland, Wencker, & Katz, 2009). Shetler and colleagues (2001) also found HRR to be prognostic of mortality in male patients (n = 2193) with ischemic coronary disease as measured during symptom limited exercise testing; however, 2-minute recovery was the strongest predictor of mortality using Kaplan-Meier analysis. In addition, HRR has also shown to be predictive of mortality following submaximal exercise. In a study of healthy (without cardiovascular disease) subjects (n = 5234) Cole et al. (2000) found that a longer time to decrease HR (i.e. prolonged HRR) predicted mortality (adjusted relative risk 1.55; *CI:* 1.22 to 1.98; $p < 0.001$ by Chi-square

test). Since it is not clear which time interval will be optimal for submaximal exercise in patients with preserved and reduced HF we monitored these parameters for three minutes.

F. Assessment of Endothelial Function: Flow-Mediated Dilation Method

In a subset of patients, vasoreactivity via ultrasound was measured using flow-mediated dilation (FMD). Flow-mediated dilation is dilation of blood vessels in response to increased blood flow or shear stress (Corretti, 2002). Measuring FMD in the brachial artery (BA) via ultrasound is a well-established non-invasive technique to assess endothelial function (Corretti et al., 2003; Phillips, Das, Wang, Pritchard, & Gutterman, 2011; Vita, 2002). Our technique of measuring FMD is based on standard protocols (Thijssen et al., 2011); with modifications for the HF patient population. Subjects were evaluated in a temperature-controlled room at late morning to avoid variations in measurements. At a 30° angle (subjects may not be able to be supine) ultrasound imaging (Telemed, LogiScan 128; Vilnius, Lithuania) of the BA was performed in a longitudinal plane at a site just proximal to the antecubital fossa of the supinated non-dominant arm abducted ~80°. The ultrasound probe (10 MHz) was positioned so that its long axis was parallel and the short axis perpendicular to the BA to visualize anterior and posterior lumen-intimal interfaces of the vessel. Images were recorded directly to the processing workstation for analysis using the subject's 3-digit identification number for image archival and storage. After recording baseline images, a forearm BP cuff was inflated to 50 mm Hg above systolic pressure for three minutes. Brachial artery diameter was measured during peak hyperemia (increase in blood flow) approximately 30 seconds or less after release of the cuff from the forearm.

Continuous (cine loop) recording of the BA diameter was captured simultaneously with pulsed wave Doppler velocity of intraluminal blood flow to detect/quantify flow induced hyperemia and the associated diameter change. Flow velocity was recorded at baseline and just after cuff release where peak (maximal) velocity was observed. The change in FMD was

calculated using the average BA diameter at baseline compared to diameter following release of forearm occlusion (from intima to intima). Shear rate was calculated as peak blood velocity (cm/sec) divided by vessel diameter ([cm]; Kizhakekuttu et al., 2010). Analysis was performed using Telemed Echowave software. All tests were performed by and results analyzed by individuals blinded to subject group and clinical information. Previously reported coefficient of variation (intra-observer) for the Phillips lab was reported as 1.5% for BA diameter and 6.3% for the FMD (Goslawski et al., 2013, In press).

G. Statistical Analyses

Demographic and health information was analyzed using descriptive statistics (means and standard error of the mean (SEM) for continuous variables, count and frequency for categorical variables). Independent *t*-tests, X^2 and Fisher's exact tests were used to assess for any differences in baseline characteristics including baseline dyspnea scores between groups. Independent *t* tests, paired *t* tests, analysis of variance (2 way repeated measures ANOVA) were used to test for differences between and within groups (HFPEF vs. HFREF; pre-test vs. post-test) related to the mean dyspnea scores, HR, BP, PP, SpO_2 values, 6MW distance, and walking speed. Comparisons for Borg score upon completion of the 6MW test were performed using analysis of co-variance adjusting for walking speed (ANCOVA). The strength and direction of the association between key physiological variables (e.g. 6MW distance, HR and HRR, change in FMD) and dyspnea score were analyzed using Pearson's correlations. Spearman's correlations were used to analyze associations between nominal level data and dyspnea scores. Vascular function measures were calculated as percent change (using the formula baseline-post-test)/baseline). All analyses were conducted using SPSS 20 statistical software (Chicago, IL). Values are expressed as means ± SEM unless otherwise noted. All tests were two-sided and an error rate of $p < 0.05$ was considered statistically significant.

IV. RESULTS

A. Introduction

In this section we report the subjects' baseline characteristics and the findings for three aims (1) describe and compare the occurrence of dyspnea at baseline, 6 minutes, and during recovery between HFPEF and HFREF subjects, (2) describe the association between selected physiologic alterations that occurred during and after the 6MW test with Borg dyspnea scores, and (3) characterize peripheral endothelial function in patients with HFPEF and HFREF by measuring FMD (assessed by ultrasound) and to determine the association to dyspnea scores.

B. Subject Demographics

Over a 13-month period (December 2012 through January 2013) the PI screened approximately 1100 HF patients attending the University of Illinois Hospital and Health Sciences System's clinic for routine HF visits (Figure 4).

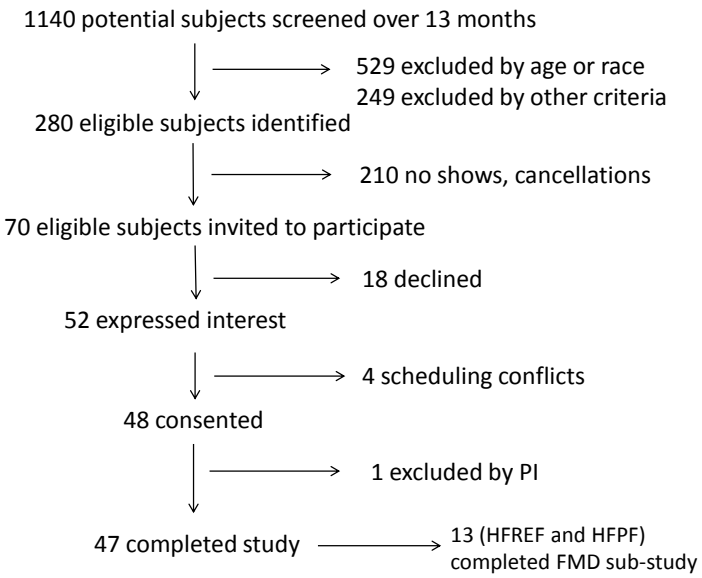

Figure 4. Flow diagram of the recruitment process over the 13-month period. Study exclusively recruited African Americans over 50 years of age. FMD = flow-mediated dilation; HFPEF = heart failure with preserved ejection fraction; HFREF= heart failure with reduced ejection fraction; PI = primary investigator.

Among the 521 subjects screened, 48 met the inclusion criteria and consented to participate; 47 subjects completed the study. Two subjects did not complete the study on the day of consent due to a change in their baseline heart rhythm detected prior to walking. Data was analyzed for 45 subjects; two subjects were excluded from analysis (rest period over 2 minutes; delayed timing for measures during recovery period).

The groups did not differ with respect to age, etiology (ischemic vs. non-ischemic), gender, and incidence of atrial fibrillation (Tables IV-VI). All subjects in both groups had history of HTN. Duration of HTN varied between 2-21 years.

TABLE IV

BASELINE CHARACTERISTICS OF SUBJECTS

Variable	HFPEF (n = 19)	HFREF (n = 26)	Test Statistic	p
Age (years)	65.68 ± 2.4	64.27 ± 1.57	t =0.513	.610
Ejection Fraction %‡	58.02 ± 1.20	28.17 ± 1.82	t = 13.68	.000*
Gender %			X^2 = 1.275	.259
Male	36.8 (7)	53.8 (14)		
Female	63.2 (12)	46.2 (12)		
Etiology of HF %			X^2 = 4.65	.098
Non-ischemic	89.5 (17)	61.5 (16)		
Ischemic	10.5 (2)	30.8 (8)		
Mixed	0	7.7 (2)		
NYHA Class %			X^2 = .530	.767
I	26.3 (5)	23 (6)		
II	52.6 (10)	46.1 (12)		
III	21.1 (4)	30.7 (8)		
Hemoglobin (g/dL)	12.55 ± .28	12.80 ± .28	t = -.598	.553
Serum Sodium (mmol/l)	140 ±. 45	139.5 ± .45	t = .767	.447
Potassium (mmol/l)	4.25 ±.15	4.28 ±.09	t =-.189	.851
BUN (mg/dL)	19.16 ± 2.75	19.92 ± 1.75	t = -.245	.808
Creatinine mg/dL	1.29 ± .114	1.36 ± .07	t = -.579	.566
LDL mg/dL	89.74 ± 7.3	88.46 ± 6.2	t =.133	.895
HDL mg/dL	48.79 ± 3.37	42.88 ± 2.48	t =1.44	.156
GFR mL/min	67.14 ± 4.97	60 ± 3.47	t =1.11	.272

Note. Values are means ± SEM or percent (n). ‡One subject with a recovered ejection fraction. BUN = blood urea nitrogen; GFR = glomerular filtration rate; HDL = high density lipoprotein; HFPEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction; LDL = low density lipoprotein; NYHA = New York Heart Association.).* p < .01. No significant differences between subjects and their baseline hemodynamic parameters. Blood pressure was not significantly different between groups.

TABLE V

BASELINE CARDIOPULMONARY PARAMETERS OF SUBJECTS

Characteristic	HFPEF	HFREF	Test Statistic	*p*
Systolic BP mmHg	123.79 ± 4	128.38 ± 4.1	*t* =-.779	.440
Diastolic BP mmHg	71.11 ± 2.94	73.23 ± 2.78	*t* = -.519	.606
Pulse pressure mmHg	52.68 ± 3.64	55.15 ± 2.75	*t* = -.521	.605
SpO_2 %	95.89 ± .381	95.69 ± .421	*t* = -1.16	.252
FEV_1 mL	1.50 ± .147	1.6.1 ± .119	*t* = -.567	.574
Respiratory rate bpm_b	16.10 ± .389	17 ± .433	*t* = -1.47	.148

Note. Values are means ± SEM. BP = blood pressure; bpm_b = breaths per minute; FEV_1 = forced expiratory volume in one second; HFPEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction; mL = milliliters; mmHg = millimeters of mercury; SpO_2 = pulse oximetry.

TABLE VI

COMORBIDITIES OF SUBJECTS

Comorbidity	HFPEF	HFREF	Test Statistic	*p*
HTN	100 (19)	96.1 (25)		
Atrial fibrillation	47.3 (10)	30.7 (8)	X^2 = 1.28	.257
Hyperlipidemia	89.4 (17)	92.3 (24)	X^2 = .319	.741
CAD	21.1 (4)	46.2 (12)	X^2 = 3.01	.082
Pulmonary disease	31.5 (6)	19.2 (5)	X^2 = .906	.341
DM	36.8 (7)	26.9 (7)	X^2 = .478	.478
CKD	26.3 (5)	26.9 (7)	X^2 = .002	.964
OSA	21.0 (4)	7.0 (2)	X^2 =1.69	.193
GI	15.8 (3)	15.4 (4)	X^2 =.001	.970
GU	15.7 (3)	15.3 (4)	X^2 =.001	.97

Note. Values are percent of the group with actual numbers in ( ). CAD = coronary artery disease; CKD = chronic kidney; DM = diabetes mellitus; GI = gastrointestinal; GU = genitourinary; HFPEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction; HTN = hypertension; OSA = obstructive sleep apnea

No significant difference in height or weight was found. Also BMI was similar between groups. The majority of subjects were overweight–obese (BMI > $25kg/m^2$) in both groups (Table VII).

TABLE VII

ANTHROPOMETRIC CHARACTERISTICS OF SUBJECTS

Variable	HFPEF	HFREF	Test Statistic	*p*
Height (cm)	170.43 ± 2.45	168.79 ± 2.12	t = .506	.615
Body weight (kg)	97.86 ± 5.02	98.33 ± 5.92	t = -.057	.955
BMI (kg/m^2)	33.67 ± 1.76	33.9 ± 1.58	t = -1.00	.921
Underweight (< 18.5 m^2/kg)	0	0		
Normal (18.5-24.9 m^2/kg	5.2 (1)	15.7 (4)		
Overweight (25-29.9 m^2/kg)	42.2 (8)	26.8 (7)		
Obese (>30 m^2/kg)	52.6 (10)	57.7(15)		

Note. Data presented as mean ± SEM or percent with actual numbers in ( ). BMI = basal metabolic index; HFPEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction; kg = kilogram; m^2 = meters squared.

Baseline medications are listed in Table VIII. All subjects with HFREF were prescribed an angiotensin-converting enzymes (ACE) inhibitors, whereas the HFPEF group was more likely to be prescribed calcium channel blockers (CCB [X^2 = 11.34, p = .001; X^2 = 5.46, p = .019 respectively]). As expected, this difference reflects the standard of care in accordance with current HF guidelines (Hunt et al., 2005) and recommendations for the treatment of HF. Unlike patients with HFREF, there are no specific recommended pharmacologic therapies for patients with HFPEF. However if patients with HFPEF have risk factors such as HTN, they should receive antihypertensive therapies. No significant differences were found between groups in the use of other medications prescribed at the time of enrollment (Table VIII).

TABLE VIII

PRESCRIBED MEDICATIONS AT THE TIME OF ENROLLMENT

Medication	HFPEF %	HFREF %	Test statistic	*p*
ACE inhibitor or ARB	63.1 (12)	100 (26)	$X^2 = 11.34$	.001*
Beta adrenergic antagonist	100 (19)	100 (26)		
Diuretics	63.1 (12)	80.8 (21)	$X^2 = 1.74$	.187
Aspirin			$X^2 = 4.85$	.088
81 mg	47.3 (9)	50 (13)		
325 mg	5.0 (1)	26.9 (7)		
Anti-coagulation warfarin, clopidogrel	68.4 (13)	84.6 (22)	$X^2 = .197^{‡}$	.281
CCB	47.3 (9)	15.4 (4)	$X^2 = 5.46$	.019*
Oral anti-glycemic	26.3 (5)	23.1 (6)	$X^2 = .062^{‡}$	.803
Insulin	5.0 (1)	11.5 (3)	$X^2 = .534^{‡}$	.465

Note. Values are percent with actual numbers in ( ).‡ Fisher exact test. ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASA aspirin; CCB = calcium channel blocker; mg = milligram; HFPEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction; *$p < .05$.

C. MRC: Types of Activities Associated with Dyspnea

The MRC is a tool that allows the investigator to score the subjects dyspnea based upon a range of activities (score = 0: dyspnea with strenuous exercise; score = 4: too dyspneic to leave the house or dyspnea with undressing). The subject selects the activity which is *most often* associated with dyspnea. Both groups reported the full range of MRC scores (Figure 5; Appendix C). Approximately half (46.2%; *n* = 12) of the subjects with HFREF selected category 1 (hurrying or walking up a slight hill), as the activity most likely to be associated with dyspnea. In

the HFPEF group, an equal number of subjects (31.6%; n = 6) selected category 1 or 3 (walking 100 yards or a few minutes on a level surface) as the activity most likely to induce dyspnea. The differences among categories of the MRC by type of HF was not significantly different (ranked X^2 =.58; p =.445).

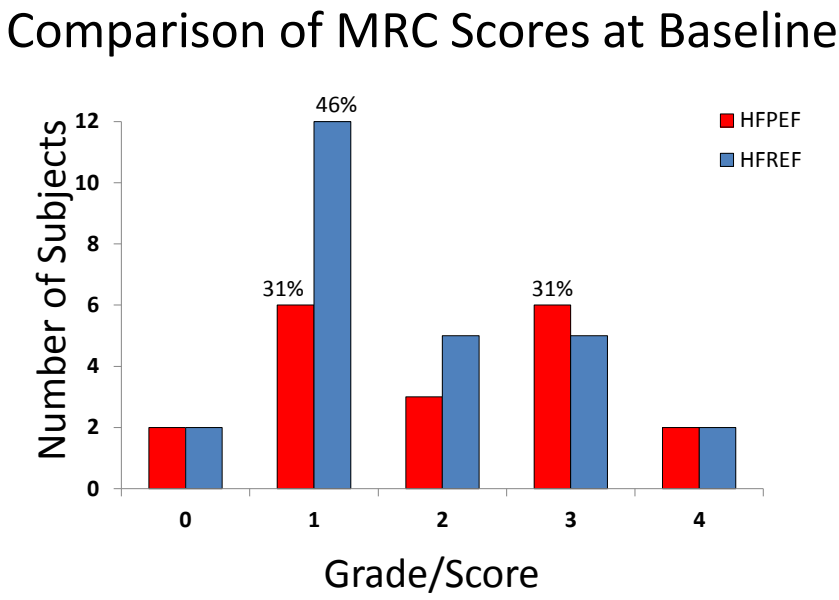

Figure 5. Comparison of Medical Research Council scores between groups for each MRC grade.

D. 6MW Test As Physical Activity

Not all HF patients are dyspneic at rest, but may become dyspneic with simple physical activity, such as walking. Therefore we used the 6MW test to evaluate the occurrence of dyspnea with physical activity for each group. It is important to consider the distances of the subjects to determine if the 6MW test was effective to this end. Table IX shows the distances divided into

100 meters quartiles for each HF group. The range of the distances for the group was (N = 45) was 76.2 to 463.1 meters.

TABLE IX

6MW DISTANCES

	<100m	101-200m	201-300m	>300m
HFPEF (n = 19)	10% (2)	37% (7)	31% (6)	21% (4)
HFREF (n = 26)	3% (1)	31% (8)	50% (13)	15% (4)
Total (N = 45)	6% (3)	33% (15)	42% (19)	8% (4)

Note. Values are percent for each group with actual number = ( ); HFPEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction; m = meter.

E. Occurrence of Dyspnea Before and After the 6MW Test Between HFPEF and HFREF

The presence of dyspnea was assessed in subjects before performing the 6MW test in order to determine if there was a difference in the occurrence of dyspnea between HFPEF and HFREF subjects. For this baseline comparison, only the VAS and Borg scales were used, since the Likert scale measures change in dyspnea and the MRC reflects the type of activity that is associated with dyspnea. Using respective cut-off scores for dyspnea, patients were categorically classified as having "dyspnea" or "no dyspnea." As shown in Table X, the data from the Borg scale indicated more HFPEF subjects reported baseline dyspnea compared to HFREF subjects (p = .058). However, when using the VAS scale the majority of both HFPEF and HFREF subjects reported dyspnea at baseline.

TABLE X

CATEGORICAL BORG AND VAS BASELINE DYSPNEA SCORES

	Borg† %		VAS‡ %	
	No Dyspnea (0)	Dyspnea (≥0.5)	No Dyspnea (100)	Dyspnea (<100)
HFPEF (*n* = 19)	36.8 (7)	63.2 (12)	26.3 (5)	73.7 (14)
HFREF (*n* = 26)	65.4 (17)	34.6 (9)	19.2 (5)	80.8 (21)

Note. Values are percentage of the group and actual number ( ). HFPEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction.
† X^2 =3.59; *p* = .058; *Eta* = 0.3 for Borg scores. ‡ X^2 =.319; *p* = .572; *Eta* = 0.08 for VAS scores.

Baseline data were also analyzed by comparing the means of the absolute scores for the Borg, and VAS scales. No differences were found in the mean baseline dyspnea scores between groups (Table XI).

TABLE XI

MEAN BASELINE DYSPNEA SCORES FOR BORG AND VAS SCALES

	HFPEF	HFREF	Test statistic Effect Size	*p*
Borg Range: 0-10 MCID: 1unit	1.10 ± 1.5	0.83 ± 1.5	$t_{(43)}$ =.602 *d* = 0.22	*p* = .550 *CI*: -0.66 to 1.21
VAS Range: 100mm-0 MCID: 10% difference	82.74 ± 4.19	78.15 ± 4.23	$t_{(43)}$ =.749 *d* = 0.23	*p* = .458 *CI*: -7.75 to 16.9

Note. Values are mean ± SEM. Effect size determined by Cohen's d using the formula: $mean_1$-$mean_2/SD$. CI = confidence interval; HFPEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction; MCID = minimal clinically important difference; VAS = Visual Analogue Scale.

F. Dyspnea Ratings Using the Borg Scale During the 6MW Test and Recovery

Using the Borg numerical scale, dyspnea was measured during and after the onset of physical activity (6MW test). During the 6MW test there were progressive increases in Borg scores; however, the magnitude of the increases were similar between HF groups (Figure 6). There were also progressive decreases in dyspnea after the 6MW and the magnitude of the decrease at each minute interval was similar between HF groups.

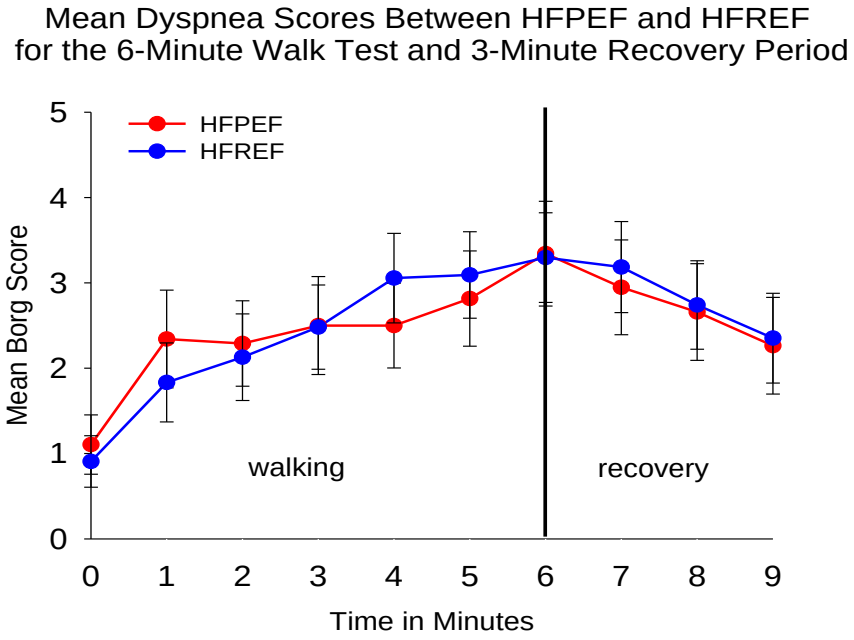

Figure 6. Comparison of the mean Borg scores at 1-minute intervals followed by 3 minutes of recovery for both groups. Values are mean Borg scores ± SEM. HFPEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction.

The 6MW was used as a surrogate of exercise and to specifically test for the presence of dyspnea during activity. In the HFPEF group, 7 subjects reported no dyspnea at baseline (36.8%;

Borg score = 0) and among these, two subjects never reported a Borg score greater than 0 throughout the 6MW test or during recovery, while 5 of the 7 subjects reported varying levels of increased dyspnea during the 6MW test and Borg scores ranged from 1 to 8. In the HFREF group, 17 subjects reported no dyspnea at baseline (65.4%; Borg score = 0). Of the 17 subjects, during the 6MW three never reported a Borg score greater than 0 during the 6MW test, while 14 subjects reported varying levels of increased dyspnea.

The categorical Borg scores for the 6MW test were analyzed at baseline, 6 minutes and at 1-minute intervals during recovery (Table XII). Again there were no statistically significant findings at the various time points between HF groups. At the end of 3- minutes of recovery 15 subjects in the HFPEF group and 17 subjects in the HFREF still continued to report dyspnea (Table XII).

TABLE XII

CATEGORICAL BORG SCORES AT BASELINE, 6 MINUTES, RECOVERY

	HFPEF		HFREF		Test Statistic
	No Dyspnea (0)	Dyspnea (≥0.5)	No Dyspnea (0)	Dyspnea (≥0.5)	
Baseline	36.8 (7)	63.2 (2)	65.4 (17)	34.6 (9)	$X^2 = 3.59$; $p = .058$
6-Min	15.8 (3)	84.2 (16)	11.5 (3)	88.5 (23)	$X^2 = .172$; $p = .679$
Recovery					
1-Min	10.5 (2)	89.5 (17)	15.4 (4)	84.6 (22)	$X^2 = .224$; $p = .636$
2-Min	15.8 (3)	84.2 (16)	26.9 (7)	73.1 (19)	$X^2 = .787$; $p = .375$
3-Min	21.1 (4)	78.9 (15)	34.6 (9)	65.4 (17)	$X^2 = .983$; $p = .321$

Note. Values are percent and actual numbers are in ( ). HFPEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction; Min = minute

G. Dyspnea Scores at Baseline and Completion of 6MW Test

Univariate analysis (independent *t*-tests) showed no significant differences in the baseline Borg or VAS scores between the HF groups (p = .550; p =.458; respectively). The data were also analyzed by repeated measures ANOVA to determine between and within group differences at baseline, at 6 minutes for the Borg scale, and at 3 minutes during recovery for all three scales (Table XIII). The scaling is different between the two dyspnea tools. With the Borg scale 0 is optimal (no dyspnea) and 10 represents the "worst shortness of breath." On the VAS scale 100 reflects optimal or "best" breathing.

TABLE XIII

REPEATED MEASURES ANOVA OF DYSPNEA SCORES

Dyspnea Scale	Time measured	HFPEF (n = 19)	HFREF (n = 26)	ANOVA results
Borg[a]	Baseline 6-min	1.10 ± .35 3.34 ± .61*	0.83 ± .30 3.19 ± .61*	Within: $F_{(1,43)} = 40.81$; $p < .001$* Between: $F_{(1,43)} = 0.147$; $p = .703$
Borg[b]	Baseline 3-min after 6MWT	1.10 ± .35 2.26 ± .56*	0.83 ± .30 2.21 ± .52*	Within: $F_{(1,43)} = 14.94$; $p < .001$* Between: $F_{(1,43)} = 0.089$; $p = .767$
VAS	Baseline 3-min after 6MWT	82.74 ± 4.1 85.98 ± 3.62	78.15 ± 4.23 82.03 ± 3.11**	Within: $F_{(1,43)} = 2.01$; $p < .163$ Between: $F_{(1,43)} = 0.39$; $p < .017$**

Note. Values are means ± SEM. *Within group differences, baseline vs. 6-min.; **Between groups, 3-min after 6MWT HFPEF vs. HFREF. There were no significant interactions. 6MWT = 6-minute walk test; HFPEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction; Min= minute; NS = non-significant

1. Borg scale

Within both HF groups significant increases were found in the 6-min and 9-min Borg scores compared to the baseline score ($F_{(1,43)} = 40.81$; $p < .001$; $F_{(1,43)} = 14.94$; $p < .001$ respectively). The scores between groups were not significantly different ($p = .703$).

2. VAS scale

Using the VAS scale, in both HF groups increases in scores (baseline to post) were found (indicating less dyspnea), however these increases were not significant in either HF group. There was a significant difference between both HF groups using the VAS score ($F_{(1,43)} = 0.39$; $p < .017$) from baseline to 3 minutes of recovery with the HFREF group reporting more dyspnea at baseline and at 3 minutes post 6MW test.

3. Likert scale

The change in the Likert scores was analyzed as categorical data. The change in score was calculated as (baseline score - score at 3 minutes of recovery) and then categorized as better, same, or worse (Table XIV). After 3 minutes of recovery, more than half of the HFPEF group (57.9%; $n = 19$) reported less dyspnea (average improved score = 0.61). In contrast, the HFREF group 30.8% ($n = 26$) reported their dyspnea was "better" (average decrease in score = -0.5) while 46.28% of subjects ($n = 12$) reported no change (Figure 7). However these differences were not significant ($X^2 = 3.87$; $p = .144$).

TABLE XIV

GROUP COMPARISON OF CHANGE IN LIKERT SCORES

Change in dyspnea	HFPEF % ($n = 19$)	HFREF % ($n = 26$)	Test statistic
Better (less dyspnea)	57.9 (11)	30.8 (8)	$X^2 = 3.87$; $p = .144$
Same	21.0 (4)	46.2 (12)	
Worse (more dyspnea)	21.0 (4)	23.1 (6)	

Note. Values are percentage of subjects and actual numbers in ( ). HFPEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction.

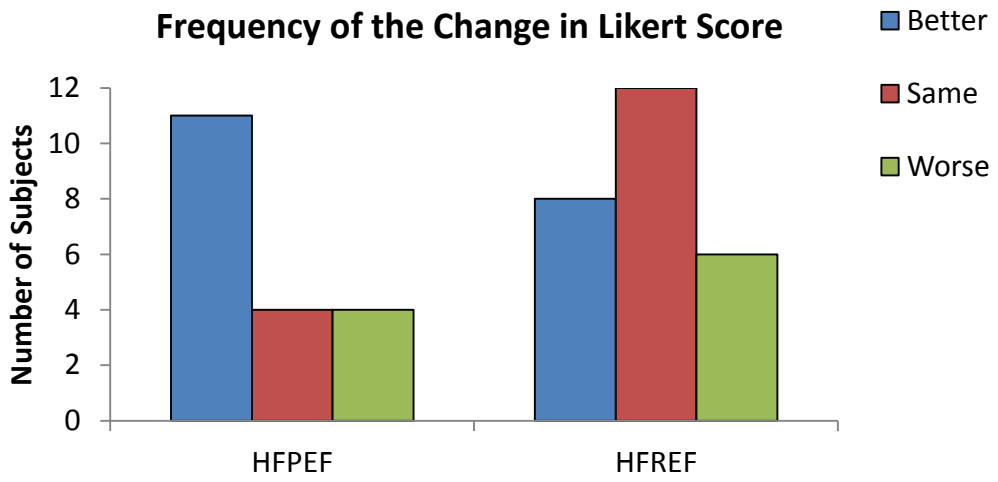

Figure 7. Frequency of the change in Likert Scores. The histogram represents the change in the Likert score from baseline to 3-minute recovery. At 3 minutes of recovery, the HFPEF group reported less dyspnea while the HFREF group reported the same to worsening dyspnea. HFPEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction.

H. Walking Speed As a Covariate

Walking speed (distance walked in meters/360 seconds) is an important covariate when using the 6MW test in older adults (Vuckovic & Fink, 2011). Therefore, we analyzed the Borg scores reported at 6 minutes using walking speed as a covariate (ANCOVA). Borg scores at 6 minutes differed significantly between groups (HFPEF compared to HFREF) when controlling for walking speed (ANCOVA; $F_{(1,41)} = 8.5$; $p = .006$) with the HFPEF group reporting a higher mean dyspnea score. To further understand this relationship we dichotomized the sample into two groups: slow walkers (0.2-0.59m/sec) and fast walkers (> .06m/sec) using the median walking speed of 0.6 m/sec as a cut point. The data was then analyzed as four categories (HFPEF slow walkers; HFPEF fast walkers: HFREF slow walkers; HFREF fast walkers). Although Tukey's post hoc comparisons showed significant differences, the differences of the mean

dyspnea scores between slow walkers with HFPEF as compared to slow walkers with HFREF were not significant (p = .952), as was the difference between the fast walkers between groups (p = .938).

The Borg scores at 6 minutes were also analyzed according to the dichotomized classification (walking speed < / > 0.6). Using the Tukey's post hoc analysis no differences among the four categories were found.

I. Summary

1. At baseline, when using categorical Borg scores (no dyspnea vs. dyspnea > 0.5) there was not a significant difference between HF groups (p = .058), with more HFPEF patients reporting dyspnea compared to HFREF. Similarly, the categorical VAS scores were not different between groups. (82% HFPEF vs. 78% HFREF; Table XI).

2. Using the Borg scale, in both HF groups significant increases were found in the 6-minute dyspnea score compared to the baseline score and increases were of a similar magnitude (Figure 6 and Table XIII).

3. Using the Borg, VAS, and Likert scales, dyspnea scores were compared before and after the 6 minute test. Again, for both HF groups, significant increases were found in the 3-minute recovery score compared to the baseline score and increases were of a similar magnitude (Figure 7 and Table XIII) for the Borg scale. In contrast, using the VAS and change in Likert scores, in both HF groups no significant changes were found between the baseline and 3-minute recovery scores within each group (Table XIII). It is important to note that the VAS took longer to administer.

4. When controlling for walking speed there was a significant between group difference (ANCOVA; $F_{(1,41)}$ = 8.5; p =.006) with the HFPEF group reporting a higher mean dyspnea score.

However, mean Borg scores at 6 minutes were not significantly different between groups when divided and re-examined as slow vs. fast walkers per group.

J. Association Between Dyspnea and Other Variables

The second aim of this study was to describe the association between selected physiologic-related variables and Borg dyspnea scores reported at baseline, during, and after the 6MW test. Since there were no significant differences between HF groups in Borg dyspnea scores, subjects were analyzed as one group ($N = 45$).

Borg scores at baseline and at the end of the 6MW test were not significantly associated with BP, HR, HRR or RR (Table XV). Other variables measured did not correlate with Borg scores measured at these same time points.

TABLE XV

CORRELATION VALUES BETWEEN BORG SCORES AND PHYSIOLOGIC PARAMETERS AT BASELINE AND 6 MINUTES

	SBP_B	DBP_B	RR_B	HR_B	SpO_{2B}	SBP_6	DBP_6	SpO_{26}	HR_6	HRR
Borg baseline $N = 45$	-.076	.100	-.253	-.072	.215	-.290	-.063	.125	-.122	-.043
Borg 6-min $N = 45$	.083	.029	-.101	-1.32	.116	.011	.011	.134	-.189	-.164

Note. Values are correlations for each variable at $_B$ = baseline value and $_6$ = value at 6 minutes. HRR was calculated as $HR_{peak} – HR_{1\ minute\ recovery\ time}$. DBP = diastolic blood pressure; HR = heart rate; min = minute; HRR = heart rate recovery; RR = respiratory rate; SBP = systolic blood pressure; SpO_2 = pulse oximetry

Walking speed and the Borg score at 6 minutes were negatively correlated (r = -.391; p < .01; N = 45). Walking speed also correlated with the duration of HTN (r_s = -.458; p < .01; N = 45).

K. FMD substudy

Patients were randomly invited (selected using a random numbers table) to participate in the FMD substudy. The groups did not differ with respect to gender, age, etiology of HF and NYHA class (Table XVI). However, more HFPEF patients were prescribed anti-glycemic agents (p = .03). Patients were not instructed to discontinue medications on the day of the FMD measurement.

TABLE XVI

BASELINE CHARACTERISTICS OF THE SUBGROUP SUBJECTS

	HFPEF (n = 6)	HFREF (n = 7)	Fisher's exact test
Age, mean ± SEM	62 ± 3.8y	62 ± 3.5y	
Gender %			
Females	83 (5)	57 (4)	.308
Etiology			
Non-ischemic	100 (6)	71.4 (5)	.155
NYHA (actual numbers)			
I	0	2	
II	4	4	
III	2	1	
Smoking %			
Active	33.3 (2)	14.3 (1)	.629
Remote	33.3 (2)	57.1 (4)	
Never	33.3 (2)	28.6 (2)	
Medications %			
ACE/ARB	100 (6)	100 (7)	
Beta blockers	100 (6)	100 (7)	
Statins	83.3(5)	57.1 (4)	.308
Oral anti-glycemics	50 (3)	0	.03
Nitrates	33.3 (2)	14.3 (1)	.416

Note. Values are mean ± SEM or percent and actual number ( ). ACE = angiotensin-converting inhibitor; ARB = angiotensin receptor blocker; HFPEF = heart failure preserved ejection fraction; HFREF = heart failure reduced ejection fraction; NYHA = New York Heart Association; y = years.

No differences were found in the BA characteristics between those measured at baseline and after the 6MW test (Table XVII) with respect to diameter, peak flow, and shear rate. Not all subjects vasodilated in response to reactive hyperemia (cuff up for 3 minutes) at baseline (Figure 8) and after the 6MW test (Figure 9). However, there were significant differences (t = 2.50; p = .029) between the mean FMD for the HFPEF group (10 ± 2.4mm) vs. the HFREF group (3.0 ± 1.55mm) after the 6MW test, with the HFPEF group showing greater vasodilation (Table XVIII). In contrast, the HFREF group showed vasoconstriction.

TABLE XVII

BRACHIAL ARTERY CHARACTERISTICS OF SUBSTUDY GROUP

	Baseline (n = 13)	Post 6MW test (n = 13)	Paired t-test P
Baseline BA diameter, mm	4.23 ± .24	4.33 ± .22	t_{12} =-.937; p =.367
Post cuff release BA diameter, mm	4.30 ±.22	4.34 ±.17	t_{12} = 1.94; p =.075
Δ in Flow, cm/s	10.9 ± 2.1	5.59 ± 1.04	t_{12} =2.16; p =.051
Flow, cm/s	72.53 ± 5.1	69.16 ± 2.7	t_{12} =.875; p =.399
Δ in shear rate, sec	103 ± 12.8	116.9 ± 12.9	t_{12} = -1.46; p .167
Peak shear rate, sec	180.9 ± 18	166.9 ± 16.2	t_{12} = 1.13; p =.280

Note. Values are the mean ± SEM. Peak flow was the maximal velocity measured 60 seconds after cuff release. Δ = change; BA = brachial artery; cm = centimeters; mm = millimeters; sec = seconds.

TABLE XVIII

COMPARISON OF BRACHIAL ARTERY CHARACTERISTICS BETWEEN GROUPS

	HFPEF (n = 6)		HFREF (n = 7)		Independent T-test p
	Pre 6MWT	Post 6MWT	Pre 6MWT	Post 6MWT	
Baseline BA diameter, mm	4.13 ± .42	4.20± .41	4.33 ± .30	4.44±.24	t_{11} =-.937 p =.367
Cuff release BA diameter, mm	4.15 ±.31	4.30±.25	4.43 ±.34	4.39±.26	t_{11} = 1.94 p =.075
Peak flow, cm/s	73.71±5.1	73.98±7.6	71.51±8.9	65.04±5.8	t_{11} =.875; p =.399
Peak SR, sec	187.91 ± 20	184 ± 28	175.9 ± 30	151.65 ± 18	t_{11} = 1.13 p =.280
ΔPeak flow, cm/s	9.16 ± 2.4		11.32 ± 4.5		t_{11} =-.398 p =.698
Δ in SR, sec	26.81 ± 6.1		41.4 ± 15.6		t_{11} = -.660 p =.523

Note. Values are the mean ± SEM. Peak flow was the maximal velocity measured within 30 seconds after cuff release. Change in peak flow and shear rate are the differences between pre 6MWT and post 6MWT values (pre-post) for each group. Δ = change; 6MWT = 6-minute walk test; BA = brachial artery; cm = centimeters; HFPEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction; mm = millimeters; sec = seconds; SR = shear rate.

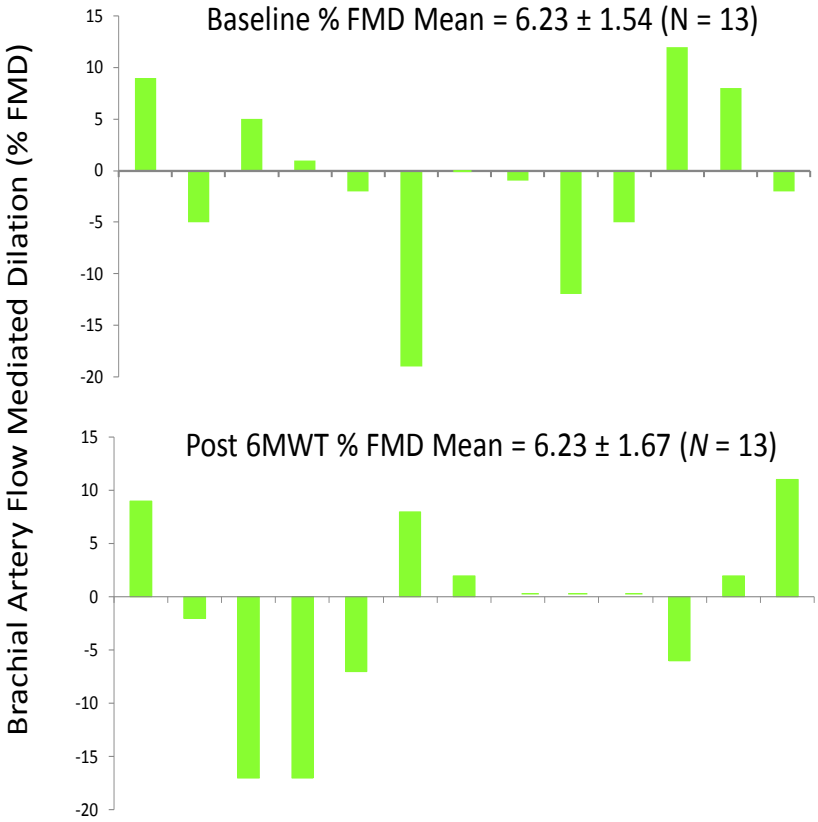

Figure 8. Comparison of percent FMD at baseline (pre 6MW test) and post 6MW test for individual subjects in the substudy illustrating the variation in responses. Values are the actual FMD scores (baseline diameter- cuff down diameter/baseline diameter). 6MWT= 6-minute walk test; FMD = flow-mediated dilation.

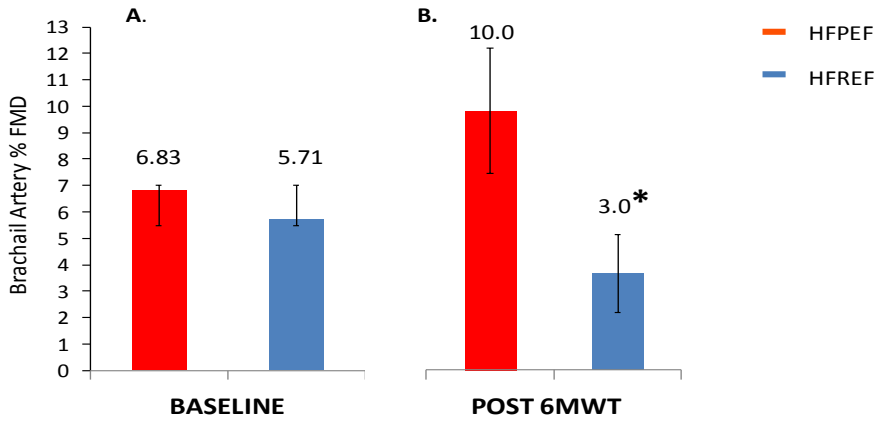

Figure 9. Comparison of % FMD at baseline and post 6MWT by HF groups. A. FMD was similar between groups at baseline (HFPEF: 6.83 ± 2.668; *n* = 6 vs. HFREF: 5.71 ± 1.91; *n* = 7). B. Post 6MWT, FMD was significantly lower in the HFREF group (HFPEF: 10.0 ± 2.42; *n* = 6 vs. HFREF 3.0 ± 1.55; *n* = 7). FMD = baseline diameter- cuff down diameter/baseline diameter; *$p < .05$. 6MWT 6-minute walk test; FMD = flow-mediated dilation; HFPEF= heart failure with preserved ejection fraction; HFREF= heart failure with reduced ejection fraction.

Baseline and post 6 MW test FMD measures did not correlate with Borg dyspnea scores in the subgroup analysis for the entire group (N = 13). However, age was positively correlated to the baseline shear rate ($r = .74$; $p < .001$). When analyzed by HF group, we found significant correlations between the Borg dyspnea scores during the 3-minute recovery time and the brachial artery diameter at baseline for the HFPEF group and FMD post 6MW test for the HFREF group (Table XIX).

TABLE XIX

CORRELATIONS BETWEEN BORG SCORES DURING RECOVERY AND VASCULAR PARAMETERS

	HFPEF (n = 6)	HFREF (n = 7)
Time	Brachial artery diameter at baseline (mm)	Flow-mediated dilation post 6MW test
Borg Score at 6 minutes	.819*	.826*
Borg Score at 7 minutes	.916*	.861*
Borg Score at 8 minutes	.813*	.881**
Borg score at 9 minutes	.813*	.874*

Note. *Denotes significance at $p < .05$. **Denotes significance at $p < .01$. HFPEF = heart failure with preserved ejection fraction. HFREF = heart failure with a reduced ejection fraction.

V. DISCUSSION

The findings of this study were (a) the majority of patients with HFPEF and HFREF reported dyspnea at rest but the percent of HF subjects reporting dyspnea varied with the dyspnea scale, (b) both groups of subjects became dyspneic during the 6MWT and continued to report dyspnea at 3 minutes of recovery, (c) self-reported dyspnea using the Borg scale did not correlate to cardiopulmonary parameters and (d) there were significant differences in the FMD measures before and after the 6MW test between HF groups. Other findings included that walking speed was an important covariate to evaluate dyspnea.

Based on the epidemiological data from HF registries (Yancy, Lopatin, Stevenson, DeMarco, & Fonarow, 2006; Fonarow et al., 2007) patients with HFPEF are often characterized as older, female and with a history of HTN and atrial fibrillation. In this study there were no significant differences in baseline characteristics between groups in terms of age ($t_{(41)} = .513$; $p = .061$), gender ($X^2_{(1)} = 1.27$; $p = .259$), HTN ($X^2_{(1)} = .747$; $p = .387$) or atrial fibrillation ($X^2_{(1)} = 1.28$; $p = .257$). The mean age of the both groups of patients was similar (HFPEF 65.6 ± 2.4 years vs. HFREF 64.2 ± 1.57). The groups did differ with respect to EF ($t_{(41)} = 13.62$; $p < 0.001$) and use of medications with the exception of ACE and CCBs. The use of ACE inhibitors was greater in HFREF patients, whereas CCBs were prescribed for the majority of HFPEF patients. The groups were not significantly different with respect to other demographics, physiologic, and metabolic parameters.

The mean age of the patients in our study, similar to that of other HF studies which included African Americans, was less than the age reported in many clinical HF trials. East, Peterson, Shaw, Gattis, and O'Connor (2004) conducted a prospective study looking at the racial

differences in the outcomes of HF patients identified from a cardiac catheterization database (n = 563 African Americans; EF > 40%). The investigators found African American patients to have a median age of 58 years compared to 65 years in Caucasian patients ($p < .01$), and more likely be female (71% vs. 55%; $p < .010$). Klapholz et al. (2004) reviewed data from a New York HF registry and found 30% of the study population were younger African Americans with a history of HFPEF, HTN and poor renal function. Similar to the findings from these studies, the patients in our study were younger with HTN and atrial fibrillation.

A. Occurrence of Dyspnea

Dyspnea is an important symptom for patients with HF, contributing to frequent hospitalizations and clinic visits, limiting functional capacity, and affecting all domains of life (Johnson, 2010). A primary aim of this study was to compare the presence or occurrence of dyspnea between HFPEF and HFREF patients, both at rest and after exercise. The occurrence of dyspnea varies among HF patients and depending on the HF patient's status; the onset of dyspnea may indicate worsening or decompensated HF and fluid overload. Some chronic HF patients are dyspneic at rest, while others develop dyspnea with daily activities. Since the exact mechanisms underlying this type of dyspnea remain incompletely understood, it underscores the need to perform some type of activity to potentially unmask or induce dyspnea in order to evaluate dyspnea. Some investigators studying dyspnea have used medications to induce dyspnea such the beta adrenergic antagonist, propranolol, or the nicotinic receptor ligand, lobeline (Grant et al., 1999; Butler et al., 2001). In the current study we used the 6MWT as an exercise test to unmask or induce dyspnea in HF patients, since this represents more of a physiologic stimulus and reflects everyday activities.

The three scales did not yield the same results in the measurement of dyspnea at baseline. The Likert scale provided a score that reflected how the subject perceived their breathing "today

compared to most days." As expected, the Likert scale did not provide information related to the intensity or level of dyspnea at baseline. The Borg and VAS scales did provide an intensity score but the results between these scales were different. When analyzing the Borg scores categorically the HFPEF subjects reported greater baseline dyspnea. However, analyses of the VAS scores indicate the HFREF group experienced slightly greater baseline dyspnea but at 3-minute recovery time dyspnea scores for both groups were of a similar magnitude (80.2% vs. 73.7%). Thus the baseline results depended upon the dyspnea scale used. This is important for investigators to note and raises potential implications for measuring dyspnea in clinical trials.

In the present study, we successfully induced or unmasked dyspnea with the 6MWT in the majority of HFPEF and HFREF subjects (84.2 % and 88.5%, respectively). This approach provided the following opportunities and advantages: (a) allowed us to study patients in a clinic setting, (b) provided a non-pharmacologic, non-invasive stimulus for dyspnea, and (c) permitted us to examine a time course for the resolution of dyspnea. In our study we found that both groups of HF patients experienced: dyspnea at rest, significantly increased dyspnea during the 6MW tests (ANOVA, $F_{(1,43)} = 40.81$; $p < 0.001$) and unresolved dyspnea at 3 minutes following the walk test (mean Borg score 3.34 ± 0.61 and 3.19 ± 0.61 for the HFPEF and HFREF, respectively). The resolution of dyspnea is recognized as a key outcome in acute HF trials yet there is no validated tool that is universally accepted to measure acute or chronic dyspnea.

B. Comparison of the Borg, VAS, and Likert Scales

Johnson and colleagues (2010) proposed that the ideal tool to measure dyspnea should be patient reported, multi-dimensional and able to detect change with an established MCID. Currently no dyspnea tool fully meets those criteria.

This study was not designed to test the metrics of the dyspnea scales. Rather the scales were used to determine the level and duration of dyspnea associated with rest and activity. All the scales have been used extensively in pulmonary research.

The MRC scale was used to determine the subject's perception of dyspnea related to everyday activities. However, seven subjects stated they had a difficult time choosing a 'MRC grade' because of the phrases paired together. For example, category 4 weighted the activity of bending when dressing equal to unable to leave the house due to dyspnea. The most common dyspnea-provoking activities selected by the subjects from those listed on the MRC were walking up a hill, hurrying, and walking 100 yards. The selection of 100 yards supports the use of the 6MW test as a method to unmask dyspnea. The MRC inversely correlated to the 6MW distance for each group (HFPEF: $r = -0.64$; $p < .01$; HFREF: $r = -0.59$; $p < .01$), suggesting that the MRC is useful scale to assess level of activity and functional capacity in NYHA Class I-III HF patients. Using a course that includes walking uphill may provide additional useful information about dyspnea.

The results from the three dyspnea scales were inconsistent. However, this inconsistency may be because each scale measured a different aspect of dyspnea. The Borg scale is time series data, therefore subjects likely rated their dyspnea compared to that of the previous minute, for example at 3 minutes in recovery subjects were rating their dyspnea with respect to their 2-minute score not baseline. In contrast, when using the Likert scale subjects had to recall the intensity of their dyspnea at baseline.

The Borg scale was used nine times during the study. In general, subjects may have found this scale easy to understand and familiar. Using a scale from (0-10) with increasing intensity is a commonly used measure. Also, subjects may have previously performed the 6MW test as part of a previous research study or to evaluate pulmonary function.

In contrast, the VAS and Likert scales were probably less familiar to the subjects. Subjects were asked to compare their dyspnea 3 minutes after the 6MW test to their dyspnea at baseline. For some, recalling their level of dyspnea at the initiation of the study may have been difficult. In the substudy the period of time between baseline measures and the 6MW test was as long as an hour. As a result, 'recall or memory' maybe a potential confounder in the use of the VAS and Likert scales. The Likert measured perceived change in dyspnea not the actual intensity, so the results from the Likert might indicate the overall perception of dyspnea over a given time or the overall experience during the study.

Subjects required more time to complete the VAS scale with times ranging from 15 seconds to over a minute. The Borg scale was quick and easy to use. Subjects may find it easier to state or choose a number rather drawing a line perpendicular to the VAS line.

In summary, the familiarity of the dyspnea scale, the timing of administration, and recall ability of the subject may have influenced the results of the study and therefore the congruence among the dyspnea tools. It is important to note that if the Borg scale had not been used we may not have concluded that 6MW test elicited dyspnea or at least at a significant level.

C. Borg Scores and Physiological Measures

We hypothesized that cardiopulmonary measures would correlate to the dyspnea scores; in particular, respiratory measures such as SpO_2. However, those associations were not significant. Instead SpO_2 correlated to GFR ($r = .361$; $p < 0.05$) and hemoglobin ($r = -.344$; $p < 0.05$) and the Borg score at 6 minutes was inversely correlated with walking speed ($r = -.391$; $p < .0.01$; $N = 45$). There could be several reasons why cardiopulmonary measures did not correlate with dyspnea scores. First, it may be related to small sample size. Our study might not have been adequately powered to detect these differences. Second, the relationship between the variables may be complex and cannot be explained by bivariate analysis. Dyspnea may be influenced by a

latent variable that is not physiological. The study was not designed to analyze the data by cluster analysis or latent variable analysis which requires continuous data. Collecting the physiologic data continuously throughout the 6MW test rather than discrete times may show patterns that were undetected with the current design. Also, the 6MW protocol used in the study followed the standard ATS protocol. This protocol allowed the subject to stop and rest. In this manner the subject can self-select their pace and activity level. For example, if the subject becomes dyspneic and stops, SpO_2 may drop but returns to normal when the subject stops. Thus it may appear that the SpO_2 was normal throughout the walk. In this study nine subjects stopped during the 6MW test (HFPEF: n= 2; HFREF: n = 7).

D. FMD Measures and Correlations to Dyspnea Scores

We analyzed the FMD data using several approaches. Initially, the FMD measures were analyzed as one group (n = 13). We found no significant differences in the BA diameter or peak flow (determinants of FMD) at baseline compared to post 6MW test. However, the change in FMD approached statistical significance (p = .051) and may have been significant with a larger sample size.

When analyzed by type of HF we found significant differences in FMD at baseline compared to post 6MW test ($p < .05$). Importantly, there were no significant differences in the baseline BA diameter and peak flow between groups. To better understand this difference we looked at the individual FMD response at baseline and after the 6MW test depicted in Figure 8. At baseline and after the 6MW test subjects show three responses: normal or blunted vasodilation (normally 8-10% in healthy individuals), no response (0% FMD), and vasoconstriction (Corretti et al., 2002). The lack of response (0%) may simply indicate that subjects were already maximally vasodilated. The reasons for vasoconstriction may be twofold. First, the vasoconstriction may be related to a methodological issue. Dean, Libonat Madonna,

Ratcliffe, and Margulies (2011) measured FMD responses to upper body exercises in HF patients (n = 9) on inotropic support awaiting transplantation using a protocol with cuff inflation for two minutes. They concluded that the paradoxical vasoconstriction seen in some subjects may have been due to two minute cuff inflation. Likewise in our study, a cuff inflation time of three minutes may be an inadequate stimulus (i.e. not enough shear stress) to induce an endothelial response. We chose a three minute cuff inflation anticipating an older, fragile population; however, the mean age of the substudy sample was 62 ± 3.6 years. In addition, the reduced brachial artery FMD response suggests that there could be impaired nitric oxide (NO) release or bioavailability and it is well established that patients with HF have reduced levels of NO (Shah, 2012). Androne et al. (2006) compared vasodilation responses to exercise and ischemia in African Americans (n = 69) vs. non-African Americans (n = 188) using brachial artery FMD. After adjusting for HTN, multivariate analyses indicated significantly impaired vascular function in response to ischemia in the African American group (p =.02). Finally, it is not clear if African Americans respond to ACE inhibitors and CCBs in the same manner as has been reported for subjects in many of the clinical trials (Shah, 2012). Consequently, the mixed FMD response may be indicative of a mixed response to the pharmacological therapies prescribed for the subjects.

We also examined the relationship between self-reported dyspnea and vasoreactivity. To our knowledge this is the first study to examine this relationship. We found that dyspnea scores reported throughout the recovery period (6 minutes to 9 minutes) strongly correlated to baseline BA diameter for the HFPEF group (r = .813-.916, p < .05) and FMD post 6MWT for the HFREF group (r = .82-.78, p < .05; r = .88, p < .01). However, the significance of this finding is not clear mainly due to the fact that other studies which have measured FMD have not reported dyspnea scores. For example, in our study the mean BA diameter was similar to that reported by Haykowsky et al. (2012) for HFPEF patients (4.13 mm vs. 4.58 respectively). Although

cardiopulmonary testing was performed by Haykowsky and colleagues dyspnea scores are not reported.

Since we did not assess the response to nitroglycerin we cannot comment on the endothelial independent vasodilation. This is a limitation of the study.

E. Conclusions

This study is novel for several reasons. First, few HF studies have been dedicated to exclusively enrolling African American patients. Second, a limited number of studies have compared vascular characteristics between subjects with HFPEF vs. HFREF. Lastly, to our knowledge this is the first study to examine the relationship between dyspnea and FMD measures. Overall the findings of this study demonstrate that the 6MW test is an effective method to unmask dyspnea in NYHA Class I-III HF patients. The Borg scale detected significant changes in dyspnea during the 6MW test in HFPEF and HFREF. Differences in vasoreactivity may be associated with FMD and type of HF.

F. Limitations

There are several limitations of this study. First, we use a convenience sample to enroll a small sample. A single investigator recruited subjects and collected all the data with the exception of performing the ultrasound. The age range of the sample was wide (50y-89y) and raises the possibility that age may have been a confounding factor in subjects over 75 years. The date of echocardiogram used to determine eligibility for the study criteria ranged from three months to two years. Subjects who were enrolled using criteria based on an "older" echo may have had a change in their EF and been allocated to the wrong group. Since our sample exclusively included African Americans the generalizability of the data to other populations are limited. In addition, several patients with an ejection fraction of 40-45% were excluded. It is

important to note that subjects who were clinically unstable were excluded and therefore, our findings do not reflect the experience of acute HF.

We had designed a recruitment plan using the HF clinic as the source to identify patients with HFPEF. However, there were fewer patients diagnosed with HFPEF than anticipated. This may be because HFPEF is underdiagnosed and undertreated with fewer referrals to cardiology.

Also, we acknowledge there is an affective component to the experience of dyspnea. This dimension was not measured but may have been a confounding factor. Repeating the 6MW test and averaging the distance is recommended when using the test as an outcome variable or assessing functional capacity due to the associated learning effect (Guyatt et al., 1985; Vuckovic & Fink, 2011). Finally, the sample size (n = 19 HFPEF patients; n = 26 HFREF patients) may have not provided adequate statistical power to detect significant differences for all the aims of the study.

There are additional limitations to the substudy. Importantly, medications were not held prior to the study. Allowing subjects to continue medications may be a confounding factor when measuring FMD and all of the subjects were taking at least one vasodilator. However, this approach may provide insights into whether or not those who are already optimized on pharmacological therapy may benefit from additional therapy. Using a protocol that included cuff up for five minutes may have yielded different results. A strength of the substudy was that personnel performing the ultrasound and analyzing the images were blinded to the patient group, reducing bias.

G. Future Research

The results of this study indicate that HFPEF and HFREF patients report dyspnea at rest, after the 6MW test (physical activity) and for 3 minutes of recovery time, but the occurrence and level of dyspnea reported varies with the dyspnea scale utilized. Also the relationship among the

physiologic variables related to dyspnea is not clear. Suggestions for future research would include:

1. Evaluating dyspnea scales utilizing larger sample sizes in an effort to detect significant or clinically meaningful findings.
2. Measuring dyspnea for an extended time (> three minutes) during the recovery period after physical activity.
3. Examining the relationship among variables using instrumentation capable of recording continuous data for physiologic date in a sample size large powered for cluster or factor analysis.
4. Utilizing a design powered to examine dyspnea by type of HF and gender.
5. Including measures of respiratory muscle function along with skeletal muscle function.

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Appendices

ID
Study

Appendix A

Medical Record Review

Age _____Sex _____Ht _____Wt _____BMI _____ NYHA class _____ Last adm AHF:_____

Etiology: Ischem NonIschm _____ Yrs with HF: _____ M/S Employed Ed_____

Date of last echo:_____ Documented EF%: _____LA size_____cm_ LA vol mild mod sev

Pulmonary Function test : Date_____ FEV1: _____

Medications:

Beta blockers metroprolol tartrate 100 200 bid ASA 81 325

Metroprolol succinate 200 daily Amiodarone _____mg qd

Carvedilol dose 25 q12 Amlodipine _____mg qd

ACE inhibitor Lisinopril 40mg _____ mg_____

Statin_____ dose_____

Furosemide ____mg _____

Comorbid Conditions

HTN_____ Years diagnosed: CAD _____ yrs HL_____y

DM Type 1: _____ Type 2: _____ CA_____y chemo

COPD: _____ y Smoker _____y Quit_____

Asthma: _____y Emphysema: _____ y Pulmonary HTN: _____y

EtOH Yes No Illicits: Yes No Hx Obesity_____ Arthritis: _____y

Thyroid: hyper /hypo _____y

EP Devices: BiV ICD Pacemaker Assistive devise: uses cane

DATE	LAB TEST	RESULT	**DATE**	LAB	RESULT
	Hemoglobin			Na	
	Hematocrit			K	
	Platelet Count			Cl	
	Blood Glucose				
	HgbA1C:			BUN (units):	
	Uric acid			Creatinine	
	BNP (ng/ml)			CrCl	
				GFR	

Appendix B

6MW DATA

Spiro #	**Pretest baseline**	**1** You are doing well	**2** Keep up the good work 4 min to go	**3** You are doing well. Half way done	**4** Keep up the good work 4 min to go	**5** You are doing well. 1 min to go	**6** At 15 sec I will tell you when to stop	**Immed**	**Post** 1 minute	**Post** 2 minute	**Post** 3 minute	**Post**
FVC		**Xx**	**xx**	**xxx**	**xx**	**xx**	**xx**	**xx**	**xx**	**xx**	**xx**	**Laps**
FEV_1												
ratio												
BP mmHg		Xx	xx	xx	xx	xx	xx					
SpO_2 %		%			%			%				
HR												
Borg	D											
	F											
RR		Xx	xx	xx	xx	xx	xx					
VAS		Xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	
Likert		Xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	
MRC		Xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx

Stops_____ Laps_____ 6MWD _____ft_____m Effort_____

Time if ended early_____ reason _____ Notes

Modified Medical Research Council Dyspnea Scale

Grade

0 "I only get breathless with strenuous exercise"

1 "I get short of breath when hurrying on the level or walking up a slight hill"

2 "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"

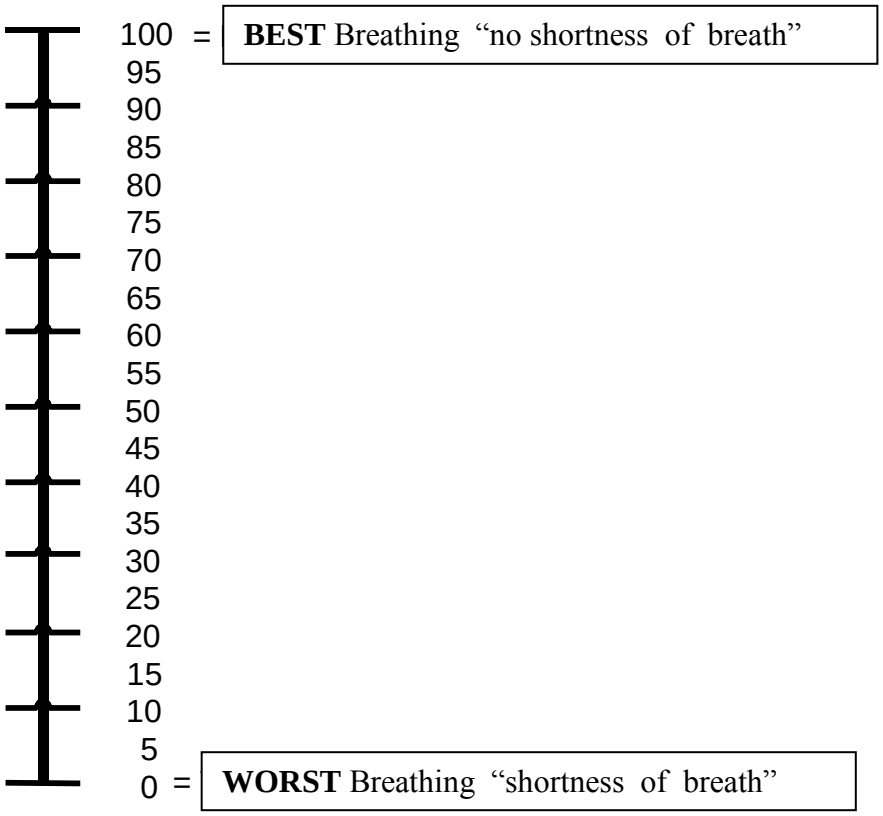
3 "I stop for breath after walking about 100 yards or after a few minutes on the level"

4 "I am too breathless to leave the house" or "I am breathless when dressing"

Adapted from Fletcher CM, Elmes PC, Fairbairn MB et al. (1959). The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. British Medical Journal 2:257-66.

Appendix D

Vertical Visual Analog Scale



Note. Patient is asked to mark their level of dyspnea with a horizontal line.

Appendix E

7- point Likert Scale

+3 Markedly better

+2 Moderately better

+1 Mildly better

0 No change

-1 Mildly worse

-2 Moderately worse

-3 Markedly worse

Appendix F
Modified Borg Scale

Modified Borg Dyspnea Scale

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Patient Instructions for Borg Dyspnea Scale

"This is a scale that asks you to rate the difficulty of your breathing. It starts at number 0 where your breathing is causing you no difficulty at all and progresses through to number 10 where your breathing difficulty is maximal. How much difficulty is your breathing causing you right now?"

Appendix G: 6-Minute Walk (6MW) Protocol

Standardized Procedure for the 6-Minute Walk Test

1. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale (see Borg scale –same scale for dyspnea and fatigue).
2. Set the lap counter to zero and the timer to 6 minutes.
3. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.
4. Instruct the patient as follows:

PI: "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

5. Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

PI: "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. Start now, or whenever you are ready." Position the patient at the starting line. You should also stand near the starting line during the test.

6. As soon as the patient starts to walk, start the timer.
7. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.
8. After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go." Record HR and pulse oximetry.
9. When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go." Record HR and pulse oximetry.
10. When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done." Record HR and pulse oximetry.
11. When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left." Record HR and pulse oximetry.

12. When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go." Record HR and pulse oximetry.
13. Do not use other words of encouragement (or body language to speed up).
14. If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.
15. When the timer is 15 seconds from completion, say this:

PI: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you." When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

16. Post-test: Record the post walk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?" Have the patient sit down and continue to monitor them for additional 3 minutes.
17. Record BP, HR, pulse oximetry at 1, 2, 3 minutes. Heart rhythm will be continued to be monitored.
18. Record the number of laps from the counter (or tick marks on the worksheet).
19. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
20. Congratulate the patient on good effort and offer a drink

Appendix H

Permission Letter

Lippincott Williams & Wilkins
251 W. Garfield Street
410 528 4000 tel
www.LWW.com

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Karen Vuckovic
18W331 Sidney Ave.
Villa Park IL 60181

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CURRICULUM VITAE

Karen M. (Janus) Vuckovic, PhD, RN, ACNS-BC, CCRN
Department of Biobehavioral Health Science
University of Illinois at Chicago

EDUCATION

2013 PhD, Nursing Science, University of Illinois, Chicago, IL
1995 MS, Northern Illinois University DeKalb, IL
1981 BS, Nursing, Creighton University, Omaha, NE
1979 BS, Biology, University of Illinois, Champaign-Urbana IL

PROFESSIONAL LICENSURE/CREDENTIALING

2004-present	Medical Staff Credentialed, University of Illinois Medical Center
2001–present	Advanced Practice Nurse, IL
2002-present	DEA License
1981-present	Registered Professional Nurse, IL License

CERTIFICATIONS

2006-present	ANCC Adult CNS
2011-present	Advanced Cardiac Life Support Certification
1998-2002	Advanced Cardiac Life Support Regional Faculty
1991-2006	Advanced Cardiac Life Support Certification/Instructor
1984-2013	Critical Care Nurse Certification (CCRN)
1981-present	CPR certification

PROFESSIONAL EXPERIENCE

2006-present	Teaching Associate, Department of Biobehavioral Nursing, University of Illinois at Chicago.
2003-2006	Clinical Faculty, Department of Medical Surgical Nursing, University of Illinois at Chicago.
2010-current	Advanced Practice Nurse; University of Illinois Medical Center at Chicago, Heart Failure Program; Outpatient Services.
2004-2008	Advanced Practice Nurse; University of Illinois Medical Center at Chicago, Heart Failure Program; Inpatient Services.
2000-2003	Advanced Practice Nurse, Department of Cardiology Heart Failure Program, Evanston Northwestern Healthcare System, Evanston, IL.
1998-2000	Clinical Nurse Specialist, Department of Nursing, Evanston Northwestern Healthcare, Evanston IL.

1993-1998	Clinical Practitioner Educator, Department of Nursing Education, Evanston Northwestern Healthcare, Evanston, IL.
1990-1992	Instructor, Health Care, Wright Junior College, Chicago, IL.
1981-1993	Staff Nurse Level IV Clinician and Educator, Intensive/Coronary Care Unit, Holy Family Hospital, Des Plaines, IL.

HONORS AND AWARDS

2013	Dean's Award for Dissertation Research, College of Nursing
2013	Excellence in Teaching Award, Graduate Student Organization, University of Illinois at Chicago.
2012	Nominated for American Academy of Colleges of Nursing Teaching Award by Dept. Head.
2012	Excellence in Teaching Award, Graduate Student Organization, University of Illinois at Chicago.
2011	Keynote address, Graduate Entry Program Commencement Ceremony. Invited by students.
2009	Departmental Teaching Excellence Award, Council for Excellence in Teaching and Learning, University of Illinois at Chicago. Award given to the Department of Biobehavioral Health Science.
2008	Awarded Golden Key for academic excellence.
2006	Excellence in Clinical Practice and Leadership Award, Sigma Theta Tau, Alpha Lambda Chapter. Nominated by peers.
2002-2003	Recognized by Metropolitan Chicago American Heart Association for contribution to the Cardiovascular Nursing Forum.
1997	"President's Award" Evanston Hospital Corporation for the implementation of a program to care for interventional cardiology patients on a telemetry unit.
1993	"President's Award" Evanston Hospital Corporation for the creation and implementation of a hospital wide conscious sedation program.
1994-present	Sigma Theta Tau, Beta Omega Chapter.
1993	Scholarship Award for graduate education, Northwest Chicago Area Chapter (NWCAC) of the American Association of Critical Care Nurses.
1986	Recognized for contribution to the patient care committee at Holy Family Hospital.
1975	Mayor Daley College Scholarship Award.

RESEARCH FUNDING

Extramural

2011-present	Vuckovic, K.M. (PI). *Dyspnea in Heart Failure with Preserved Ejection Fraction.* Midwest Roybal Dissertation Award (P30) center grant from the National Institute on Aging/NIH (PI: Susan L. Hughes, DSW; Grant # 5P30AG022849-07; UIC PAF # 2009-02182; Parent Protocol for the center grant #2009-0668). (Direct costs $4,000).

Intramural

2012 *Dyspnea in Heart Failure with Preserved Ejection Fraction*. Seth Rosen Graduate Research Award, College of Nursing ($1,000 in direct costs).

2011 *Dyspnea in Heart Failure with Preserved Ejection Fraction.* University of Illinois Alumni Research Award ($1,000).

ONGOING RESEARCH

2012-ongoing Co-investigator, "Comparison of Outcomes Between Nursing Students Taking Exams With and Without Notes in a Pharmacotherapeutic Course"

2011-ongoing PI, "Dyspnea in Heart Failure with a Preserved Ejection Fraction"

PUBLICATIONS (*denotes peer reviewed manuscripts)

*Vuckovic, K.M., Piano, M.R., Phillips, SA. Effects of exercise training on peripheral vascular endothelial vasoreactivity in patients with heart failure with reduced ejection fraction. Heart, Lung, and Circulation. 2013 Jan.19;. (Australian Cardiovascular Society Journal; Heart Failure edition; Invited).

*Vuckovic, K.M., Fink, A. M. The 6-min walk test: Is it an effective method for evaluating heart failure therapies. Biologic Research in Nursing. 2012 April;14(2):147-159.

*Vuckovic, K., Richlin, D. Bradycardia induced by hyperkalemia. American Association of Occupational Health Nurses Journal. 2004 May;52(5):186-7.(Invited.)

*Moyer-Knox, D., Mueller, T., Vuckovic, K., Mischke, L., Williams, R. Remote titration of carvedilol for heart failure patients by advanced practice nurses. Journal of Cardiac Failure. 2004 June;10(3): 219-24. Article was the subject of the editorial comment for the issue.

*Mueller, T., Vuckovic, K., Knox, D., Williams, R. Telemanagement of heart failure: a diuretic treatment algorithm, for advanced practice nurses. Heart and Lung. 2002 Sep-Oct;31(5): 340-7.

BOOK CHAPTERS

Piano, M. R., Vuckovic, K. Hypertension & Peripheral Vascular Disease. In D. Klein, K. Lauer, L. Quinn (Eds.), Concepts of Pathophysiology: Common Health Problems & Risk Factors. McGraw Hill. Submitted Sept, 2011, (in review).

MEDIA

Vuckovic K. Reading Nutrition Labels. Gazette, 2010 January;27(9):28.

INTERNET

Vuckovic, K. Cardiovascular Update for Occupational Health Nurses (2005). Available to members only at www.aaohn.org

ORAL PRESENTATIONS (*denotes invited presentation)

National

Vuckovic, K.M., Phillips, S.A. Research on Exercise Interventions on Peripheral Vascular Health in Patients with Heart Failure: Methods and Clinical Implications. National Harbor, Maryland; June 10, 2011. (Joint presentation).

*Vuckovic, K.M. Glycemic Control: Definitions, Standards and Controversies. American Heart Association Scientific Sessions, Orlando, FL; November, 2007.

Regional

*Vuckovic, K.M. What part of NO Don't You Understand: The Contribution of Nitric Oxide. American Association of Critical- Care Nurses Northwest Chicago Area Chapter Midwest Conference, Lincolnshire, IL; March, 2009.

*Vuckovic, K.M. Glycemia in Heart Failure. American Association of Critical- Care Nurses Northwest Chicago Area Midwest Conference, Lincolnshire, IL; March, 2009.

*Vuckovic, K.M. Metabolic Syndrome. American Association of Critical- Care Nurses Northwest Chicago Area Midwest Conference, Arlington Heights, IL; March, 2005.

*Vuckovic, K.M. From Ischemia to Infarct. Preventive Cardiovascular Nurses Association Midwest Regional Meeting, Oakbrook, IL; October, 2003.

*Vuckovic, K.M. Optimizing Beta Blockade. American Association of Critical- Care Nurses Northwest Chicago Area Midwest Conference, Arlington Heights, IL; March, 2003.

Vuckovic, K.M. Evidence Based Lipid Management. Association of Critical- Care Nurses Northwest Chicago Area Midwest Conference, Arlington Heights, IL; March, 1998.

Local

*Vuckovic, K.M. Shock. American Association of Critical- Care Nurses East Central Illinois Annual Meeting, Urbana, IL; April, 2008.

Vuckovic, K.M. Heart failure 101. Lutheran General Hospital, Park Ridge IL, December, 2003.

Vuckovic, K.M. The Electrical Management of Heart Failure. Evanston Northwestern CHF Nursing Forum, Glenview, IL; April, 2002.

*Vuckovic, K.M. CRT: Cardiac Resynchronization Therapy. American Heart Association Cardiovascular Nursing Forum, Chicago, IL; May, 2002.

*Vuckovic, K.M. The Pathophysiology of Unstable Plaque. American Heart Association Cardiovascular Nursing Forum, Chicago, IL; August, 1999.

Vuckovic, K.M. Salinger, M. Lipid Management, Glenbrook Hospital Grand Rounds, Evanston, IL September, 1997.

POSTER PRESENTATIONS (presenting author(s) underlined, * presented at professional meeting)

Dickens, C., Franklin, C., Vuckovic, K., Nehmer, M. DiDomenico, R., Kerbow, D., Stamos, T., Kondos, G. Improving the Heart Failure Readmission Rate at an Urban Medical Center, University of Illinois Medical Center Nursing Research Symposium, May, 2011.

*Fink A., Vuckovic, K., Piano M., Fatigue in Systolic Heart Failure, American Association of Heart Failure Nurses 2008 Annual Meeting, Boston, MA, June, 2008.

*Fontana, D., Vuckovic, K., DiDomenico, R., Kondos, G. The Effectiveness of Implementation of Medical Center Guidelines and Focused Education of the JCAHO Quality Measures in Patients Hospitalized for HF, Fourth International Evidence-Based Nursing Preconference, Sigma Theta Tau 17th International Nursing Research Congress, July, 2006. Oral presentation.

*Fontana, D., Didomenico, R., Vuckovic, K., Kondos G. Long-Term Outcomes in Patients Hospitalized for Acute Decompensated Heart Failure Stratified by Baseline Renal Function and Blood Pressure, American Heart Association Outcomes Symposium, May 2006.

*Kowalski, J., Prince, S., Vuckovic, K., To Bis or Not to Bis: A Look at the Usage of Bis Monitoring in Academic vs. Community Institutions, University of Illinois Research Day, April, 2006.

*Williams, R., Mueller, T., Knox, D., Vuckovic, K. Mischke, L. Development and Application of a Clinical Decision Algorithm to Guide Nurse Management of CHF Patients Through Daily Telemonitoring: Reductions in Hospitalizations and Practitioner Variation. Association of Critical- Care Nurses Northwest Chicago Area Midwest Conference, Arlington Heights, IL March, 2002

*Mayer, K., Vuckovic, K., Williams, R. Integrated CHF Rounds, Association of Critical-Care Nurses Northwest Chicago Area Midwest Conference, Arlington Heights, IL March, 1997

Vuckovic, K. Evaluating the Effectiveness of Resuscitation, Northern Illinois Research Day, May, 1995.

PUBLISHED ABSTRACTS (abstract was presented in a poster format at professional meeting; presenting author underlined)

Groo, V., Moyer, D., Mueller, M., Vuckovic, K.M., Williams, R., Effectiveness of Toprol XL in heart failure patients intolerant to Coreg. Journal of Cardiac Failure 9(5)supplement: 2003. Poster at the Heart Failure Society of America 7th Annual Meeting, Boca Raton FL, September, 2003.

Knox, D., Mueller, T., Vuckovic, K.M., Acker, K., Mischke, L., Just, V., Williams, R. Remote titration of beta-blocker therapy for heart failure by advanced practice nurses, titration protocols, and daily patient management. Journal of Cardiac Failure 8(5)supplement: 2002. Poster at the Heart Failure Society of America 6th Annual Meeting, Boca Raton FL, September, 2002.

Williams, R., Mueller, T., Knox, D., Vuckovic, K.M., Mischke, L. Development and application of a clinical decision algorithm to guide nurse management of CHF patients through daily telemonitoring: Reductions in hospitalizations and practitioner variation. Published in the Journal of Cardiac Failure 7(5) supplement : 2001. Poster at the Heart Failure Society of American 5th Meeting, Washington DC, September, 2001.

PROFESSIONAL MEMBERSHIP

2007-present	The American Physiological Society
2006-present	American Association of Heart Failure Nurses
2000-present	Council on Cardiovascular Nursing, National American Heart Association
2005-present	Heart Failure Society of America
1995-1997	Society of Critical Care Medicine, invited member
1994-present	Sigma Theta Tau, Beta Omega Chapter member
1985-present	American Association of Critical Care Nurses, Local
1981-present	American Association of Critical Care Nurses, National

PROFESSIONAL AND COMMUNITY SERVICE

Reviewing

2013	Abstract reviewer, Nursing Research Award, University of Illinois Health Care Systems
2006	Book review, *Advanced Health Assessment and Diagnostic Reasoning*

2004, 2005	Student Scholarship Applications Northwest Chicago Area Chapter of American Association of Critical Care Nurses.
2003-2007	Abstract reviewer, American Heart Association Council on Cardiovascular Nursing Research Award.

Service

2013	American Heart Association, Cardiovascular Nursing Council Clinical Practice Award Committee (Invited).
2004-2005	Board of Directors Member, Northwest Chicago Area of American Association of Critical Care Nurses (NWCAC-AACN), Awards and Scholarship Chair.
2000-2004	Co-chair of the Midwest American Heart Association, Cardiovascular Nursing Forum.
1995	Chair, Exhibits/Posters for the Midwest Conference for NWCAC.
1994-2004	Committee member, Local AHA Cardiovascular Nursing Forum.
1991-1993	Board of Directors NWCAC-AACN, Marketing Chair.
1985-1994	Committee member (education, seminars, membership, marketing), Local AACN Northwest Chicago Area Chapter.

Media

1994	Interviewed for an article regarding nursing in feature section "Jobs," Chicago Tribune.

Precepting Graduate Students

2006-present	Preceptor, University of Illinois
2001-2003	Preceptor, UIC PharmD students, Heart Failure Clinic, Glenbrook Hospital, Glenview, IL
2001-2003	Adjunct Faculty, North Park College, Chicago IL
1996-2005	Adjunct Faculty, Rush University, Chicago, IL
1998-2002	Adjunct Faculty, Loyola University, Maywood, IL

UIC Committees

2005-2006	Ad hoc Committee Member, Integrating evidence based practice into the nursing curriculum
2004-2007	Medical-Surgical representative for the Nursing Service Plan College of Nursing
2005-2006	Member, Doctorate in Nursing Practice Curriculum Committee
2003-present	Member, Quality Team for Heart Failure/Acute Myocardial Infraction, University of Illinois Health Care Systems at Chicago

Community Service

2012	Tell a Friend: CV disease and women, Presenter, Faith Community Church, Bensenville, IL
2006-2012	Volunteer, Night Ministry
2004	Stomp Out Stroke, Coordinator, Peace Church, Bensenville, IL
1986-1988	Volunteer, PADS, Peace Church, Bensenville, IL

ACADEMIC TEACHING EXPERIENCE (University of Illinois at Chicago) GEP= graduate entry program; non-traditional nursing students)

2013	Guest lecturer, Update on Atrial Fibrillation, UIC, CON 30 Acute Care and Adult NP students.
2011, 2012	Lecturer, Kyung Hee University semester abroad, taught cardiac section (24 hours via translator) to 10 undergraduate Korean nursing students; (8 hours of instruction in 2012).
2011	Guest lecturer, Management of Acute and Chronic Heart Failure, Rush University, 75 APN students, Chicago, IL.
2010-2013	Guest lecturer, PT 506 Physical Therapy Rehab Seminar, "Heart Failure and Exercise" 15 students.
2010-present	Coordinator and Lecturer, Pathophysiology and Pharmacotherapeutics, NUSC 401 and 402, 7 SEM). Core GEP course. Content taught: all CV disorders, basic pharmacology, cell injury, inflammation, genetics, pharmacogenomics, sensory, oxygenation, reproduction. Revised course 2010.
2010-2011	Lecturer, Urban Health Program. Taught respiratory and cardiac lectures to 5-10 incoming masters level students.
2009-present	Guest lecturer, Heart failure management and arrhythmia recognition (PT 635) 56 Physical Therapy students (3 SEM).
2006-present	Lecturer, (NUSC 531 Pharmacotherapeutics) Core course for the master's program (5 SEM) 90-100 students.
2006-2011	12 EKG recognition for 20-30 APN students (1-2 hours) annually.
2006-2010	GEP senior clinical synthesis and capstone project. Converted student schedules and journal entries to online format. Supervised 7-12 students and staff preceptors in critical care settings at UIC Medical Center. Developed Jesse Brown VA hospital as new clinical site. In 2009 student invited to present capstone project as featured evidence-based practice presentation for nurses week at Jesse Brown VA hospital.
2007-2009	Guest lecturer. Undergraduate special topic course in critical care nursing (3 SEM) 10-15 undergraduate nursing students.

2007	Co-coordinated fundamentals of nursing for undergraduates (NUSC 225, 1 SEM) 70 undergraduate nursing students.
2006-2007	Instructor for undergraduate research section (NUSC 322, 2 SEM). Students placed first and third in poster competition in 2006.
2005-2006	Coordinator, GEP fundamentals course and lab (7 hr credits); coordinated clinical placements, lab simulations, and physical assessment for first GEP class (40 students).
2004-2006	Guest lecturer, cardiac and respiratory lectures in physical assessment 100 undergraduate class (2 SEM).
2003-2006	Clinical Instructor for 8-10 junior/senior undergraduate medical-surgical practicum (3 SEM).

NON-ACADEMIC TEACHING EXPERIENCE

1994-2000	Taught 12-lead, basic EKG and critical care courses every 8 weeks to new nursing orientees.
1985-1994	Taught basic principles of EKG interpretation to staff nurses. Designed and implemented unit orientation for new staff in critical care units.