# THE IDENTIFICATION OF BIOMARKERS THAT PREDICT IMPENDING HEART FAILURE PRESERVED EJECTION FRACTION (HFpEF)

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## ABSTRACT

CAROLYN L. LEKAVICH: The Identification of Biomarkers that Predict Impending Heart Failure Preserved Ejection Fraction (HFpEF)
(Under the direction of Dr. Debra J. Barksdale)

The overall purpose of this investigation was to utilize pathophysiologic, methodologic and empirical approaches to address gaps in our understanding about the identification of biomarkers that predict impending HFpEF. To guide this exploration, three papers were developed that outline the current scope of the problem, define strategies to contribute to the current science, analyze the patient population, report the results of one empirical study and report on the impact and implications for future research.

## ACKNOWLEDGEMENTS

The privilege of pursuing my PhD over the last four and a half years has brought many incredible gifts into my life. I have deep appreciation for many family members, friends, and colleagues and for the experiences that this journey enabled.

Throughout this process I consistently relied on my spiritual practice and the primary themes of kindness and respect.

To my mother, Florence, for her unwavering support and love regardless of the situation or time. I know that Dad would have loved to have shared this time with us. To my daughter Venia who teaches me every day about what matters most in life. To my brothers Ken, Tom, late brother, Barry, and my sister in law, Mary, thank you for your care and willingness to 'always be there'. To my godmother, MaryAnn, who is a mentor and inspired me to become a nurse.

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**TABLE OF CONTENTS**

## LIST OF TABLES

Tables

# CHAPTER 1

## INTRODUCTION

Heart failure (HF) is a clinical syndrome defined by characteristic symptoms and physical findings resulting from structural or functional impairment of left ventricular (LV) filling or ejection in which the heart is unable to pump enough blood to meet the metabolic needs of the body (Borlaug & Paulus, 2011; Redfield et al., 2003; Yancy et al., 2013). Based on HF guidelines published in 2013 by the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA), HF can result from disorders of the great vessels, myocardium, endocardium, pericardium, heart valves and from metabolic abnormalities, however, most commonly HF is a disease of the left ventricle (LV) (Yancy et al., 2013).

The pathophysiological understanding of HF has changed notably over the last 25 years (Little & Zile, 2012). Previously, HF was typically associated with ischemia due to coronary artery disease that resulted in LV systolic dysfunction "pump failure" with reduced ejection fraction (EF). With emerging evidence that symptoms of HF could be associated with a wide range of LV function ranging from severe dilatation and reduced EF to preserved EF suggested that HF was not just a condition of systolic dysfunction (Little & Zile, 2012; Yancy et al., 2013). Terminology evolved to include HF syndromes with EF $\geq$50% described as diastolic heart failure (DHF) and as the pathophysiological mechanisms of HF became clearer the terms were changed to heart failure preserved ejection fraction (HFpEF)

and heart failure reduced ejection fraction (HFrEF) (Little & Zile, 2012). The extent to which HFpEF and HFrEF overlap versus represent distinct phenotypes is controversial (Owan et al., 2006). A more recent paradigm suggests that HFPEF is a pro-inflammatory state driven by multiple co-morbidities (Paulus & Tschope, 2013).

To more precisely describe this syndrome, the term HF is not synonymous with terms such as cardiomyopathy or LV systolic or diastolic dysfunction; instead these terms describe possible structural or physiological states that contribute to HF (Yancy et al., 2013). To be comprehensive in describing the scope of this syndrome a list of conditions that may contribute to the development of HF include: a) familial causes (found through genotyping), b) metabolic causes; obesity (excessive adipose tissue causing an increase in circulating blood volume), diabetic (considered a risk factor for HF), thyroid disease (hyperthyroidism associated with sinus tachycardia or hypothyroidism associated with bradycardia and decreased ventricular filling), c) toxic causes; alcohol (causes biventricular dysfunction and dilation), cocaine (dilatation), cancer therapies/chemotherapy (anthracyclines, Herceptin, cyclophosphadmide, taxoids, mitomycin-C, 5-fluirouracil and interferons, d) other toxins causes; ephedra, anabolic steroids, chloroquine, clozapine, amphetamine, methyphenidate and catecholamines and nutritional deficiencies such as anorexia, AIDS, pregnancy (thiamine deficiency related) definciency in l-carnitiine, e) tachycardia induced causes; (duration and rate of the increased heart rate) such as atrial fibrillation with rapid ventricular rate or supraventricular tachycardia, f) inflammatory/infectious causes; postvirus, medications, systemic diseases such as systemic lupus erythematosus, HIV cardiomyopathy, post partum cardiomyopathy, giant cell, refractory ventricular arrthymias, Chagas (biventricular enlargement, thinning or thickening of ventricular walls, apical aneurysms and mural

thrombi), g) inflammatory/noninfectious causes; allergy/hypersensitivity (peripheral eosinophilia-drug induced such as Amphtericin B, streptomycin, phentyoin, isoniazid, tetanus toxoid, hydrocholorthiazaide, dobutamine, chlorthalidone), rheumatologic/connective tissue (pericarditis, pericardial effusion atrioventricular heart block), scleroderma, peripartum cardiomyopathy (last trimester of pregnancy, risk factors maternal age, mulitparity, African descent- focus on hemodynamic and immunologic causes), iron overload (hemochromatosis, beta thalassemia major), amyloidosis (deposition of insoluble proteins as fibrils in the heart, 3-4% of African Americans carry an amyloidogenic allele of the human serum protein transthyretic which appears to increase cardiac amyloid deposition), sarcoidosis (cardiac sarcoid may affect as many as 25% of patients with sarcoid), stress (Takotsubo) (acute reversible LV dysfunction in the absence of significant CAD, triggered by acute emotional or physical stress with a distinctive pattern of apical ballooning that most often affects postmenopausal women with similar presentation to acute coronary syndrome) (Yancy et al., 2013).

***Physiology of Diastolic and Systolic Function***

Diastole starts when the aortic valve closes and includes LV pressure fall, rapid filling, diastasis and atrial contraction (Brutsaert, Sys, & Gillebert, 1993). Key aspects of diastolic function are: a) myocardial relaxation and passive LV filling, properties modulated by myocardial tone, b) myocardial relaxation determined by load, and c) myocardial stiffness determined by the myocardial cell and interstitial matrix (Wang & Nagueh, 2009).

Systole starts when the mitral valve closes and lasts until aortic valve closes (Otto, 2004). In terms of ventricular pressure changes, systole begins when LV diastolic pressure exceeds left atrial pressure, resulting in closure of the mitral valve, ventricular pressure

increases, exceeds aortic pressure and the aortic valve opens, ejection occurs, LV volume drops and the aortic valve closes (Otto, 2004). LV systolic function is best described by contraction and is affected by heart rate, preload and afterload (Otto, 2004).

Optimal performance of the LV is dependent upon the ability of heart to cycle two states; a) a compliant left ventricle that allows the LV to fill during diastole from low left atrial pressures, and b) a firm LV chamber in systole that ejects the stroke volume (volume of blood pumped from one ventricle of the heart with each beat) at arterial pressures (Wang & Nagueh, 2009). In addition, the stroke volume (SV) must accommodate to meet the metabolic needs of the body, as with exercise without much increase in left atrial (LA) pressure (Brutsaert et al., 1993).

The primary measurements of systolic function are measures of contractility that include EF, cardiac output (CO) and SV (Otto, 2004). Global cardiac function is most commonly assessed with echo by measuring the EF (Otto, 2004). EF is directly calculated from ventricular volumes and is load dependent, rather than a true measure of cardiac contractility (Braunwald & Zipes, 2001). Although EF may not consistently be a valid or reliable estimate of true myocardial contractility, it is the most commonly used method for assessing LV function (Feigenbaum, Armstrong, & Ryan, 2005). As a result, myocardial EF is used as an important classification in distinguishing patient demographics, co-morbid conditions, prognosis and treatment (Yancy et al., 2013). It is recognized that most HF patients may have varying degrees of systolic and diastolic LV abnormalities not reflected in the EF (Borlaug & Paulus, 2011). Although EF is maintained in HFpEF, myocardial systolic function and LV systolic elastance, (Ees) is not normal (Gladden, Linke, & Redfield, 2014). Studies have confirmed that Ees is increased in the setting of impaired myocardial

contractility (systole) suggesting a reduction in myocardial contractility (Borlaug & Paulus, 2011). This is an important pathophysiological finding given that reduced myocardial contractility has been associated with increased mortality (Borlaug, Lam, Roger, Rodeheffer, & Redfield, 2009). As a measure of systolic function, contractility is more accurately represented by measures that reflect the interaction of ventricular and arterial elastance (Borlaug & Paulus, 2011).

***Diastolic and Systolic Dysfunction***

The two main mechanisms involved in diastolic dysfunction (DD) are abnormal relaxation and passive stiffness (decreased compliance of the LV) that manifests as prolonged isovolumetric relaxation, slow LV filling and increased diastolic stiffness as the cause (Braunwald & Zipes, 2001; Libby, 2008). Cardiac relaxation is dependent upon calcium (Ca2+) reuptake and elastic recoil related directly to the sarcoplasmic reticulum Ca2 ATPase pump (Gladden et al., 2014). Elevated filling pressures are the main physiological consequence of diastolic dysfunction (Brutsaert et al., 1993). As an important early finding, LV pressures and relaxation can be normal at rest, exercise testing can reveal impaired LV relaxation at elevated heart rates (measured by elevated LV mean and LV end diastolic pressure LVEDP) (Hay, Rich, Ferber, Burkhoff, & Maurer, 2005)

In previous studies evaluating potential causes of HFpEF, DD was considered a primary antecedent to HFpEF (Hanrath, Mathey, Siegert, & Bleifeld, 1980). HFpEF was commonly thought to represent a process of maladaptive age and HTN related remodeling which resulted in DD (Dunlay, Roger, Weston, Jiang, & Redfield, 2012). However, with the progression of Doppler echo imaging and new science describing physiology, evidence of DD was found to be one of several factors that impact the development of HFpEF (Borlaug

& Paulus, 2011). Other factors with important mechanisms underlying HFpEF include resting and exercise systolic dysfunction, impaired ventricular-arterial coupling, chronotropic incompetence (Borlaug, Olson, et al., 2010; Dunlay et al., 2012), endothelial dysfunction, microvascular CAD (Borlaug & Paulus, 2011) and pulmonary arterial hypertension (Lam et al., 2009).

HFpEF is typically characterized by EF≥50% (Borlaug & Paulus, 2011). Four sets of diagnostic criteria for the diagnosis of HFpEF have so far been published from ("How to diagnose diastolic heart failure. European Study Group on Diastolic Heart Failure," 1998; Paulus et al., 2007; Vasan & Levy, 2000; Yturralde & Gaasch, 2005). All of the guidelines require the presence of signs or symptoms of HF, evidence of normal systolic LV function, and evidence of diastolic dysfunction or surrogate markers that include LV hypertrophy, LA enlargement, atrial fibrillation or elevated BNP levels (Paulus et al., 2007). None of the guidelines have been validated (Borlaug & Paulus, 2011) and consistent use in the literature is lacking. The first set came from the Working Group on Myocardial Function of the European Society of Cardiology ("How to diagnose diastolic heart failure. European Study Group on Diastolic Heart Failure," 1998). The second set came from the National Heart Lung Blood Institute Framingham Heart Study in which invasive evidence of diastolic dysfunction was required (Vasan & Levy, 2000). The third set came from the Lahey Clinic where a scoring system was designed along with surrogate markers for DD by LVH and LAE (Yturralde & Gaasch, 2005). The last set of guidelines came from the ESC requiring signs and symptoms of HF, LVEF >50%, evidence of DD (elevated left ventricular end diastolic pressure (LVEDP)>16mmHg, pulmonary capillary wedge pressure>12mmHg, E/E'>15, mitral flow velocity Doppler signal showing E/A ratio<0.5+deceleration time (DT) >280ms,

LA size>40mL/m2, or LV mass>149g/m2-men or >122g/m2-women (Paulus et al., 2007). In addition the ACCF/ACC 2013 HF Guidelines for the Management of Heart Failure published a chart with HFpEF and HFrEF definitions (Yancy et al., 2013); however, a specific endorsement of HFpEF diagnostic criteria was not mentioned. Lastly, no improvements in early detection or therapeutic intervention for HFpEF have been established within the last two decades (Owan et al., 2006).

As a measure of systolic function, contractility is more accurately represented by measures that reflect the interaction of ventricular and arterial elastance (Borlaug & Paulus, 2011). The impact of ventricular-arterial (vascular) coupling (measured by the ratio of effective arterial elastance (Ea) to LV end systolic elastance (Ees) may play a key role in understanding the pathogenesis of HFpEF (Borlaug & Redfield, 2011).

***Diastolic and Systolic Dysfunction***

The two main mechanisms involved in diastolic dysfunction (DD) are abnormal relaxation and passive stiffness (decreased compliance of the LV) that manifests as prolonged isovolumetric relaxation, slow LV filling and increased diastolic stiffness as the cause (Braunwald & Zipes, 2001; Libby, 2008). Cardiac relaxation is dependent upon calcium (Ca2+) reuptake and elastic recoil related directly to the sarcoplasmic reticulum Ca2 ATPase pump (Gladden et al., 2014). Elevated filling pressures are the main physiological consequence of diastolic dysfunction (Brutsaert et al., 1993). As an important early finding, LV pressures and relaxation can be normal at rest, exercise testing can reveal impaired LV relaxation at elevated heart rates (measured by elevated LV mean and LV end diastolic pressure LVEDP) (Hay et al., 2005)

In previous studies evaluating potential causes of HFpEF, DD was considered a primary antecedent to HFpEF (Hanrath et al., 1980). HFpEF was commonly thought to represent a process of maladaptive age and HTN related remodeling which resulted in DD (Dunlay et al., 2012). However, with the progression of Doppler echo imaging and new science describing physiology, evidence of DD was found to be one of several factors that impact the development of HFpEF (Borlaug & Paulus, 2011). Other factors with important mechanisms underlying HFpEF include the inflammatory effect of multiple co-morbidities, resting and exercise systolic dysfunction, impaired ventricular-arterial coupling, chronotropic incompetence (Borlaug, Olson, et al., 2010; Dunlay et al., 2012) endothelial dysfunction, microvascular CAD (Borlaug & Paulus, 2011) and pulmonary arterial hypertension (Lam et al., 2009).

HFpEF is typically characterized by EF$\geq$50% (Borlaug & Paulus, 2011). Four sets of diagnostic criteria for the diagnosis of HFpEF have so far been published from ("How to diagnose diastolic heart failure. European Study Group on Diastolic Heart Failure," 1998; Paulus et al., 2007; Vasan & Levy, 2000; Yturralde & Gaasch, 2005). All of the guidelines require the presence of signs or symptoms of HF, evidence of normal systolic LV function, evidence of diastolic dysfunction or surrogate markers that include LV hypertrophy, LA enlargement, atrial fibrillation or elevated BNP levels (Paulus et al., 2007). None of the guidelines have been validated (Borlaug & Paulus, 2011) and consistent use in the literature is lacking. The first set came from the Working Group on Myocardial Function of the European Society of Cardiology ("How to diagnose diastolic heart failure. European Study Group on Diastolic Heart Failure," 1998). The second set came from the National Heart Lung Blood Institute Framingham Heart Study in which invasive evidence of diastolic

dysfunction was required (Vasan & Levy, 2000). The third set came from the Lahey Clinic where a scoring system was designed along with surrogate markers for DD by LVH and LAE (Yturralde & Gaasch, 2005). The last set of guidelines came from the ESC requiring signs and symptoms of HF, LVEF >50%, evidence of DD (elevated left ventricular end diastolic pressure (LVEDP)>16mmHg, pulmonary capillary wedge pressure>12mmHg, E/E'>15, mitral flow velocity Doppler signal showing E/A ratio<0.5+deceleration time (DT) >280ms, LA size>40mL/m2, or LV mass>149g/m2-men or >122g/m2-women (Paulus et al., 2007). In addition the ACCF/ACC 2013 HF Guidelines for the Management of Heart Failure published a chart with HFpEF and HFrEF definitions (Yancy et al., 2013); however, a specific endorsement of HFpEF diagnostic criteria was not mentioned. Lastly, no improvements in early detection or therapeutic intervention for HFpEF have been established within the last two decades (Owan et al., 2006).

Substantial evidence supports the enormity of the HFpEF as a major public health problem requiring focused inquiry. HFpEF is without treatment, lacks consistent diagnostic criteria, is without defined early markers and there is controversy in defining those most affected (Gladden et al., 2014; Yancy et al., 2013). To build on the current science of HFpEF the following study plan outlines a research guide to address the gaps outlined in the current literature. The study design was an observational retrospective secondary data analysis that included: a) retrospective matched case-control analysis and b) an analysis of the case group.

***Research plan***

The dissertation was organized into three publishable manuscripts. The first manuscript (Chapter 2) presents an integrated and strategic review of the current literature on HFpEF. The purpose of this manuscript is to present the current state of the science on

HFpEF, demonstrate gaps in the literature and suggest new approaches to study the syndrome of HFpEF. This paper includes a description of patient characteristics, pathophysiology, current role and definitions of echocardiography and physiological markers, diagnostic criteria, treatment approaches and outcomes.

The second manuscript (Chapter 3) presents the original data based findings from a retrospective matched case-control study. This paper presents the results of this proposed study that analyzes the differences between the case group (patients discharged with incident HFpEF) and the control group (no prior history of HFpEF or HFrEF), matched by age, race and sex, on echocardiographic and physiologic markers.

The third manuscript (Chapter 4) presents an analysis of the incident HFpEF patient population. This paper presents key details about race, age at diagnosis and time to death as it relates to incident HFpEF.

The final chapter consists of an overall discussion and conclusion. The purpose of this chapter is to integrate findings from each of the three publishable manuscripts that synthesize the current literature, study methodology and results and implications for research and practice. In summary, this dissertation report includes background and significance, a review of the literature, results of an empirical study, an analysis of the incident HFpEF patient population and a synthesis and discussion of the three papers.

**Study aims**

The overall purpose of this dissertation is to identify biomarkers that predict impending HFpEF but precedes the actual onset of HFpEF. This study addressed the following hypotheses: 1) that subjects with HFpEF demonstrate differences in biomarkers compared to subjects without HFpEF/HF, 2) within the subgroups of HFpEF patients,

age/race/sex function as moderators that impact the extent to which biomarkers predict HFpEF, and 3) case group analysis of the incident HFpEF group demonstrate differences in key attributes that define this patient population. The impact of this study contributes to the current literature by enabling early recognition of potential biomarkers that precede the development of HFpEF, use of diagnostic criteria to consistently identify the patient population and provides new perspectives on the populations most affected, thus making a substantial contribution to the current science of HFpEF.

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# CHAPTER 2

## PAPER 1: HEART FAILURE PRESERVED EJECTION FRACTION (HFpEF): AN INTEGRATED AND STRATEGIC REVIEW

### Overview

#### *Background*

In the United States (U.S.), 5.1 million Americans ≥20 years have heart failure (HF) and heart failure preserved ejection fraction (HFpEF) accounts for at least 50% of all hospital admissions for HF. HFpEF has no single guideline for diagnosis or treatment, the patient population that is heterogeneously and inconsistently described and longitudinal studies are lacking.

#### *Objective*

The primary aims of this manuscript were to present an integrated review of the current state of the science on heart failure preserved ejection fraction (HFpEF), demonstrate gaps in the literature and provide the rationale for the design and implementation of future research to yield insight into the syndrome of HFpEF.

#### *Methods*

The scientific literature was comprehensively reviewed on HFpEF pathophysiology, patient characteristics, diagnostic criteria, echocardiography biomarkers, treatment approaches and outcomes. Discrepancies in patient characteristics, diagnostic criteria, study methods, and echocardiographic biomarkers were identified.

***Discussion***

This review indicates that no single test or guideline exists for diagnosis or treatment for HFpEF; heterogeneity of the population is complicated by multiple comorbidities that factor into onset, race and age are likely important factors and the absence of longitudinal studies that identify early markers of impending HFpEF. Studies designed and powered to include race and age stratification, concisely defined biomarkers and consistent use of defined diagnostic criteria are critical study attributes for future HFpEF research.

# PAPER 1: HEART FAILURE PRESERVED EJECTION FRACTION (HFpEF): AN INTEGRATED AND STRATEGIC REVIEW

## *Objective*

This manuscript presents an integrated review of the current state of the science on heart failure preserved ejection fraction (HFpEF), demonstrates gaps in the literature and provides the rationale for the design of future research. A description of current theories of pathophysiology and associated biomarkers, limitations of the current diagnosis and treatment guidelines and inconsistencies in defining the patient populations most affected by incident HFpEF are key areas of focus.

## *Background*

Heart failure preserved ejection fraction (HFpEF) is a clinical syndrome resulting from increased resistance in the filling of the left ventricle (LV) leading to symptoms of congestion (Yancy et al., 2013) although the exact cause continues to be unknown and the identification of markers that predict HFpEF risk have not been proven (Owan et al., 2006; Wong et al., 2013). Data from the National Health and Nutrition Examination Survey (NHANES) suggests an estimated 5.1 million Americans $\geq$20 years have HF, HFpEF accounts for at least 50% of all HF hospital admissions and forecasts a 46% increase in HFpEF prevalence by 2030 (AlJaroudi et al., 2012; Heidenreich, Albert, Allen, Bluemke, & Trogdon, 2013). However, biomarkers that enable prevention, diagnostic and treatment guidelines and population specific characteristics are not evident in the literature (Gladden et al., 2014; Wong et al., 2013; Yancy et al., 2013).

The pathophysiologic understanding of HF has changed notably over the last 25 years (Little & Zile, 2012). Terminology has evolved to include HF syndromes with ejection

fraction (EF) ≥50% described as diastolic heart failure (DHF) and as the pathophysiological mechanisms of HF became clearer the terms were changed to HFpEF and heart failure reduced ejection fraction (HFrEF) which are currently used (Little & Zile, 2012). Although the understanding of HFpEF pathophysiology has progressed, definitive research on population specific pathophysiology, consistent use of biomarkers and guidelines for diagnosis and treatment are not yet established.

***Pathophysiology and Biomarkers of HFpEF***

Because HFpEF is a complex syndrome an integrated approach best explains the phenomenon (Gladden et al., 2014). Multiple aspects of pathophysiology are involved in the progression from asymptomatic dysfunction to incident HFpEF and include: systemic inflammation, LV hypertrophy, slow LV relaxation, LV diastolic stiffness, decreased LV systolic performance, left atrial remodeling, peripheral vascular resistance, impaired epithelial function, increased pulmonary arterial and venous resistance, neurohormonal activation and ventricular-arterial coupling (Gladden et al., 2014). Borlaug and Kass (2011) described one possible physiological theory of the progressive maladaptive process in the context of ventricular-arterial coupling, defined as LV systolic elastance (Ees) and arterial elastance (Ea) (Borlaug & Kass, 2011). With vascular dysfunction, acute afterload elevation combined with ventricular-arterial stiffening contributes to increases in blood pressure (Borlaug et al., 2011). This mechanism then impairs diastolic LV relaxation leading to further increases in blood pressure contributing to dramatic increases in LV filling pressures during stress thus the adaptive physiologic response evolves to a pathologic response such as incident HFpEF (Borlaug, Olson, et al., 2010).

Paulus and colleagues (2013) describe HFpEF from the perspective of the pro-inflammatory effect of multiple co-morbidities such as obesity, diabetes, hypertension and chronic kidney disease that factor into the onset of HFpEF (Paulus & Tschope, 2013). This conceptual paradigm shifts emphasis from LV overload excess to including coronary microvascular inflammation (Paulus & Tschope, 2013). From this perspective, comorbidities and plasma markers of inflammation should be factored into diagnostic algorithms for HFpEF (Paulus & Tschope, 2013).

Hypertension (HTN) or elevated blood pressure is a well-documented antecedent to the development of HF and as many as 90% of HF cases are preceded by the diagnosis of HTN (Pickering, 2004). In the setting of elevated blood pressure, LV and arterial stiffening are abnormally elevated in patients with HFpEF (Borlaug & Kass, 2011; Borlaug & Paulus, 2011). One application of ventricular/arterial coupling (Ees/Ea) physiology suggests that HTN is antecedent to the development of HFpEF (Antonini-Canterin et al., 2013). In the Efficacy in Diastolic Dysfunction (EXCEED) trial, 527 patients with early stage HTN, after 24-48 weeks of antihypertensive therapy, there was evidence of an increase in the effective Ea/Ees ratio ($r=-0.25$, $p<0.01$) (Lam et al., 2013). The impact of antihypertensive treatment on patients with HTN and diastolic dysfunction (DD) on the Ea/Ees suggests that blood pressure control is one method to prevent the progression of hypertensive heart disease to decompensated HFpEF, even in the early stages of disease (Lam et al., 2013).

***Physiology of Diastolic and Systolic Function***

Diastole starts when the aortic valve closes and includes LV pressure fall, rapid filling, diastasis and atrial contraction (Brutsaert et al., 1993). Key aspects of diastolic function are: a) myocardial relaxation and passive LV filling, properties modulated by

myocardial tone, b) myocardial relaxation determined by load, and c) myocardial stiffness determined by the myocardial cell and interstitial matrix (Nagueh et al., 2009).

Systole starts when the mitral valve closes and lasts until aortic valve closes (Otto, 2004). In terms of ventricular pressure changes, systole begins when LV diastolic pressure exceeds left atrial pressure, resulting in closure of the mitral valve, ventricular pressure increases, exceeds aortic pressure and the aortic valve opens, ejection occurs, LV volume drops and the aortic valve closes (Otto, 2004). LV systolic function is best described by contraction and is affected by heart rate, preload and afterload (Otto, 2004).

Optimal performance of the LV is dependent upon the ability of heart to cycle two states; a) a compliant left ventricle that allows the LV to fill during diastole from low left atrial pressures, and b) a firm LV chamber in systole that ejects the stroke volume (volume of blood pumped from one ventricle of the heart with each beat) at arterial pressures (Nagueh et al., 2009). In addition, the stroke volume (SV) must accommodate to meet the metabolic needs of the body, as with exercise without much increase in left atrial (LA) pressure (Brutsaert et al., 1993).

The 2-D (dimensional), M (motion)-mode Doppler echocardiogram (echo) is the most commonly used imaging technique to evaluate diastolic and systolic function in addition to evaluating functional abnormalities of the heart muscle, valves and pericardium (Nagueh et al., 2009; Yancy et al., 2013). In describing physiology the term biomarker will be used as defined by the National Institute of Health (NIH) as an objective functional or physiologic measure of biological, pathological or therapeutic interventions (2001).

***Physiology of Diastolic and Systolic Dysfunction***

The two main mechanisms involved in diastolic dysfunction (DD) are abnormal relaxation and passive stiffness (decreased compliance of the LV) that manifests as prolonged isovolumetric relaxation, slow LV filling and increased diastolic stiffness (Braunwald & Zipes, 2001; Libby, 2008). Cardiac relaxation is dependent upon calcium (Ca2+) reuptake and elastic recoil related directly to the sarcoplasmic reticulum Ca2 ATPase pump (Gladden et al., 2014). The primary biomarkers of diastolic function are mitral inflow that include peak early filling (E-wave) and late diastolic filling (A-wave) velocities, the E/A ratio reflects grade of diastolic dysfunction (DD), (Nagueh et al., 2009). Different DD grades suggest varying levels of dysfunction and are reflected by the following parameters (Nagueh et al., 2009) Please see Appendix A. for a complete list of all abbreviations.

Based on diagnostic guidelines from the European Society of Cardiology (ESC), in addition to clinical symptoms, early mitral valve annular velocity (E'), and the ratio of E (early ventricular filling)/e'(early mitral valve annular velocity) are important in estimating LV filling pressures (Nagueh et al., 2009). Evidence of E/e'>15 is diagnostic of LV DD and E/e'<8 is diagnostic of absence of HFpEF and E/E' ranges from 8-15 are suggestive of LV DD that require further evaluation with biomarkers such as E/A ratio or brain natriuretic peptide BNP (Paulus et al., 2007).

In previous studies evaluating potential causes of HFpEF, DD (diastolic dysfunction grade 1, 2 or 3/4) was considered a primary antecedent to HFpEF (Hanrath et al., 1980). HFpEF was commonly thought to represent a process of maladaptive age and HTN related remodeling which resulted in DD (Dunlay et al., 2012). However, with the progression of Doppler echo imaging and new science describing physiology, evidence of DD was found to be one of several factors that impact the development of HFpEF (Borlaug & Paulus, 2011).

Reasons to consider an integrated physiology approach to HFpEF include the multiple other factors with important mechanisms underlying HFpEF, such as: stiff cardiomyocytes and fibrosis, resting and exercise systolic dysfunction, impaired ventricular-arterial coupling, chronotropic incompetence (Borlaug, Olson, et al., 2010; Dunlay et al., 2012) endothelial dysfunction, microvascular CAD (Borlaug & Paulus, 2011) and pulmonary arterial hypertension (Lam et al., 2009). Therefore DD likely plays a key role in the cause of symptoms in HFpEF however, DD is not necessarily required to produce HFpEF (Redfield et al., 2003).

The primary measurements of systolic function are measures of contractility that include EF, cardiac output (CO) and stroke volume (SV) (Otto, 2004). Global cardiac function is most commonly assessed with echo by measuring the EF (Otto, 2004). EF is directly calculated from ventricular volumes and is load dependent, rather than a true measure of cardiac contractility (Braunwald & Zipes, 2001). Although EF may not consistently be a valid or reliable estimate of true myocardial contractility, it is the most commonly used method for assessing LV function (Feigenbaum et al., 2005). As a result, myocardial EF is used as an important classification in distinguishing patient demographics, co-morbid conditions, prognosis and treatment (Yancy et al., 2013). It is recognized that most HF patients may have varying degrees of systolic and diastolic LV abnormalities not reflected in the EF (Borlaug & Paulus, 2011).

Evidence of decreased exercise reserve is likely the first sign of early HFpEF (Gladden et al., 2014). Both systolic and diastolic reserve are impaired with HFpEF and exercise may reveal the mild defects (Borlaug & Paulus, 2011). One theory that explains the impairment of cardiac reserve is related to ventricular-arterial stiffness. As stiffness

increases, wide pressure swings occur that interfere with flow and worsen pressure (Borlaug & Kass, 2011) The increase in pressure results in greater work requiring greater oxygen consumption, this increase in work-load results in impaired reserve, labile BP, decreased coronary flow and increased diastolic filling pressures (Borlaug & Kass, 2011). In addition, exertional intolerance is common with HFpEF due to elevated filling pressures reflected in elevated E/E' (Gladden et al., 2014). Many patients have exercise intolerance without evidence of volume overload (Borlaug & Paulus, 2011). Pulmonary artery pressures correlate closely with left heart filling pressures in early stage HFpEF (Borlaug, Nishimura, Sorajja, Lam, & Redfield, 2010), therefore tracking pulmonary pressures (PCWP>12mmHg and LVEDP>16mmHg) with echo may be an optimum screening tool in detecting early HFpEF in patients with normal EF and exertional dyspnea (Borlaug & Paulus, 2011).

As a measure of systolic function, contractility is more accurately represented by ventricular-arterial coupling versus ejection fraction alone suggesting that EF does not reflect all aspects of LV contractility (Borlaug & Paulus, 2011). The impact of ventricular-arterial coupling, (Ees) to effective arterial elastance (Ea) likely has a key role in understanding the pathogenesis of HFpEF (Borlaug & Redfield, 2011). In the context of ventricular-arterial coupling and vascular dysfunction, acute afterload elevation combined with ventricular-arterial stiffening contributes to increases in blood pressure (Borlaug & Paulus, 2011). In the setting of HFpEF, systemic vasorelaxation during exercise is diminished, impairing blood flow to skeletal muscle (Borlaug, Olson, et al., 2010; Borlaug & Paulus, 2011). Patients with HFpEF have systolic-ventricular and arterial stiffening beyond that associated with aging and/or HTN and is attributed to stress (Kawaguchi, Hay, Fetics, & Kass, 2003). Elevated Ees/Ea likely exacerbates the HTN stress response by delaying relaxation, limiting filling and

raising diastolic pressures (Kawaguchi et al., 2003), although EF is maintained (Gladden et al., 2014). Lam and colleagues (2013) demonstrate that blood pressure control decreases measures of arterial stiffness and ventricular arterial coupling and acts to prevent HFpEF, however, once HFpEF occurs, antihypertensive medications have not significantly altered HFpEF death outcomes (Gladden et al., 2014).

The single beat method of measuring ventricular elastance (Ees) has been validated against invasive hemodynamic measurement of LV performance (Borlaug & Kass, 2009; Borlaug et al., 2009; Chen et al., 2001; Ky et al., 2013). Both measures; Ees and Ea are expressed in mmHg/ml and therefore comparable mathematically in a ratio. Normal Ea and Ees values in resting subjects are 2.2 ± 0.8 mmHg/ml and 2.3 ± 1.0 mmHg/ml, respectively, and when the Ea/Ees ratio is 0.5-1.0, this suggests optimal function, but when the ratio is >1.0, this suggests that the LV becomes progressively less efficient (Antonini-Canterin et al., 2013; Borlaug et al., 2009).

The following is the single beat formulae used to calculate Ees(sb) (Chen et al., 2001):

$Ees=(DBP - (E_{nd(est)} \times SBP \times 0.9))/E_{nd(est)} \times SV$ - with the $E_{nd(est)}$=estimated normalized ventricular elastance at the onset of ejection, SV=Doppler derived stroke volume (Chen et al., 2001).

The following formulae is used to calculate arterial afterload (Ea):

Ea=0.9 x ESP (brachial systolic pressure (mmHg)/SV with SV=Doppler derived stroke volume (Borlaug & Kass, 2011).

One of the main applications is the Ea/Ees physiology is the application to HTN as a determinant of HF (Antonini-Canterin et al., 2013). In the setting of elevated blood pressure,

Ees/Ea are abnormally elevated in patients with HFpEF (Borlaug & Paulus, 2011). Also in the Efficacy in Diastolic Dysfunction (EXCEED) trial, the impact of antihypertensive treatment on patients with HTN and DD on the Ees/Ea ratio suggested that blood pressure control may be one way to prevent progression of hypertensive heart disease to decompensated HFpEF, even in the early stages of disease (Lam et al., 2013). In addition, studies have confirmed that Ees is increased in the setting of impaired myocardial contractility (systole) suggesting a reduction in myocardial contractility (Borlaug & Paulus, 2011). This is an important pathophysiological finding given that reduced myocardial contractility has been associated with increased mortality (Borlaug et al., 2009).

Also measured by echo, another marker of LV contractility is strain rate imaging. Specifically global longitudinal strain (GLS) has been shown to have diagnostic and predictive morbidity/mortality benefit in studying HFpEF superior to measurement of EF. GLS has been closely coupled with evaluating diastolic function, acute decompensated HFpEF, acute MI and evaluating reduced exercise capacity in HFpEF patients (Ersboll et al., 2013; Hasselberg et al., 2015; Yoon et al., 2014).

In addition to echo, cardiac magnetic resonance imaging (cMRI) has demonstrated utility in detecting functional abnormalities for both diastolic and systolic dysfunction and especially myocardial fibrosis (Borlaug & Paulus, 2011; Mewton, Liu, Croisille, Bluemke, & Lima, 2011). However the finding of fibrosis on cMRI is not an early finding of HFpEF and may not be specific to HFpEF (Desai et al., 2014).

Neurohormonal activation has not been extensively studied in HFpEF but limited evaluation suggests activation of the adrenergic and renin-angiotensin-aldosterone system (RAAS) contributes to progressive remodeling and contractile dysfunction (Dunlay et al.,

2012). Given that HTN, specifically systolic HTN, is present in most patients with HFpEF it strengthens the hypothesis that activation of the RAAS is a unifying concept in the genesis of HFpEF (Gladden et al., 2014; Steinberg et al., 2012). Given the high associated comorbidity of chronic kidney disease associated with HFpEF, this further supports that multiple systems are involves in the genesis of this syndrome (Paulus & Tschope, 2013).

Cardiac arrhythmia, specifically atrial fibrillation associated with left atrial remodeling may be a marker for HFpEF. The left atrium is typically enlarged with HFpEF and the degree of enlargement may be a rough estimate of the chronicity of HFpEF (Melenovsky et al., 2007). Structural remodeling of the LA leads to electrical remodeling which predisposes HFpEF patients to atrial fibrillation (AF) (70% of patients with HFpEF have AF) (Zakeri, Chamberlain, Roger, & Redfield, 2013). It is unclear if AF is a marker of more advanced LV dysfunction or contributor to the pathophysiology (loss of atrial-ventricular synchrony, irregular heart rate, impaired LA compliance) associated with HFpEF (Gladden et al., 2014).

***Guidelines for HFpEF Diagnosis***

HFpEF is typically characterized by EF≥50% (Borlaug & Paulus, 2011). Four sets of diagnostic criteria for the diagnosis of HFpEF have so far been published, including the ACCF/ACC HF Guidelines for the Management of Heart Failure ("How to diagnose diastolic heart failure. European Study Group on Diastolic Heart Failure," 1998; Paulus et al., 2007; Vasan & Levy, 2000; Yturralde & Gaasch, 2005). All of the HFpEF guidelines require the presence of signs or symptoms of HF, evidence of normal systolic LV function, evidence of diastolic dysfunction or surrogate markers that include LV hypertrophy, LA enlargement, atrial fibrillation or elevated BNP levels (Paulus et al., 2007). None of the guidelines have

been validated (Borlaug & Paulus, 2011). The first set came from the Working Group on Myocardial Function of the European Society of Cardiology ("How to diagnose diastolic heart failure. European Study Group on Diastolic Heart Failure," 1998). The second set came from the National Heart Lung Blood Institute Framingham Heart Study in which invasive evidence of diastolic dysfunction was required (Vasan & Levy, 2000). The third set came from the Lahey Clinic where a scoring system was designed along with surrogate markers for DD by LVH and left atrial enlargement (Yturralde & Gaasch, 2005). The fourth set of guidelines was initially published in 1998 by the European Society of Cardiology (ESC) and then was revised in 2007 including signs and symptoms of HF, LVEF >50%, evidence of DD (elevated left ventricular end diastolic pressure (LVEDP)>16mmHg, pulmonary capillary wedge pressure>12mmHg, E/E'>15, mitral flow velocity Doppler signal showing E/A ratio<0.5+deceleration time (DT) >280ms, LA size>40mL/m2, or LV mass>149g/m2-men or >122g/m2-women (Paulus et al., 2007). The ACCF/ACC 2013 HF Guidelines for the Management of Heart Failure published a chart (Table 1) with HFpEF definitions (Yancy et al., 2013), however a specific endorsement of HFpEF diagnostic criteria was not suggested.

The most commonly referenced diagnostic HF criterion is the Framingham criteria. The Framingham criteria was published by McKey et al., in 1971 to describe symptoms suggestive of congestive heart failure and requires that major and minor clinical symptoms be present such as paroxysmal nocturnal dyspnea, neck vein distention or acute pulmonary edema (there are 16 possible symptoms (McKee, Castelli, McNamara, & Kannel, 1971). Although the Framingham criteria is the most commonly used criteria for HF diagnosis,

biomarkers are not incorporated into the Framingham criteria and the criteria is not specific to HFpEF.

***HFpEF Treatment***

Pharmacologic trials including ace inhibitors, ARBs, β-blockers, statins and aldosterone antagonists and the consideration of electrophysiology trials have all been evaluated in the treatment of HFpEF. Pharmacologic treatments for HFpEF typically manage symptoms and have otherwise been ineffective in showing benefit (Yancy et al., 2013) with the exceptions of one trial evaluating statins and a post hoc analysis of a second trial that showed benefit with aldosterone-antagonist (Fukuta, Sane, Brucks, & Little, 2005; Pfeffer et al., 2015). Details of each treatment option for HFpEF are detailed in the following summary.

Ace1-inhibitors/ARBs. The effect of ace inhibitors and ARBs on HF is not completely understood and likely has mechanistic properties that include more than decreasing preload and afterload (Haywood et al., 1997). The perindopril in elderly people with chronic heart failure (PEP-CHF) trial was the first prospective randomized trial that evaluated ace inhibitors in HFpEF patients (Cleland et al., 2006). The study evaluated 850 patients with EF>40%, and ≥70 years of age on perindopril 4mg daily (Cleland et al., 2006). The trial was insufficiently powered to meet the primary endpoint of morbidity and mortality but patients on treatment reported improved symptoms, exercise capacity ($p=0.011$) and fewer hospitalizations ($p=0.033$) in the first year on therapy (Cleland et al., 2006). In the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved Trial, an ARB was evaluated in HFpEF patients on the effect on mortality and re-hospitalization (Yusuf et al., 2003). The study evaluated 3023 patients with

EF>40% Candesartan 32mg daily, and reduced hospitalizations (p=0.017) but showed no difference in mortality (p=0.118) (Yusuf et al., 2003). In the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE) trial an ARB was evaluated in HFpEF patients on the effect on mortality, hospitalization and quality of life (Massie et al., 2008). This study evaluated 4128 patients with EF≥45% and ≥60 years of age with findings that that irbesartan did not improve outcomes in patients with HFpEF (Massie et al., 2008). With HFpEF, both LV and arterial elastance are increased suggesting the LV and arterial system are functioning at maximum capacity (stretched) which explains why arterial vasodilatation (ace inhibitors) work with HFrEF but not with HFpEF (Borlaug & Paulus, 2011; Schwartzenberg et al., 2012).

Beta-blockers. Traditionally β-blockers have been recommended for the treatment of HFpEF for the negative chronotropic (decrease heart rate) effect to increase the diastolic filling period (Borlaug & Paulus, 2011). However studies have shown that chronotropic incompetence is highly prevalent in HFpEF and use of β-blockers in the absence of tachycardia decreases exercise capacity (Borlaug, Nishimura, et al., 2010). In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, the use of β-blockers was evaluated in HFpEF and HFrEF patients (Hernandez et al., 2009). The study evaluated 7154 hospitalized patients, ≥72years of age, with HF and divided EF <30%, 30-39%, 40-49% and >50% and showed that β-blockers had no effect on 1 year mortality or hospitalization rates in HFpEF patients but significantly improved both endpoints in the HFrEF group (Hernandez et al., 2009).

Statins. The effect of statin therapy (Hydroxymethylglutaryl coenzyme A – (HMG Co-A) reductase inhibitors) for patients with HFpEF statins may have a role with ventricular

remodeling (Indolfi et al., 2002), sympathetic nervous system activation (Pliquett, Cornish, Peuler, & Zucker, 2003), inflammation (Rauchhaus, Coats, & Anker, 2000) and endothelial function (Bates, Ruggeroli, Goldman, & Gaballa, 2002). Fukuta and colleagues studied the mortality effect of statin therapy on 185 HFpEF patients with EF≥50%, on statin (atorvastatin, mean dose 22mg, simvastatin mean dose 37mg, pravastatin mean dose 30mg, fluvastatin mean dose 80mg daily) and showed a statistically significant (p=0.013) reduction in mortality in patients with HFpEF on mortality (Fukuta et al., 2005). The cause remains unclear but may be related to microvascular myocardial ischemia (50% of HFpEF patients have a diagnosis of CAD) (Chattopadhyay et al., 2010) (Mohammed et al., 2014), impaired β-adrenergic signaling (Phan et al., 2009), or abnormal calcium handling (Liu et al., 1993). Observational studies have demonstrated better outcomes in HFpEF patients treated with statins however it is unclear if this is due to the effect on CAD progression or decrease in endothelial inflammation (Paulus & Tschope, 2013). To date studies have not been conducted to evaluate microvascular chronic ischemia as a cause of HFpEF (Hoenig, Bianchi, Rosenzweig, & Sellke, 2008).

Aldosterone-antagonists. Aldosterone and the pathogenesis of vascular stiffening and endothelial dysfunction has been studied in both HFpEF and HFrEF (Weber, 2001). In the Treatment of Preserved Cardiac Function in Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, spironolactone titrated up to 45mg daily was studied in HFpEF patients for the effect on mortality and hospitalization rate (Pitt et al., 2014). This international study conducted in 6 countries that included Russia and Georgia, United States, Canada, Argentina and Brazil evaluated 3445 patients with EF>45% and ≥50 years of age, randomized to either spironolactone or placebo and used the Framingham criteria to define HFpEF. The initial

results did not suggest statistical significance in mortality benefit (p=0.14) but did show benefit in reducing hospitalizations (p=0.04), (Pitt et al., 2014). However, post hoc analysis of TOPCAT suggested regional variation in the Americas with statistically significant benefit in both mortality and hospitalization with a hazard ratio for treatment with spironolactone with respect to cardiovascular death 0.74 (95% CI, 0.57–0.97), and hazard ratio for heart failure hospitalization with spironolactone treatment was 0.82 (95% CI, 0.67–0.99) (Pfeffer et al., 2015). Inconsistencies in HFpEF diagnostic criteria in Russia and Georgia have been referenced as the cause of mortality insignificance with the initial reporting of TOPCAT (Pfeffer et al., 2015).

Calcium Channel Blockers. Experimental investigations with a selective calcium channel inhibitor *ivabradine* have demonstrated benefit with short term treatment (Kosmala et al., 2013). Tested in prospective trial of 30 patients in the placebo group and 30 patients treated twice daily for 7 days with ivabradine. The treatment group showed improved exercise capacity (4.2 ± 1.8 METs vs. 5.7 ± 1.9 METs, p = 0.001) and peak oxygen uptake (14.0 ± 6.1 ml/min/kg vs. 17.0 ± 3.3 ml/min/kg, p = 0.001). This benefit may be explained by improved diastolic filling as a result of the rate slowing effect and improved myocardial relaxation (Kosmala et al., 2013). To date, evidence is lacking to support longer term treatment with ivabradine.

Electrophysiology. Although chronotropic incompetence is found in patients with incident HFpEF, a therapeutic indication for cardiac pacing in HFpEF patients has not been established (Borlaug & Paulus, 2011). Atrial fibrillation is common with HFpEF but treatment is focused on AF management not the underlying pathophysiology (Zakeri et al., 2013).

Exercise. Exercise training in HFpEF has shown benefit in improving exercise tolerance and managing obesity (Taylor et al., 2012). IN the HF-Action trial, O'Connor and colleagues demonstrated that exercise had a modest reduction for both all-cause mortality and re-hospitalization but was focused on HFrEF patients (O'Connor et al., 2009). In a meta-analysis of exercise training in HFpEF, findings suggest that exercise training was associated with a fold improvement in cardiovascular fitness 2.72 (CI 1.79-3.65), and 4 fold increase in quality of life, 3.97 (CI -7.21, -0.72) and non-significant changes in LV systolic or diastolic function, 1.26 (CI -0.13, 2.66), 0.08 (CI -0.01-0.16) (Pandey et al., 2015). Interestingly, this study used EF and diastolic parameters (such as diastolic grade) as the primary measures of systolic and diastolic function.

***Population Stratification: Age Race and Sex as Key Attributes***

Controversy exists in the scientific literature on the description of patient populations most commonly affected by incident HFpEF. The ACCF/AHA guidelines suggest that White women, >65 years of age with a history of HTN are most commonly affected by HFpEF (Crowder, Irons, Meyerrose, & Seifert, 2010; Yancy et al., 2013). However, studies with a racially diverse sample that included subjects <65 years of age, indicate Black women are most commonly affected by incident HFpEF (Desai et al., 2013; Wong et al., 2013). Given that at least 90% of HFpEF cases are preceded by a diagnosis of HTN (Pickering, 2004) and that Black patients had twice the incidence of new HTN compared to White patients over a 10 year period (Egan, Zhao, & Axon, 2010; Ford & Cooper, 1991; Gillum, 1991) more definitive exploration of race and age in future HFpEF is indicated.

In a trial evaluating the relationship of race to HFpEF incidence and outcomes, 13,437 adults with HFpEF from 2005 to 2008 from four regionally different health systems

within the U.S. were suggested that Blacks had a 48% higher risk of hospitalization compared to Whites and Asians and with patients <65 years of age and that incident HF admission occurred more commonly in Blacks compared to Whites and Asians (Gurwitz et al., 2014). Also the prevalence of HF among different ethnic and racial groups is expected to increase substantially (Al-Dubai, Alshagga, Rampal, & Sulaiman, 2012) with the highest prevalence to be among Black patients increasing by 29% between 2012 and 2030, from 2.8% to 3.6% of the Black population (Heidenreich et al., 2013), followed by Hispanic, White, and Chinese (Bild et al., 2005). In addition to alarming trends in incidence and prevalence, mortality data suggest a 34% higher five year mortality rate for Blacks with HFpEF compared to White patients (East, Peterson, Shaw, Gattis, & O'Connor, 2004)

***Conclusions***

HFpEF is a complex clinical syndrome with increasingly significant health and fiscal implications (Gladden et al., 2014). Multiple co-morbidities and the associated pro-inflammatory state contribute to the onset of HFPEF (Paulus & Tschope, 2013). Although this syndrome is not limited to a problem of LV contractility, the use of Ea and Ees to reflect arterial-ventricular coupling have demonstrated physiologic utility in studying the phenomenon of HFpEF (Borlaug & Paulus, 2011). In addition to the complexity of pathophysiology, diagnostic guidelines for HFpEF are not consistently used. In the TOPCAT trial the study initially reported non-significant mortality findings; however, post hoc analysis stated ‘regional variation’ in the Americas and re-analysis did show mortality benefit (Pitt et al., 2014). In TOPCAT the diagnostic criteria used for inclusion was the Framingham HF criteria which is not specific to HFpEF and does not include biomarkers in making the diagnosis (only clinical findings). Although study of the etiology of HFpEF is

evolving and the exact cause remains unclear, without consistent use of current diagnostic criteria in studying HFpEF, more confusion in defining this heterogeneous population is likely to result.

This review outlines the pathophysiology of current and novel biomarkers and consideration of the pro-inflammatory effect of multiple co-morbidities, demonstrates the infrequent use of diagnostic criteria and emphasizes the importance of implementing a diverse study sample. Incorporating each component (diagnosis, biomarkers, co-morbidities, representative population) into comparisons between adults with and without HFpEF over time would greatly contribute to our current scientific knowledge base. In summary, consistent use of HFPEF diagnostic criteria with standardized measures of biomarkers, studied overtime, are areas requiring further exploration.

# CHAPTER 3

## PAPER 2: COMPARING NOVEL BIOMARKERS ASSOCIATED WITH HEART FAILURE PRESERVED EJECTION FRACTION (HFpEF): A MATCHED CASE-CONTROL ANALYSIS

### Overview

***Objectives:***

This study was designed to detect differences in biomarkers associated with incident heart failure preserved ejection fraction (HFpEF) when comparing matched case-control groups.

***Background:***

Evidence continues to demonstrate increasing prevalence, cost and mortality implications of HFpEF. Early identification of biomarkers associated with incident HFpEF would contribute greatly to the current science.

***Methods:***

A study cohort of 310 patients, that included case (incident HFpEF patients, n=155) and matched control (patients with no prior HF, n=155) groups were retrospectively identified. Matching criteria included race, sex, age (within 3 years) and previously acquired echocardiogram biomarkers (within 1year). Physiologic and echocardiogram biomarkers were collected from previously acquired 2-D (dimensional) M-mode Doppler echocardiograms. Echo images were re-analyzed from previously obtained echo to calculate measures factored into calculating ventricular-arterial coupling. To estimate ventricular elastance, the single beat method was used. Covariates and model fit were tested. Using

conditional logistic regression and controlling for covariates, models were fit to detect differences in HFpEF biomarkers between the matched case-control groups.

***Results:***

Statistically significant differences in biomarkers that reflect ventricular elastance (Ees) (p=0.0030) and left atrial diameter (LAdiam) (p=0.0002) were detected when comparing the case and control groups. Conditional logistic regression analyses suggested a 30% higher odds of converting to the case group with every 1 unit increase in Ees, OR 1.315 (1.097, 1.575) and a 4.57 times higher odds of being in the case group for every 1 unit increase in LAdiam, OR 4.565 (2.038, 10.223).

***Conclusions***

Ees and LAdiam may have a role in tracking physiology as it relates to HFpEF. This study demonstrates that it is feasible to calculate both the Ees and LAdiam from routinely obtained echo images without increasing cost or risk. Prospective studies are indicated that explore the use of Ees and LAdiam as predictors of impending HFpEF.

# PAPER 2: COMPARING NOVEL BIOMARKERS ASSOCIATED WITH HEART FAILURE PRESERVED EJECTION FRACTION (HFpEF): A MATCHED CASE-CONTROL ANALYSIS

## *Objective*

This manuscript presents the findings of a matched case-control study. The case group consisted of patients previously discharged with incident (first case) heart failure preserved ejection fraction (HFpEF). The control group consisted of patients with no prior history of heart failure (HF). Groups were matched based on age, race, sex and date of echocardiogram. This paper includes an analysis of differences within the matched cohorts comparing physiologic and echocardiographic biomarkers.

## *Background*

Heart failure preserved ejection fraction (HFpEF) accounts for at least 50% of all hospital admissions for heart failure (HF) in the United States (U.S.) yet measures that predict risk and onset of HFpEF are lacking (Gladden et al., 2014; Heidenreich et al., 2013). HFpEF is a heterogeneous syndrome likely affected by multiple comorbidities with inflammatory precursors (Lam et al., 2011; Paulus & Tschope, 2013). Clinical diagnosis is typically based on patient history and physical examination; however, epidemiologic studies suggest that some patients are asymptomatic but have evidence of abnormal biomarkers such as diastolic dysfunction (Owan & Redfield, 2005; Yancy et al., 2013). The relative risk associated with specific biomarkers (Ky et al., 2013) and the impact of age, gender and race have not been established (Shah, 2012). Therefore, studies that include samples stratified by age, race and sex that identify biomarkers that predict impending HFpEF may help identify targets for larger samples over time.

Previous studies predicting risk or outcomes in HFpEF patients, most of which compared HFpEF and HFrEF groups to control groups and some of which matched on age and gender, suggested utility in echo biomarkers that include measurement of left ventricular hypertrophy (LVH), estimates of left ventricular filling (E/e'), left atrial (LA) size, global longitudinal strain (GLS), arterial elastance (Ea), ventricular elastance (Ees) and ventricular-arterial coupling (Borlaug et al., 2009; Mohammed et al., 2012; Shuai et al., 2011; Stampehl et al., 2015). However, none of the studies included race in the matched groups. In addition, the pathophysiology of HFpEF is complex reflected by LV hypertrophy, pro-inflammatory markers, slow LV relaxation, LV diastolic stiffness, decreased LV systolic performance, left atrial remodeling, peripheral vascular resistance, impaired epithelial function, increased pulmonary arterial and venous resistance, neurohormonal activation and mismatched ventricular-arterial coupling (Gladden et al., 2014; Paulus & Tschope, 2013).

LV ejection fraction (EF) is an important volumetric measure and predictor of outcome, however, EF does not incorporate load, contractility and the interaction of ventricular-arterial stiffening (Borlaug et al., 2009). Non-invasive measures have been established such as LV systolic elastance (Ees)(mmHg/ml) which incorporates measures of LV end-diastolic volume (EDV), LV size and cardiac remodeling and the end-systolic pressure volume relationship (ESPVR) which is a load-dependent measure of contractile function (Ky et al., 2013). Arterial elastance (Ea)(mmHg/ml) is a measure that incorporates end-systolic pressure (ESP) and end-diastolic volume to incorporate stroke volume (SV), therefore Ea=ESP/SV (Ky et al., 2013). The net interaction of the ventricular and arterial systems is measured by Ea/Ees which significantly impacts cardiac performance (Borlaug & Kass, 2009, 2011).

Previous studies suggest that optimal ventricular-arterial functioning is reflected in an Ea/Ees ratio of 0.5-1.0 which is maintained with normal aging but reportedly declines in women because of ventricular stiffening increases out of proportion to vascular load (Borlaug et al., 2009; Kawaguchi et al., 2003). However, studies that evaluate Ea, Ees and Ea/Ees and incorporate a diverse range of age, race and gender into the study design have not been completed to date. Ea (arterial elastance) and Ees (ventricular elastance) are measures that reflect the interaction of ventricular-arterial coupling. Therefore in order to better understand the phenotype of HFpEF, collecting data on Ea, Ees in addition to stratifying the study group by age, race and sex are greatly needed. For a complete list of all abbreviations used in this study, please refer to Appendix A.

## *Methods*

### Design

The study was observational with a retrospective matched case-control design. The procedure of case-control group selection began with the consideration of key methodological principles in control group selection (Wacholder, Silverman, McLaughlin, & Mandel, 1992a). This framework includes three principles to maximize comparability between case-control. The concepts include compariability of: a) study base, b) deconfounding, and c) comparative accuracy (Wacholder, McLaughlin, Silverman, & Mandel, 1992). To control the study base, for both the case and control groups, the study samples only included residents of Durham County, North Carolina. Given that the selected academic institution is a regional, national and international referral instituion, selecting only residents of Durham County helped control; a) socioeconomic, b) racial and c) access to medical care variables, which preserved both the heterogeneity and the homogeniety of the study sample. To further control the study base, only previously completed 2-D

(dimensional) M (motion)-mode Doppler echocardiograms, ordered within the health system, read at a core laboratory that is certified, regulated and adhered to standards set by the American Society of Echocardiography (ASE) (Wang & Nagueh, 2009) on patients that met the inclusion and exclusion criteria, were eligible for this study.

The case group only included patients with an incident (first) HFpEF hospital admission and the control group only included patients with no history of incident HFpEF (or any type of HF) hospital admission. Matching on the variables age, race and sex also helped reduce the effects of confounding variables (Wacholder, Silverman, McLaughlin, & Mandel, 1992b).

To maximize comparable accuracy, this study included data extracted from previously obtained (derived) data with the exception of echo image measurements for ventricular-arterial coupling. For the coupling variables, two nationally certified echo sonographers obtained measures of the LV outflow tract diameter at the pulse wave Doppler signal and measures of the flow onset time and end time from the LVOT waveform. For both the case and control groups, all echos had previously been ordered, interpreted and reported based on standards created by the ASE (Wang & Nagueh, 2009) and thus favorably contributed to the validity of group to group comparisons.

**Sample and Setting**

Based on power analysis, the number of matched pairs required for this study was n=90 or a total of 180 subjects. Patients in both the case and control groups were required to be 18 years of age or older. All study data were extracted from pre-existing electronic sources that included a storage data base, medical record, echocardiogram database and imaging database. In the medical record, race was a self-reported datapoint that was

collected from the storage data base and obtained for this study by electronic query. Self reporting of race most accurately reflects the group (Geronimus, Hicken, Keene, & Bound, 2006). To prevent racial under-representation from occurring in this study, an a priori objective of a racially representative study group relative to the geographic location was operationalized into the study design. Based on 2012 U.S. Census Data, in Durham County the general population is 38% White, 41% Black and 14% Hispanic (Commerce, 2012).

Case Group. The case group consists of inpatients discharged from a large academic medical center in North Carolina from January 1, 2007 thru January 1, 2014 with a primary discharge diagnosis of HFpEF for the incident HFpEF admission based on coding of the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9_CM) code book with codes for 428.30 (diastolic heart failure, unspecified), 428.31 (acute diastolic heart failure), 428.32 (chronic diastolic heart failure), 428.33 (acute on chronic diastolic heart failure). Incident HFpEF diagnosis was verified by the reviewer based on the European Society of Cardiology (ESC) diagnostic criteria for HFpEF (Paulus et al., 2007), required to have at least 1 echo completed one month prior to hospitalization. The ESC diagnostic criteria for HFpEF, described as heart failure normal ejection fraction (HFNEF) is one of four published criteria, however, the ESC guide is the only document that incorporates clinical symptoms and echo markers into the diagnostic guideline without using invasive measures. Specificially, the ESC diagnostic criteria require clinical signs and symptoms of HF (dyspnea, fluid overload or congestion), LVEF >50%, evidence of diastolic dysfunction (DD) (elevated left ventricular end diastolic pressure (LVEDP)>16mmHg, pulmonary capillary wedge pressure (PCWP)>12mmHg, E/E'>15, mitral flow velocity Doppler signal showing early ventricular filling (E)/ late diastolic filling (A) ratio<0.5+deceleration time

(DT) >280ms, LA size>40mL/m2, or LV mass>149g/m2-men or >122g/m2-women (Paulus et al., 2007).

Patients were excluded from the case group if chart review as far back as 1995, indicated prior HF hospitalization for either HFpEF or heart failure reduced ejection fraction (HFrEF), prior echo ejection fraction (EF)<50%, if diastolic function, pulse wave (PW) or LV outflow tract (LVOT) imaging could not be obtained from the echocardiogram, presence of severe moderate/severe mitral valve disease, history of aortic or mitral valve surgery or vegetation, heart transplantation, hypertrophic obstructive cardiomyopathy, persistent tachycardia due to chronic atrial fibrillation, congenital heart disease, severe pulmonary arterial hypertension (not due to diastolic dysfunction), connective tissue disorders such as rheumatoid arthritis, advanced malignancy, shock.

Control Group. The control group patients were identified by previously completed medical evaluation based on ICD-9 codes for shortness of breath (786.05) at Duke University from January 1, 2007-January 1, 2014 through an electronic query of a data repository. This time period was selected because echo protocols and imaging improved in 2007. Criteria set for inclusion were age ≥18years, Durham County zip codes, ICD-9 code for shortness of breath (ICD-9 code 786.05) presenting either through the emergency department or to an outpatient clinic for evaluation and management of shortness of breath. Patients were matched one to one to the case group based on age (3 years or less), race, sex and a record of at least 1 echocardiogram completed within 1 year of the matched case. Controls had no prior hospital admissions for HF, no prior evidence of LV dysfunction based on ICD-9 codes, and the individual medical records of each patient were reviewed to confirm no prior HFpEF, HF history or echo evidence of LV dysfunction.

Exclusion Criteria. Patients were excluded if chart review indicated prior HF hospitalization for either HFpEF or heart failure reduced ejection fraction (HFrEF), prior echo ejection fraction (EF)<50%, if diastolic function, pulse wave or LV outflow tract image could not be measured from the echocardiogram, presence of severe moderate/severe mitral valve disease, history of aortic or mitral valve surgery or vegetation, heart transplantation, hypertrophic obstructive cardiomyopathy, persistent tachycardia due to chronic atrial fibrillation, congenital heart disease, severe pulmonary arterial hypertension (not due to diastolic dysfunction), connective tissue disorders such as rheumatoid arthritis, shock or advanced malignancy.

This study was approved by the University of North Carolina at Chapel Hill and Duke University institutional review boards and all data processing was completed with strict adherence to the Health Insurance Portability and Accountability Act (HIPAA).

Echocardiogram

Data from previously obtained two-dimensional (2D), M (motion)-mode Doppler transthoracic echocardiograms within the Duke University Health System were used for study analysis. All previously obtained echos were acquired using standardized techniques recommended by the American Society of Echocardiography (Nagueh, Middleton, Kopelen, Zoghbi, & Quinones, 1997). All echo image measurements used by the reviewer for the following formulas were obtained by echo sonographers nationally certified by the American Society of Echocardiography. The utility and relevance of arterial-ventricular coupling in HFpEF were previously reviewed. The following measurements are incorporated into a calculation that estimates ventricular-arterial elastance.

Calculation of arterial elastance (Ea), end-systolic pressure volume (ESP) and stroke volume (SV) were derived. The ESP was estimated as 0.90 X systolic blood pressure (SBP) by manual cuff at the time of echo as recommended (Chen et al., 2001). Stroke volume (SV) was measured from the LV outflow tract (LVOT) diameter at the pulse wave (PW) Doppler signal (Chen et al., 2001).

Ea = ESP/SV (measure of arterial elastance)
Ees (ventricular elastance) was calculated using the single-beat method outlined by Chen and colleagues (Chen et al., 2001).

Ees(sb) = (DBP-(Endest*ESP))/(SV*Endest)

Endest = 0.0275-(0.165*EF)+0.3656*(DBP/ESP)+(0.515*Endavg)
Endavg = (0.35695*1)+(-7.2266*tn^1)+(74.249*tn^2)+(-307.39*tn^3)+(684.54*tn^4)+(-856.92*tn^5)+(571.95*tn^6)+(-159.1*tn^7)
ESP = 0.9 * SBP
SV ($cm^3$)
tn (ms) = R wave to flow onset time/R wave to flow end time; determined noninvasively from LVOT Doppler waveform

*Statistical Methods*

Baseline characteristics of the case and control cohorts were represented with frequency data. The total number of incident HFpEF identified, those excluded and the most common reasons for exclusion are reported. The total number of controls identified and rationale for inclusion and exclusion were reported. All approximately normally distributed variables were displayed as mean and standard deviation, and non-normally distributed variables were displayed as median and interquartile range.

Bivariate associations between case status and biomarkers (SBP DBP, HR, BMI, Ea, Ees, Ea/Ees, LAdiam) were assessed using paired t-tests. Biomarkers with $p<0.1$ in the bivariate analysis were entered into the model in a single multivariable conditional logistic regression model for case status. Using backward elimination, the full model was reduced to

the final model, and the final odds ratios are reported. To assess the validity of pooling the two sources of controls (ED and outpatient), we examined whether the effect differed by source by adding the interaction between each biomarker and an indicator of source.

Statistical significance was defined as $p<0.05$. Statistical analyses were performed using SAS, Inc., 9.4, statistical software (SAS Institute Inc., Cary, North Carolina) and JMP, version 11.2.0 (SAS Institute Inc., Cary, North Carolina).

***Results***

*Study Population*

Of the 876 potential case patients (incident HFpEF) identified, 624 were excluded leaving a case group of 252 incident HFpEF patients eligible for matching. The most common reasons for exclusion included a) evidence of EF<50% on prior echo (n=296, 49%), b) no incident HFpEF (n=188, 30%) defined by the HFNEF diagnostic criteria outlined by the European Society of Cardiology (Paulus et al., 2007), c) severe mitral or aortic valve disease (n=89, 14%).

Of the potential 1035 control patients that were identified electronically who had previously presented to the emergency department, 720 were excluded due to death (67%) or echo evidence of EF<50% (20%), leaving 315 eligible for the control group. Of the potential 1175 patients identified electronically who had presented to outpatient clinics, 1007 were excluded mostly due echo evidence EF<50% (67%), leaving 168 patients eligible for the control group. The rationale for including patients from both emergency department and outpatient clinics in the control group was to insure an adequate sample size of potential matched patients that previously had an echo completed.

The study included 155 matched pairs for a total sample of 310 patients. The mean age for the entire cohort is 69 years (SD 12.56), 74% are female and 60% are Black. Though the groups were matched on age, the control group ended up slightly older than the case group (mean of 70 versus 67 years). In comparing the means of biomarkers at the time of echo between the case and control groups, there were statistically significant differences between the case-control with regard to SBP, HR, BMI, Ees and LAdiam. See Table 3.1.

Table 3.1. Comparison of biomarkers for the matched case-control

| Matched case n=155<br>Matched control n=155 | Characteristics Matched Case-Control Paired t-tests | | | | | |
|---|---|---|---|---|---|---|
| | **Matched group** | **N** | **Mean** | **SD** | **t** | **p** |
| SBP(mmHg) | Case<br>Control | 146<br>146 | 143.95<br>133.30 | 25.66<br>18.25 | 4.14 | **<0.0001** |
| DBP(mmHg) | Case<br>Control | 146<br>146 | 74.51<br>73.30 | 12.61<br>11.68 | 0.99 | 0.3223 |
| HR(bpm) | Case<br>Control | 144<br>144 | 76.92<br>72.53 | 14.85<br>13.16 | 2.80 | **0.0059** |
| BMI | Case<br>Control | 120<br>120 | 37<br>31 | 10.71<br>7.34 | 5.24 | **<0.0001** |
| EF(%) | Case<br>Control | 152<br>152 | 54.95<br>55.11 | 0.43<br>2.04 | -1.02 | 0.3109 |
| Ea(mmHg/ml) | Case<br>Control | 87<br>87 | 2.04<br>1.86 | 0.87<br>0.61 | 1.74 | 0.0855 |
| Ees(mmHg/ml) | Case<br>Control | 87<br>87 | 6.38<br>4.81 | 3.56<br>2.25 | 3.89 | **0.0002** |
| Ea/Ees | Case<br>Control | 87<br>87 | 6.39<br>4.81 | 3.55<br>2.25 | -0.60 | 0.5499 |
| LAdiam(cm) | Case<br>Control | 87<br>87 | 124<br>124 | 4.25<br>3.65 | 8.35 | **<0.0001** |

*Analysis results*

All effects that had a bivariate $p<0.1$ were considered and included in the analysis. This included DBP, SBP, BMI, LAdiam, Ea, Ees, Ea/Ees. The final model included Ees and LAdiam, selected based on a backward selection retaining effects with $p\leq0.1$.

The results of the conditional logistic regression comparing the case-control suggest statistically significant effects of Ees (0.0030) and LAdiam (0.0002). For Ees, every unit

increase is associated with a 30% higher odds, 1.315(CI 1.097, 1.575) of being in the case group. For LAdiam, every unit increase is associated with a 4.57 times of odds (CI 2.0, 10.22) of being in the case group. See Table 3.2.

Table 3.2. Conditional logistic regression results, combined matched case-control

**Conditional logistic regression results for matched case-control final model**

| Model test Likelihood <0.0001 Score <0.0001 Wald <0.0001 | Parameter | Parameter Estimate | Standard Error | Odds Ratio | CI | P |
|---|---|---|---|---|---|---|
| | Ees | 0.2735 | 0.0922 | 1.315 | (1.097, 1.575) | **<0.0030** |
| | LAdiam | 1.5183 | 0.4114 | 4.565 | (2.038, 10.223) | **<0.0002** |

The interactions between control source and Ees and LAdiam were included to assess homogeneity of the effect across sources, and both were found to be non-significant (p=0.7557, 0.5108, respectively).

***Discussion***

In comparing characteristics of the matched pairs, the case group had significantly higher SBP, HR, BMI, Ees and LAdiam. These findings are consistent with other studies evaluating HFpEF (Borlaug, Olson, et al., 2010; Mohammed et al., 2012; Paulus & Tschope, 2013). In the Borlaug, et al., and Mohammed et al., studies, age and gender groups were compared in the analysis; however, none of the other studies comparing biomarker of incident HFpEF were case-control designs matched on age, race and gender. Elevated SBP has been considered the cause for increased afterload in HFpEF (Hart et al., 2001), however ace inhibitors and angiotensin receptor blockers are not effective in reducing mortality but microvascular inflammation may have a role (Paulus & Tschope, 2013). Elevated heart rate has been associated with increased cardiovascular death in HFpEF but use of beta blockers has not been associated with decreased mortality (Takada et al., 2014). Ees elevation in

HFpEF has been associated with passive myocardial stiffening, fibrosis and increased mortality (Borlaug et al., 2009; Mohammed et al., 2014). Increases in LAdiam in HFpEF have been associated with obesity more so than systolic HTN (Stritzke et al., 2009) and linked to increases in mortality (Rossi et al., 2006).

The findings of the conditional logistic regression showed that one unit increases in Ees and LAdiam were associated with an increased risk of being in the case group. Studies have demonstrated increases in Ees and LAdiam with older women and suggested that this difference was due to age related LV stiffening (Redfield, Jacobsen, Borlaug, Rodeheffer, & Kass, 2005). In this study, even with controlling for age, race and gender, incremental increases in Ees and LAdiam were associated with higher odds of being in the case group. This suggests changes in Ees and LAdiam are important to monitor regardless of age, race or gender.

***Limitations***

A limitation of this study is related to the importance of associated co-morbidities and inflammatory markers in studying HFpEF. Patients with HFpEF often have hypertension, diabetes and renal disease. This study focused primarily on physiologic and echocardiographic markers of HFpEF and did not specifically collect data points related to co-morbidities or pro-inflammatory markers. As suggested by Paulus and Tschope, the unique characteristics of HFpEF may be caused by inflammation more so than increases in LV load. Future studies that combine markers of inflammation and physiologic performance such as LAdiam and Ees, may help define HFpEF.

***Conclusions***

From this matched case-control study, we found that the case group had significantly higher SBP, HR, BMI, Ees and LAdiam and that incremental increases in Ees and LAdiam were associated with higher odds of being in the case group, regardless of age, race or gender. The clinical utility of these findings require further investigation with more than one data point for comparison and in prospective designs with larger sample sizes.

# CHAPTER 4

## PAPER 3: INCIDENT HEART FAILURE PRESERVED EJECTION FRACTION (HFpEF): RECOGNIZING KEY PATIENT ATTRIBUTES

### Overview

***Objectives:***

This study describes patient attributes, physiologic and echocardiographic biomarkers associated with incident HFpEF.

***Background:***

The prevalence of HFpEF continues to rise with 50% mortality within 3 years of incident hospitalization and the $31billion annual costs of HF are expected to double by 2030. Yet the science continues to build on the understanding of population(s) at greatest risk.

***Methods:***

Incident HFpEF patients (n=252) were retrospectively identified using HFpEF diagnostic criteria defined by the European Society of Cardiology, and physiologic biomarkers (systolic blood pressure, diastolic blood pressure, heart rate, body mass index) and echocardiogram biomarkers (ejection fraction, diastolic function grade, left atrial diameter, arterial-ventricular elastance) were collected from previously acquired 2dimentional M-mode Doppler echocardiograms and images were re-analyzed for Ea, Ees calculations. Descriptive statistics were used to define characteristics and biomarkers of the incident HFpEF group. Arterial (Ea) and left ventricular (LV) end-systolic (Ees) stiffness, ventricular-arterial coupling

(Ea/Ees ratio) were calculated on a group of n=191 patients. Factors associated with age at diagnosis, age at death and time to death were analyzed.

***Results:***

The sample was 58% Black and 73% female, ages 33 to 99 years. Baseline characteristics showed significantly higher age of incident HFpEF in Whites than Blacks (77 vs. 65 years, $p<0.0001$). This trend was present in both genders, with Black females age 67 years, White females age 77 years ($p<0.0001$) and Black males 62 years, White males 75 years, ($p=0.0002$) . For biomarkers, with regard to race, heart rate and body mass index was significantly higher in Black compared to White patients ($p=0.0228$, $p=0.0012$, respectively). With regard to gender, measures of Ea, Ees were significantly higher in women compared to men ($p=0.0004$, $p=0.0005$, respectively). Of the 252 incident HFpEF patients, 125 (50%) died within 2 years of incident HFpEF admission. The time to death after diagnosis was not significantly different between Black and White patients, but the age at death was significantly younger for Black patients compared to White patients (72 versus 81 years, $p=0.0002$).

***Conclusions****:*

Race significantly impacts the age of incident HFpEF diagnosis and time at death. Future incident HFpEF studies, when possible, need to include diverse study samples with careful attention to diagnostic criteria and screening techniques.

# PAPER 3: INCIDENT HEART FAILURE PRESERVED EJECTION FRACTION (HFpEF): RECOGNIZING KEY PATIENT ATTRIBUTES

## *Objective*

This manuscript presents an analysis of incident HFpEF patients previously discharged with heart failure preserved ejection fraction (HFpEF), defined by diagnostic guidelines from the European Society of Cardiology (ESC) and inclusive of a diverse study sample, reporting on baseline characteristics, echo biomarkers, markers of ventricular-arterial coupling and details of death.

## *Background*

HFpEF is a progressive disorder responsible for at least 50% of all hospital admissions for heart failure (HF) and will likely become the predominant HF in coming years (Oktay & Shah, 2014; Owan et al., 2006). Although the increase in prevalence of HFpEF is frequently attributed to the aging population, diverse populations are frequently understudied and controversy exists on the populations most affected (Kitzman & Upadhya, 2014). In addition, there are multiple co-morbidities that impact those most at risk (Paulus & Tschope, 2013). Studies that incorporate specific measures, such as biomarkers associated with HFpEF into age, race and sex stratified samples will likely provide normative data that can be expanded upon to help explain this heterogeneous syndrome (Borlaug et al., 2009; Chang et al., 2014).

Concise description and measurement of biomarkers that defines incident heart failure preserved ejection fraction (HFpEF), (ejection fraction $\geq$50%), in a representative sample of the population is essential to identifying early markers of impending HFpEF. First, the most commonly used diagnostic criteria for HFpEF is the Framingham Criteria published in 1971

(McKee et al., 1971) This criteria is not specific to HFpEF and does not use specific echocardiographic parameters. Second, in the current literature, inconsistencies exist, in the population(s) most affected by HFpEF (East et al., 2004; Gurwitz et al., 2013), yet studies that set the priority of including a broad range of age and race samples into the design are few. This study focuses on the combination of physiologic and echocardiographic indicators associated with HFpEF within a diverse study group.

Pro-inflammatory markers such as interleukin 6 and tumor necrosis factor α have been found to be associated with incident HFpEF (Kalogeropoulos et al., 2010) and comorbidities such as diabetes, hypertension and kidney disease are frequently associated with this syndrome (Paulus & Tschope, 2013). Thus, multiple systems are involved in explaining the etiology and heterogeneity of incident HFpEF (Gladden et al., 2014). To study one aspect of this complex syndrome, identifying feasible markers of cardiac physiology associated with HFpEF within a representative sample is indicated. In conjunction, diagnostic criteria that incorporate these markers will provide clarity to defining unique characteristics of incident HFpEF patients.

Ejection fraction (EF), measured from ventricular volume and dependent upon load (Braunwald, 2001), is a commonly used parameter to define left ventricular (LV) contractility and classify mortality risk, prognosis and treatment (Yancy et al., 2013). However, EF may not account for varying degrees of systolic or diastolic function that impact contractility such as ventricular size, physiologic parameters, myocardial contractility and afterload (Borlaug & Paulus, 2011; Ky et al., 2013). Invasive hemodynamic measurement is the gold standard to reflect LV performance, but noninvasive methods have also been validated (Chen et al., 2001; Ky et al., 2013; Nagueh et al., 2009).

In addition to diastolic dysfunction (DD), measures of LV end diastolic volume that incorporate LV size, end-systolic pressure and volume are key attributes to consider in measuring LV contractility (Borlaug & Kass, 2008). Ejection fraction (EF) is the most commonly used to define LV function as a volumetric measure, but does not incorporate LV size, pressure and volume throughout systole (contraction) and diastole (relaxation) (Borlaug, 2014; Ky et al., 2013). Used in conjunction with EF, measures that incorporate LV volume, load and contractility into a measure of ventricular elastance (stiffness) is reflected in Ees (Gladden et al., 2014). In addition to Ees, linking end-systolic pressure-volume to end diastolic volume incorporates afterload and is reflected in measuring arterial elastance (Ea). Ea and Ees provide a method to explain and measure the interaction arterial-ventricular coupling. Cardiac performance is greatly influenced by the ventricular-arterial coupling, measured by the Ea/Ees ratio (Borlaug & Kass, 2011; Ky et al., 2013). The Ees, Ea and ventricular-arterial coupling have been studied in patients with HTN (Borlaug et al., 2009), older White patients (Borlaug & Redfield, 2011) and HFrEF (Ky et al., 2013) but not yet in a racially diverse, age stratified populations over time.

Use of consistent and clearly defined diagnostic criteria in addition to reproducible measures of LV function are required to build on the current understanding of HFpEF (Gladden et al., 2014). Diagnostic criteria outlined by the European Society of Cardiology (ESC) incorporate clinical symptoms and specific noninvasive echo markers (Paulus et al., 2007). The criteria specifically outlines the importance of early mitral valve annular velocity (E'), and the ratio of E (early LV filling)/E' in estimating LV filling pressures (Nagueh et al., 2009). Evidence of E/e'>15 is diagnostic of LV DD and E/e'<8 is diagnostic of absence of HFpEF and E/e' ranges from 8-15 are suggestive of LV DD that require further evaluation

with biomarkers such as E/A ratio or brain natriuretic peptide (BNP) (Paulus et al., 2007). Given that there are limited studies that incorporate diverse samples in HFpEF trials and that there is inconsistent use diagnostic criteria to define the study population, this study was designed to use ESC guidelines to identify patients with incident HFpEF and stratify them by age, race and sex and to describe patient characteristics, physiologic and echocardiographic biomarkers associated with incident HFpEF diagnosis and time to death after incident HFpEF diagnosis.

***Methods***

*Study population*

Patients discharged with incident (first episode of) HFpEF, identified by International Classification of Diseases, 9$^{th}$ revision, Clinical Modification (ICD-9_CM) code book with codes for 428.30 (diastolic heart failure, unspecified), 428.31 (acute diastolic heart failure), 428.32 (chronic diastolic heart failure), 428.33 (acute on chronic diastolic heart failure) from an academic university in the southest, from January 1, 2007-January 1, 2014 were identified. This time range was selected to insure an adequate study sample and because protocols were improved before this time period. To be enrolled, the medical record of each patient discharged with incident HFpEF was verified by the reviewer incorporating the European Society of Cardiology diagnostic criteria for heart failure normal ejection fraction (Paulus et al., 2007) and met ICD-9 criteria.

Because this retrospective evaluation specifically focused on biomarkers leading to incident (first episode) HFpEF patients were excluded if chart review indicated prior HF hospitalization for either HFpEF or heart failure reduced ejection fraction (HFrEF), prior echo ejection fraction (EF)<50%, if diastolic function, pulse wave or LV outflow tract

imaging could not be obtained from the echocardiogram, presence of severe moderate/severe mitral valve disease, history of aortic or mitral valve surgery or vegetation, heart transplantation, hypertrophic obstructive cardiomyopathy, persistent tachycardia due to chronic atrial fibrillation, congenital heart disease, severe pulmonary arterial hypertension (not due to diastolic dysfunction), connective tissue disorders such as rheumatoid arthritis, advanced malignancy, shock.

All study data were extracted from pre-existing electronic sources that included a storage data base, medical record, echocardiogram database and imaging database. Within the medical record, race was typically self reported when a patient account was created within the health system. An a priori objective of a racially representative study group relative to the geographic location was operationalized into the study design. That is, close attention was focused on the consistency of the study sample and the demographic outlined by the 2012 U.S. Census Data, in Durham County, that describes the general population as 38% White, 41% Black and 14% Hispanic (Commerce, 2012). This study was approved by the University of North Carolina at Chapel Hill and Duke University institutional review boards and all data processing was completed with strict adherence to the Health Insurance Portability and Accountability Act (HIPAA).

*Echocardiogram*

Data from previously obtained two-dimensional (2D) M (motion)-mode Doppler transthoracic echocardiograms within the health system were used for study analysis. All previously obtained echos were acquired using standardized techniques recommended by the American Society of Echocardiography. All echo image measurements for the following

formulas were obtained by two echo sonographers nationally certified by the American Society of Echocardiography.

End-systolic pressure volume (ESP) was estimated as 0.90 X systolic blood pressure (SBP) by manual cuff at the time of echo as recommended (Chen et al., 2001). Stroke volume (SV) was measured from the LV outflow tract (LVOT) diameter at the pulse wave (PW) Doppler signal (Chen et al., 2001). Ees was calculated using the single beat method (Chen et al., 2001).

Stroke volume (SV)=
(LVOT diameter$^2$)(0.785)=LVOT area(cm$^2$)
(LVOT area(cm$^2$)) (TVI)=SV (cm$^3$)

Arterial elastance (Ea) was defined as the ratio of ESP/SV (Lam et al., 2007).

Ea = ESP/SV
ESP = 0.9 * SBP
SV (cm$^3$)

Ees was calculated using the single-beat method outlined by Chen and colleagues (Chen et al., 2001).

Ees(sb) = (DBP-(Endest*ESP))/(SV*Endest)

Endest = 0.0275-(0.165*EF)+0.3656*(DBP/ESP)+(0.515*Endavg)
Endavg = (0.35695*1)+(-7.2266*tn^1)+(74.249*tn^2)+(-307.39*tn^3)+(684.54*tn^4)+(-856.92*tn^5)+(571.95*tn^6)+(-159.1*tn^7)
ESP = 0.9 * SBP
SV (cm$^3$)
tn (ms) = R wave to flow onset time/R wave to flow end time; determined noninvasively from LVOT Doppler waveform

Ventricular-vascular coupling was defined as Ea/Ees ratio (Antonini-Canterin et al., 2013; Borlaug & Kass, 2011). With normal physiologic response the Ea/Ees ratio varies from 0.50-1.00 (Borlaug et al., 2009) or 0.60-1.2 to maintain optimal work efficiency (Borlaug et al., 2009). Previous studies have shown that the Ea/Ees ratio decreases in elderly

women because ventricular stiffness increases out of proportion to vascular load (Borlaug & Kass, 2008).

*Statistical Methods*

Characteristics of the study cohort were described with frequency data and included incident HFpEF patients who died for any cause after the incident hospitalization. T-tests were used to compare mean physiologic and echocardiographic biomarkers. Analysis of variance was used to compare mean age of incident HFpEF diagnosis and median age at death by race and sex. Cox regression was used to assess hazard of death by age at diagnosis, race and sex. Statistical significance was defined as $p<0.05$. All statistical analyses were performed using SAS, Inc., 9.4, statistical software (SAS Institute Inc., Cary, North Carolina) and JMP, version 11.2.0 (SAS Institute Inc., Cary, North Carolina).

***Results***

*Study Population*

The potential sample for this study included 876 patients whose charts were screened and 624 patients were excluded, leaving 252 for the incident HFpEF cohort that met inclusion criteria. The most common reasons for exclusion were: a) history of echo EF<50%, (n=296, 49%), b) incident HFpEF criteria not met, (n=188, 30%), c) severe aortic or mitral valve disease (n=89, 14%). Across the cohort, the mean age was 70 years (14.83) and the majority of participants were female (73%) and Black (59%). Demographic characteristics of the study population represented a study group of 252 patients, 59% Black and 73% female, ages 33 to 99 years. See Table 4.1.

Table 4.1. Characteristics of incident HFpEF group

| **Characteristics of incident HFpEF group** | | | | **N=252** |
|---|---|---|---|---|
| **Variable** | **N** | **%** | **Mean** | **SD** |
| Age(years) | 252 | | 70 | 14.83 |
| Race (Black) | 147 | 59 | | |
| Female | 182 | 73 | | |
| SBP(mmHg) | 252 | | 144 | 24.77 |
| DBP(mmHg) | 252 | | 73 | 13.05 |
| HR(bpm) | 252 | | 75 | 15.11 |
| BMI(kg/m$^2$) | 200 | | 36 | 11.40 |
| EF(%) | 252 | | 54.94 | 0.47 |

*Race, Age at Diagnosis and Time to Death*

The mean age of incident HFpEF for Black patients was 65 years and for White patients was 77 years, ($p<0.0001$). See Table 4.2. The mean age of incident HFpEF admission for Black females was 67 years, for White females was 77 years, $p<0.0001$. The mean age of incident HFpEF admission for Black males was 62 years, for White males was 75 years, $p=0.0002$.

Table 4.2. Age at Diagnosis by Race

| **Age of incident HFPEF by Race** | | | | |
|---|---|---|---|---|
| Race | Variable | Mean | SD | P value |
| Black | age | 65.32 | 15.15 | **<0.0001** |
| White | age | 76.69 | 11.51 | |

Comparing physiologic biomarkers, for Black patients the heart rate and BMI were significantly higher compared to White patients ($p=0.0228$, $p=0.0012$). See Table 4.3. Comparing echocardiogram biomarkers, for female patients the Ea and Ees, were significantly higher compared to males ($p=0.0004$, 0.0005). See table 4.4.

Table 4.3. Physiologic biomarkers of the incident HFpEF group

| Physiologic biomarkers of incident HFpEF group by race and sex | | | | | |
|---|---|---|---|---|---|
| | **Race** | **Mean** | **SD** | **t** | **p** |
| SBP(mmHg) | Black | 143.60 | 24.26 | 0.40 | 0.6927 |
| | White | 142.20 | 25.83 | | |
| | Female | 143.70 | 23.44 | 0.61 | 0.5432 |
| | Male | 141.30 | 28.44 | | |
| DBP(mmHg) | Black | 74.99 | 13.63 | 1.72 | 0.0877 |
| | White | 71.61 | 12.9 | | |
| | Female | 73.34 | 13.41 | -0.48 | 0.6350 |
| | Male | 74.38 | 13.54 | | |
| HR(bpm) | Black | 78.61 | 14.13 | 2.30 | **0.0228** |
| | White | 73.47 | 13.98 | | |
| | Female | 77.57 | 15.02 | 1.63 | 0.1052 |
| | Male | 73.68 | 12.86 | | |
| BMI(kg/m$^2$) | Black | 38.07 | 11.11 | 3.30 | **0.0012** |
| | White | 32.25 | 9.47 | | |
| | Female | 36.80 | 11.45 | 1.47 | 0.1425 |
| | Male | 34.00 | 9.24 | | |

Table 4.4. Echo biomarkers of the incident HFpEF group

| Echo biomarkers of incident HFpEF by race and sex | | | | | |
|---|---|---|---|---|---|
| | **Race** | **Mean** | **SD** | **t** | **p** |
| Ea(mmHg/ml) | Black | 2.07 | 0.97 | -0.92 | 0.3614 |
| | White | 2.23 | 0.96 | | |
| | Female | 2.25 | 01.04 | 3.57 | **0.0004** |
| | Male | 1.61 | 0.67 | | |
| Ees(mmHg/ml) | Black | 6.30 | 3.50 | -1.70 | 0.0922 |
| | White | 7.30 | 3.87 | | |
| | Female | 7.67 | 3.85 | 3.86 | **0.0005** |
| | Male | 4.72 | 2.34 | | |
| Ea/Ees | Black | 0.3704 | 0.1282 | -0.76 | 0.4494 |
| | White | 0.4418 | 0.7918 | | |
| | Female | 0.4124 | 0.6159 | 0.39 | 0.8383 |
| | Male | 0.3718 | 0.1220 | | |
| LAdiam(cm) | Black | 4.14 | 0.66 | -1.54 | 0.1258 |
| | White | 4.30 | 0.61 | | |
| | Female | 4.19 | 0.69 | -0.32 | 0.6289 |
| | Male | 4.25 | 0.51 | | |

Patients who died for any cause after incident HFpEF admission were studied. Of 252 incident HFpEF patients, 125 died (50%) within 2 years. The median age at death was

79 years, (IQR 68, 87). Of the incident HFpEF patients, 49% of the women died, 50% of the men died, 44% of the Blacks died and 57% of the Whites died.

Using analysis of variance, comparing age at death by sex, the mean age was 77 years for females and 76 years for males (p=0.5142). Comparing age at death by race, the mean age was 72 years for Blacks and 81 years for Whites (p=0.0002). Comparing age at death of Black females versus White females, the mean age was 73 years for Black females and 82 years for White females (p=0.0010). Comparing age at death of Black males versus White males, the mean age was 70 years for Black males and 79 for White males, (p=0.0308). Using Cox regression, assessing the hazard of death by race and by sex, the findings were non-significant (p=0.3732, p=0.3551, respectively). However, assessing the hazard of death by age at diagnosis, the findings were significant (p<0.0001), that is, for every one unit increase in age, there was a 4% higher hazard of death.

***Discussion***

The impact of race in defining the age of diagnosis of incident HFpEF and age at death was significant and carried through to age and sex. In this study, Blacks represented 58% of the overall study group, had higher BMI and heart rate and were diagnosed with incident HFpEF 12 years younger than White patients and age at death was 9 years younger for Black patients compared to White patients.

As compared with other racial groups, Black patients are at increased risk for the development of HF (Bibbins-Domingo et al., 2009), at younger ages and with higher prevalence of DM and HTN (Thomas et al., 2011). Most HFpEF studies have limited representation of Black patients and subsequently limited understanding of the factors that contribute to HFpEF (Shah, 2012). In the Atherosclerosis Risk in Communities Study

(ARIC), evaluating decompensated HF due to HFrEF and HFpEF from 4 regional communities in the United States (Forsyth County, North Carolina, Jackson, Mississippi, Minneapolis, Minnesota and Washington County, Maryland) showed that white women had the highest proportion of HFpEF admissions (70%) (Chang et al., 2014). In the analysis section of this study, it states that because Minneapolis and Washington County were predominately white, Blacks from the 2 counties were not included in the final analysis (Chang et al., 2014). However when reporting the proportion of HFpEF admissions as predominately 70% White women, it is unclear how the Blacks in Forsyth County, North Carolina (20% Black) and Jackson, Mississippi (61% Black) were weighted in the analysis. That is, it is unclear if the proportion of Black and White patients in each location were compared or if the HFpEF proportion was calculated from the total number of Black and White patients enrolled in the study. In a subgroup analysis of ARIC, only Black patients were included (Gupta et al., 2013). But of the 6168 records reviewed in the ARIC trial, and a cohort sample in Jackson, Mississippi of 2445 patients, only 85 HFpEF patients and 31 HFrEF patients were included in the subgroup analysis (Gupta et al., 2013).

Racial and ethnic differences in HF mortality have been inconsistent with some studies reporting similar or lower survival for Black patients compared to White patients and some studies suggesting no difference in survival (East et al., 2004; Yancy et al., 2008). In the East et al., study, the mortality rate for Black HFpEF patients was 34% higher compared to White patients (East et al., 2004). In the Yancy et al., study, the post discharge outcomes between Black and White patients were similar (Yancy et al., 2008).

Based on a retrospective analysis of 78,801 patients from 257 hospitals, Black patients developed HF at younger ages, with more cardiovascular risk factors such as HTN,

DM and had a greater risk of death, but had similar in-patient mortality and equitable care compared to White patients (Thomas et al., 2011). Therefore, race is a key factor in studying incident HFPEF and needs to be incorporated into the design when studying incident HFpEF trials/

In addition, use of diagnostic criteria, such as the ESC guidelines, in defining incident HFpEF and careful attention to the use of ICD-9 codes are critical when identifying incident HFpEF study groups. In this study, of the 876 potential incident HFPEF patients, only 252 patients were kept in the study group. Of the patients excluded, 50% had previous echo evidence of EF <50% and an additional 30% did not meet diagnostic criteria for incident HFpEF, therefore 80% patients identified by ICD-9 code were not incident HFpEF patients after chart review. As large studies use retrospective data based on ICD-9 codes to study incident HFpEF, careful attention to patient screening is required to insure that patients with incident HFpEF are appropriately included and that HFrEF patients are appropriately excluded.

***Limitations***

This study includes a diverse sample however, did not collect data points specific to associated co-morbidities and inflammatory markers. Given that incident HFpEF is a heterogeneous clinical syndrome possibly linked to multiple co-morbid conditions, the collection of inflammatory markers would be beneficial in understanding HFpEF etiology.

### *Conclusions*

The results of this study demonstrate the significant impact of race on the age of incident HFpEF diagnosis and age at death. Future studies that prospectively evaluate incident HFpEF would benefit from incorporating consistent diagnostic HFpEF criteria, selection of a diverse study group, and use of physiologic markers in combination.

# CHAPTER 5

DISCUSSION AND CONCLUSION

## Summary

### Heart Failure Preserved Ejection Fraction (HFpEF): An Integrated and Strategic Review

The first manuscript reviewed key aspects of the literature and state of the science on HFpEF. Areas of review included scope of the problem, pathophysiology, diagnostic criteria, biomarkers and the current status of treatment for HFpEF. The focus of this manuscript was developed based on findings from a previously completed pilot study evaluating the role of diastolic dysfunction in HFpEF and from a review of the literature that found controversy over the populations most affected in addition to under-representation of diverse groups in HFpEF trials. This review noted the changes in pathophysiologic understanding between HFrEF and HFpEF, controversies in defining the population(s) most affected by HFpEF, and presented a methodology to define and measure the pathophysiology of HFpEF. In addition, the key role of multiple co-morbidities that factor into the development of HFpEF was identified. The calculation of Ees using the single beat technique was reported in 2001 (Chen et al., 2001) and describing ventricular-arterial stiffening in HFpEF was reported in 2002 (Kawaguchi et al., 2003). Biomarkers associated with HFpEF were reviewed as a description of the single beat method for measuring

ventricular elastance and the interaction of arterial-ventricular stiffness. This manuscript highlighted the need for consistent use of diagnostic criteria and presented a very recent example of a very large international trial that used a non-specific diagnostic guide in an international study to identify HFpEF.

As a road map to future manuscripts the literature review set the ground work to explore HFpEF. As defined in the dissertation proposal the primary objective of all subsequent studies was to identify early markers that precede the development of HFpEF. Three primary hypotheses were established, a) the case group would demonstrate differences in biomarkers compared to the control group, b) within the subgroups age/race/sex would function as moderator that impact the extent to which biomarkers predict HFpEF and c) subgroups within the case group would demonstrate significant differences between race in age of incident HFpEF diagnosis. The first two hypotheses were addressed in manuscript 2 and the third hypothesis was addressed in manuscript 3. As outlined in the literature review, future studies that include diverse populations, use HFpEF diagnostic guidelines, incorporate consider pro-inflammatory markers and use biomarkers that reflect arterial-ventricular coupling will likely have a significant impact on HFpEF.

**Comparing Novel Biomarkers Associated with Heart Failure Preserved Ejection Fraction** (HFpEF): A Matched Case-Control Study

The second manuscript presented the results of an observational retrospective matched case-control analysis comparing patients with an incident HFpEF to a control group with no prior history of HFrEF or HFpEF. The groups were matched 1:1 by age (within 3 years), race, sex and timing of echo and the results suggested statistically significant differences in biomarkers between the case and control groups. This study demonstrated that

measures of ventricular-arterial coupling could feasibly be obtained from routinely acquired echo and that Ees and LAdiam may be important markers to evaluate over time, however the clinical utility of Ees and LAdiam require further study with prospective designs.

**Incident Heart Failure Preserved Ejection Fraction (HFpEF): Recognizing Key Patient Attributes**

This manuscript focused on patient attributes of age, race and sex and measures of physiologic and echocardiographic biomarkers in defining the patient population of incident HFpEF. The analysis demonstrated the key role of race in describing the age if incident HFpEF diagnosis and age at death. This study also demonstrated the importance of confirming incident HFpEF when patients are selected retrospectively by ICD-9 codes. Although this study did not incorporate co-morbidities in defining the incident HFpEF group, future studies that incorporate pro-inflammatory markers that result from co-morbid conditions in addition to markers of physiology such as Ea and Ees, within diverse samples, will add to understanding the complex syndrome of incident HFpEF. .

**Implications for Nursing Research**

There are two distinct areas that appear to have great potential for nurses in furthering the study of ventricular-arterial coupling. The effect of co-morbidities and the impact of neurohormonal activation have not been extensively studied in the setting of arterial ventricular elastance. Nor has the effect of acute and chronic stress on Ea, Ees and Ea/Ees. Considering markers such as waist circumference and cortisol as covariates to Ea, Ees in studying the impact of stress on incident HFpEF has not been explored widely. There is substantial evidence in the literature that describes pro-inflammatory markers and stress in

the context of the context of co-morbid conditions, however, a marker of physiology such as ventricular-arterial coupling has not been evaluated.

A second area of future nursing research may be studying echo, co-morbid conditions and genetic markers in addition to physiologic measurements associated with incident HFpEF patients. By using genetic information, physiologic biomarkers within the context of know co-morbid conditions, new insights into the phenotype of HFpEF are likely to emerge. Cath Gen is a pre-existing data warehouse that stores both genetic samples linked to biomarkers from cardiac catheterization.

**Implications for Nursing Practice**

The utility of using arterial-ventricular coupling in the clinical management of HFpEF patients may be an important aspect of clinical care for nurses and nurse practitioners. For patients who are asymptomatic or difficult to assess functionally, the use of Ea Ees biomarkers in defining physiologic state in conjunction with monitoring symptoms may serve a very important role in patient clinical management.

The nurse's role as educator may be especially important in this setting. Helping patients understand the complexity of HFpEF that requires consistent use of medications, regular monitoring of home BP and dietary modification will significantly impact care.

Nurses could also be instrumental in helping patients find avenues for adequate support. HF is a progressive illness that can be debilitating without adequate monitoring and care. Effective management requires a great deal of patient education and ongoing monitoring.

In addition, although not discussed within the context of this dissertation, nursing interventions to reduce stress may have an indication in this patient population. Interventions

such as relaxation, exercise and yoga have all been associated with decreasing inflammatory markers and improvements in blood pressure control (Kiecolt-Glaser et al., 2010; Okonta, 2012; Tyagi & Cohen, 2014). Interventions involving nurses need further investigation.

**Conclusion**

HFpEF is a major public health issue with serious mortality and fiscal implications (Dunlay & Roger, 2014). Patients with HFpEF likely have multiple phenotypes within multiple co-morbidities that explain this heterogeneous syndrome (Gladden et al., 2014; Paulus & Tschope, 2013). Concise use of diagnostic guidelines in studies that employ diverse research designs, with biomarkers associated with HFpEF will contribute to our current understanding of the types of patients most affected and help identify those at risk.

Findings from the literature review suggested that gaps exist in HFpEF research in the identification of biomarkers that predict risk, consistent use of diagnostic guidelines, and study designs that incorporate race. Given that HFpEF is a heterogeneous syndrome, clearly defined guidelines and stratified samples are essential. Regional variation in HFpEF patient characteristics is expected. However, when possible, ensuring an adequately sampled population would help provide insight into HFpEF patient characteristics.

In the second manuscript that reported the findings of the matched case-control analysis using conditional logistic regression suggests that specific biomarkers; suggested that patients in the case group had higher SBP, HR, BMI, Ees and LAdiam and that incremental increases in Ees and LAdiam were associated with a higher odds of being in the case group.

In the third manuscript that reported on key patient attributes of incident HFpEF, statistically significant differences in age of diagnosis of incident HFpEF and age at death

were demonstrated when comparing Black and White patients. There were also significant differences that carried through to gender in that Black women and men were diagnosed with incident HFpEF significantly younger than White women and men.

To conclude, the incidence of HFpEF continues to increase, yet no specific treatment modality other than symptom management has been effective. Multiple co-morbidities factor into the context of etiology and pro-inflammatory markers likely have a role. Race is a key patient attribute in understanding the phenotype of incident HFpEF.

The matched-case control study suggested statistical significance with Ees and LAdiam and analysis of the incident HFpEF group demonstrated the statistically significant role of race in age of diagnosis and age at death. Although markers such as Ea and LAdiam do not comprehensively reflect the physiologic impact of the multiple systems involved with incident HFpEF, they may reflect one aspect of this complex clinical phenomenon that can be measured over time. Future studies that prospectively test Ea, Ees, LAdiam, in the context of racially diverse samples, considering co-morbidities and use consistent diagnostic criteria, will significantly impact the trajectory of HFpEF.

## Appendix A

Appendix A. – List of Abbreviations (alphabetically)

| **Term** | **Abbreviation** |
|---|---|
| American College of Cardiology | ACC |
| American College of Cardiology Foundation | ACCF |
| American Heart Association | AHA |
| American Society of Echocardiography | ASE |
| Angiotensin Receptor Blockers | ARB |
| Arterial Elastance | Ea(mmHg/ml) |
| Arterial/Ventricular Elastance | Ea/Ees(ratio) |
| Atrial Fibrillation | AF |
| Body Mass Index | BMI(kg/m²) |
| Brain Natriuretic Peptide | BNP(pg/mL) |
| Cardiac Magnetic Resonance Imaging | cMRI |
| Cardiac Output | CO(L/min) |
| Coronary Artery Disease | CAD |
| Creatinine Clearance | CrCl(ml/min) |
| Diabetes | DM |
| Diastolic Dysfunction | DD(grade) |
| Diastolic Blood Pressure | DBP(mmHg) |
| Early (E) and late (A) diastolic filling | E/A ratio |
| Early Mitral Valve Annular Velocity | (e')(cm/s) |
| Early Ventricular Filling | E(cm/s) |
| Ejection Fraction | EF(%) |
| End Systolic Pressure Volume | ESP |
| European Society of Cardiology | ESC |
| Global Longitudinal Strain | GLS(%) |
| Health Insurance Portability and Accountability Act | HIPAA |
| Heart Failure | HF |
| Heart Failure Normal Ejection Fraction | HFNEF |
| Heart Failure Reduced Ejection Fraction | HFrEF |
| Heart Failure Preserved Ejection Fraction | HFpEF |
| Heart Rate | HR(bpm) |
| Hematocrit | Hct(%) |
| Hemoglobin | Hgb(g/dL) |
| Hemoglobin A1C | HgbA1C(%) |
| High Sensitivity C Reactive Protein | Hs-CRP (mg/L) |
| Homocysteine | (µmol/L) |
| Hypertension | HTN |
| Institutional Review Board | IRB |
| International Classification of Diseases, 9$^{th}$ revision | ICD-9 |
| Isovolumic Relaxation Time | IVRT (ms) |

| | |
|---|---|
| Late Diastolic Filling | A(cm/s) |
| Left Atrial Diameter | LAdiam(cm) |
| Left Atrial Enlargement | LAE |
| Left Ventricle | LV |
| Left Atrial | LA |
| Left Ventricular End Diastolic Pressure | LVEDP(mmHg) |
| Left Ventricular Filling Pressure | E/e'(ratio) |
| Left Ventricular Hypertrophy | LVH(grade) |
| Left Ventricular Outflow Track | LVOT(cm) |
| Left Ventricular Systolic Elastance | Ees(mmHg/ml) |
| National Health and Nutrition Examination Survery | NHANES |
| Pulmonary Capillary Wedge Pressure | PCWP (mmHg) |
| Renin-Angiotensin-Aldosterone System | RAAS |
| Stroke Volume | SV($cm^3$) |
| Systolic Blood Pressure | SBP(mmHg) |
| Treatment of Preserved Cardiac Function in Heart Failure with an Aldosterone Antagonist | TOPCAT |
| United States | U.S. |
| Weight | WT(lbs) |

## Appendix B

Appendix B. HFpEF Early Markers Code Sheet

Demographics

ID# __ __ __ __
1 2 3 4

Age __ __
5 6

Race __
7

Sex __
8

---

Date of Admission __ __/__ __ __ __
9 1011 12 13 14

SBP A __ __ __
15 16 17

DBP A__ __ __
18 19 20

HR A __ __
21 22

BMI A__ __
23 24

Past Medical History at the time of HFpEF admission
List of options: DM 250.00, HTN 401.09, AFIB 427.31

a. __ __ __: __ __
25 26 27 28 29

b. __ __ __: __ __
30 31 32 33 34

c. __ __ __: __ __
35 36 37 38 39

d. __ __ __: __ __
40 41 42 43 44

---

Echocardiogram
A.

Date __ __ /__ __ __ __
45 46 47 48 49 50

EF 1 __ __
51 52

LVH 1 __ (0-none, 1-mild, 2-moderate, 3-severe)
53

DD 1 __ (0-none, 1-grade1, 2-grade2, 3-grade 3/4)
54

SBP 1 __ __ __
55 56 57
DBP 1 __ __ __
58 59 60
HR 1 __ __
61 62
BMI 1 __ __
63 64

B.
Date __ __ /__ __ __ __
65 66 67 68 69 70
EF 2 __ __
71 72
LVH 2 __ (0-none, 1-mild, 2-moderate, 3-severe)
73
DD 2 __ (0-none, 1-grade1, 2-grade2, 3-grade 3/4)
74

SBP 2 __ __ __
75 76 77
DBP 2 __ __ __
78 77 79
HR 2 __ __
80 81
BMI 2 __ __
82 83

C.
Date __ __ /__ __ __ __
84 85 86 87 88 89
EF 3 __ __
90 91
LVH 3 __ (0-none, 1-mild, 2-moderate, 3-severe)
92
DD 3 __ (0-none, 1-grade1, 2-grade2, 3-grade 3/4)
93

SBP 3 __ __ __
94 95 96

DBP 3 __ __ __
97 98 99
HR 3 __ __
100 101
BMI 3 __ __
102 103

D.
Date __ __ /__ __ __ __
104 105 106 107 108 109
EF 4 __ __
110 111
LVH 4 __ (0-none, 1-mild, 2-moderate, 3-severe)
112
DD 4 __ (0-none, 1-grade1, 2-grade2, 3-grade 3/4)
113

SBP 4 __ __ __
114 115 116
DBP 4 __ __ __
117 118 119
HR 4 __ __
119 120
BMI 4 __ __
121 122

---

Echocardiogram database
Echocardiogram #1
Date __ __ /__ __ __ __
123 124 125 126 127 128
Early ventricular filling (E) __ __ __
129 130 131
Late diastolic filling (A) __ __ __
132 133 134
Early mitral valve annular velocity (E') __ __ __
135 136 17
LV filling pressure (E/E') __ __ __
138 139 140
Arterial elastance (Ea) __ __ __
141 142 143
LV systolic elastance (Ees) __ __ __

144 145 146

Arterial/ventricular elastance (Ea/Ees) __ __ __
147 148 149

Mean LV end diastolic pressure (mLVEDP) __ __ __
150 151 152

Mean pulmonary capillary wedge pressure (mPCWP) __ __ __
153 154 155

LV ejection fraction (LVEF) __ __ __
156 157 158

Global longitudinal strain (strain %) __ __ __
159 160 161

LV hypertrophy (LVH) __ __ __
162 163 164

Echocardiogram #2

Date __ __ /__ __ __ __
165 166 167 168 169 170

Early ventricular filling (E) __ __ __
171 172 173

Late diastolic filling (A) __ __ __
174 175 176

Early mitral valve annular velocity (E') __ __ __
177 178 179

LV filling pressure (E/E') __ __ __
180 181 182

Arterial elastance (Ea) __ __ __
183 184 185

LV systolic elastance (Ees) __ __ __
186 187 188

Arterial/ventricular elastance (Ea/Ees) __ __ __
189 190 191

Mean LV end diastolic pressure (mLVEDP) __ __ __
192 193 194

Mean pulmonary capillary wedge pressure (mPCWP) __ __ __
195 196 197

LV ejection fraction (LVEF) __ __ __
198 199 200

Global longitudinal strain (strain %) __ __ __
201 202 203

LV hypertrophy (LVH) __ __ __

204 205 206

Echocardiogram #3

Date __ __ /__ __ __ __
207 208 209 210 211 212

Early ventricular filling (E) __ __ __
213 214 215

Late diastolic filling (A) __ __ __
216 217 218

Early mitral valve annular velocity (E') __ __ __
219 220 221

LV filling pressure (E/E') __ __ __
222 223 224

Arterial elastance (Ea) __ __ __
225 226 227

LV systolic elastance (Ees) __ __ __
228 229 230

Arterial/ventricular elastance (Ea/Ees) __ __ __
231 232 233

Mean LV end diastolic pressure (mLVEDP) __ __ __
234 235 236

Mean pulmonary capillary wedge pressure (mPCWP) __ __ __
237 238 239

LV ejection fraction (LVEF) __ __ __
240 241 242

Global longitudinal strain (strain %) __ __ __
243 244 245

LV hypertrophy (LVH) __ __ __
246 247 248

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