Symptom Biology and Accelerated Aging in Heart Failure

By

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Abstract

Background: Heart failure (HF) is the fastest growing cardiovascular condition in the United States, and along with the growth of the elderly population, the number of adults affected by HF will increase both nation- and worldwide. To those individuals affected by HF, this condition confers enormous symptom burden, severe functional limitations, and reduced quality of life. Despite the importance of symptom burden in HF, however, there is a limited understanding of the biological underpinnings of symptoms in HF, including how accelerated biological aging intersects with symptoms.

Purpose: The purpose of this program of research was to elucidate the biological underpinnings of symptoms among adults with HF, particularly the role of accelerated biological aging in explaining symptoms in HF. Five specific aims were set forth towards achieving this purpose: 1) quantify relationships between objective biomechanical indices of heart function and physical and affective symptoms among adults with HF; 2) quantify the relationship between metabolic senescence and physical symptoms among adults with HF; 3) synthesize the literature on the prevalence of frailty in HF and examine the relationship between chronological age and prevalence of frailty in HF; 4) quantify the prevalence of physical frailty in a sample of adults with moderate to advanced HF, and quantify differences in invasive hemodynamics, along with demographic and clinical characteristics, between physically frail and non-physically frail adults with HF; and 5) quantify associations among measures of physical frailty and symptoms among adults with HF.

Methods: First, we performed a secondary analysis of data from two cohort studies among adults with HF to quantify the relationship between cardiac biomechanics and

symptoms in HF. Second, we performed a secondary analysis of data from a case-control study to quantify the relationship between metabolic senescence and physical symptoms among adults with HF. Third, we performed a systematic review and meta-analysis of the literature on frailty in HF to quantify the prevalence of frailty in HF and identify the relationship between age and prevalence of frailty in HF. Fourth, in a cross-sectional study, we assessed physical frailty among adults with HF who were scheduled for a right heart catheterization and quantified the relationship between physical frailty and invasive HF hemodynamics. Fifth, from that same study, we quantified associations among measures of physical frailty and symptoms.

Results: The cumulative results from this body of work identified significant factors that influence symptoms in HF and advanced the science on symptom biology, accelerated biological aging, and physical frailty in HF. Specifically, we found 1) several cardiac biomechanics are associated with physical and affective symptoms in HF; 2) beta-adrenergic receptor kinase-1 is associated with physical symptoms in HF. 3) frailty in HF is highly prevalent and demonstrates a U-shaped relationship with age in HF; 4) several invasive hemodynamics are associated with physical frailty in HF, including low mixed venous oxygen and low cardiac output; and 5) those with physical frailty in HF have worse dyspnea, wake disturbances, and depressive symptoms.

Conclusions: This program of research made meaningful contributions to the literature on symptom biology, accelerated biological aging, and physical frailty in HF by providing evidence of potential underlying mechanisms of symptoms in HF, including the role of accelerated biological aging in HF symptom biology. The work presented herein provides targets for future research aimed at ameliorating symptom burden in HF.

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Chapter I

Introduction

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Background and Significance

Heart failure (HF) currently affects almost 6 million Americans (Mozaffarian et al., 2015). As a common endpoint of highly prevalent cardiovascular diseases such as hypertension (Ong, Cheung, Man, Lau, & Lam, 2007) and coronary artery disease (Ford et al., 2007), HF is the fastest growing cardiovascular condition in the U.S. (Heidenreich et al., 2011) and is projected to affect over 8 million Americans by 2030 (Mozaffarian et al., 2015). Along with the growth of the elderly population, the number of adults affected by HF will increase worldwide (Bleumink et al., 2004; Najafi, Jamrozik, & Dobson, 2009). Moreover, HF is the most common reason for hospitalization and re-hospitalization among older adults (Jencks, Williams, & Coleman, 2009; Mozaffarian et al., 2015; Ross et al., 2010). With more than 1 million hospital admissions for HF annually (Mozaffarian et al., 2015), the already exorbitant medical cost of HF is expected to triple by 2030 (Heidenreich et al., 2013). On a personal level, the average life-span after a first hospitalization for HF is a little over 5 years, and more concerning, 27% will die within one year (Alter et al., 2012). Furthermore, for adults living with HF, daily life is often fraught with significant symptom burden, severe functional limitations and reduced quality of life (QOL) (Bekelman et al., 2007; Moser, Doering, & Chung, 2005; Westlake, Dracup, Fonarow, & Hamilton, 2005). Thus, HF places an enormous burden on patients themselves, the nation, and the world; hence, there is a critical need to improve clinical management strategies for adults with HF.

Heart Failure Symptoms

In HF, symptoms are considered important aspects of the clinical syndrome as they are the primary drivers of hospitalization (Adams et al., 2005; De Luca et al., 2007;

Felker et al., 2004; Gheorghiade et al., 2005; Goldberg et al., 2010), independent predictors of clinical event-risk (C. S. Lee, Gelow, et al., 2014; K. S. Lee et al., 2010; Song, Moser, Rayens, & Lennie, 2010), significantly associated with QOL (Bekelman et al., 2007; Rector, Anand, & Cohn, 2006; Zambroski, Moser, Bhat, & Ziegler, 2005), and along with objective markers of heart function, guide clinical management strategies (Yancy et al., 2013). Moreover, HF is a clinical diagnosis based on a history of symptoms (e.g. dyspnea and fatigue) along with a physical examination (Yancy et al., 2013). As such, managing symptoms is a critical component of HF care.

There is a wide variety of symptoms reported in HF in both physical and affective domains. Physical symptoms in HF include dyspnea, orthopnea, fatigue, pain, edema, loss of appetite, and sleep-wake disturbances (Bekelman et al., 2007; Goebel et al., 2009; Moser et al., 2011; Redeker et al., 2010; Riegel et al., 2012). Affective symptoms in HF include depression, anxiety, and hostility (Easton, Coventry, Lovell, Carter, & Deaton, 2015; Konstam, Moser, & De Jong, 2005; Moser et al., 2010). Within each symptom there are important elements to assess, including frequency, variability, severity, and distress (Hauptman et al., 2004; Moser et al., 2011; Webel, Frazier, Moser, & Lennie, 2007); merely documenting the presence or absence of symptoms does not adequately capture the entire symptom experience in HF clinical management. Moreover, adults with HF commonly report a constellation of symptoms at any given time (Bekelman et al., 2007). Thus, the symptom presentation of the HF patient is complex and requires astute clinical management to mitigate the effects of symptoms on poor clinical- and patient-oriented outcomes.

Heart Failure Symptom Biology

Despite the importance of symptoms in HF, there is little-to-no association between what is measured objectively about heart function and what adults living with HF experience as symptoms and/or QOL (Bhardwaj et al., 2012; Gottlieb et al., 2009; Guglin, Patel, & Darbinyan, 2012; Lewis et al., 2007; Myers et al., 2006; Rector et al., 2006; Shah et al., 2002). In HF, there is a common assumption that improved markers of hemodynamics would predict improved symptoms (Shah et al., 2002). However, this has not been the case. Shah et al. (2002) demonstrated that no hemodynamic measure significantly predicted symptom score among subjects enrolled in the Flolan International Randomized Survival Trial (Shah et al., 2002). Rector et al. (2006) tested the conceptual model of relationships between HF pathology, symptoms, and QOL and found that pathologic measures only explained about 17% of the variance in HF symptoms and about 7% in QOL (Rector et al., 2006). Lewis et al. (2007) found no significant difference in QOL between those with HF with reduced ejection fraction and those with HF with preserved ejection fraction (Lewis et al., 2007). In a sample of 41 male patients with HF, Myers et al. (2006) showed only modest, and very few significant, relationships of peak oxygen uptake (i.e. peak VO^2) with symptom and health status questionnaires (Myers et al., 2006). In the only study looking at psychological symptoms, Gottlieb et al. (2009) found that depression was minimally related to objective markers of heart function such as ejection fraction, B-type natriuretic peptide, and peak VO^2 (Gottlieb et al., 2009). Bhardwaj et al. (2012) showed that absolute QOL scores were not associated with absolute values of N-terminal pro-B-type natriuretic peptide (NT-proBNP); although they did find that changes in QOL were associated with changes in NT-proBNP (Bhardwaj et al., 2012). Finally, Guglin et al. (2012) examined many additional hemodynamic and

clinical variables from a large clinical trial and found extremely weak correlations between objective markers and symptoms (Guglin et al., 2012). In sum, the existing literature has revealed very weak relationships between what adults with HF are presenting with objectively and what they are experiencing subjectively. As such, we are severely hampered in our ability to address the burdensome symptoms of HF using the objective markers of heart function we currently assess.

Recently, a few other studies have examined other angles of HF symptom biology, including biomarkers of inflammation and a newly-described HF symptom. Heo et al. (2014) examined a marker of inflammation (i.e. soluble tumor necrosis factor receptor-1 (sTNF-R1)) in relation to physical symptoms and found that sTNF-R1 was significantly associated with physical symptoms but only in patients without depression (Heo et al., 2014). Also looking at the role of inflammation, Moughrabi et al. (2014) found that there was a significant relationship between depressive scores and both sTNF-R2 and interleukin-6 in HF (Moughrabi et al., 2014). The newly-described symptom of "bendopnea" was found to be associated with the hemodynamic measures of right atrial pressure and pulmonary capillary wedge pressure among adults with HF (Thibodeau et al., 2014). Cumulatively these studies demonstrate 1) we are still deprived of critical knowledge regarding the biological underpinnings of symptoms in HF, and 2) there are other frontiers in HF symptom biology that warrant investigation.

Heart Failure as a Condition of Accelerated Biological Aging

In the past decade, HF has been, and continues to be, studied as a condition of accelerated biological aging. Indicators of accelerated biological aging, such as metabolic senescence (Huang, Gao, Chuprun, & Koch, 2014; Iaccarino et al., 2005) and frailty

(Buck & Riegel, 2011; Cacciatore et al., 2005; Chung et al., 2014; Dominguez-Rodriguez et al., 2015; Dunlay et al., 2014; Lupon et al., 2008; McNallan, Singh, et al., 2013) have recently been shown to be significantly associated with HF severity and outcomes. While these indicators of accelerated biological aging have been explored in HF, they have not been studied in relation to HF symptoms. As such, there are two large and unexplored gaps in HF symptom biology research in particular that warrant further study: metabolic senescence and physical frailty.

Heart failure and metabolic senescence. Markers of accelerated biological aging – also termed markers of senescence – have been shown to be significantly associated with the pathogenesis of HF and have provided further evidence of HF as a condition of accelerated biological aging (L. S. M. Wong et al., 2010). As one indicator of accelerated biological aging, metabolic senescence has recently been studied in the pathogenesis of HF (Ferrara et al., 2014) and thus may also play a role in explaining variations in HF symptomatology. One area of active inquiry into metabolic senescence involves β-adrenergic receptor kinase-1 (βARK1; also called G-protein coupled receptor kinase-2 (GRK2)). β-adrenergic receptors are essential molecules in the sympathetic nervous system control of cardiac function and play a major role in neurohormonal activation in HF (C. S. Lee & Tkacs, 2008; Packer, 1992). Under normal conditions, β-adrenergic receptor stimulation with catecholamines, like norepinephrine, results in positive increased contractile force and an enhanced rate of relaxation (Hasan, 2013). In HF, persistently increased βARK1 causes decreased receptor responsiveness to norepinephrine and eventually receptor internalization and dysfunction (Ahmed, 2003; Iaccarino et al., 2005; Santulli & Iaccarino, 2013), termed metabolic senescence.

Despite the significant strides in advancing the understanding of accelerated biological aging in HF, however, markers of metabolic senescence have not been studied in relation to the symptoms experienced by adults with HF. Accordingly, studying the association of metabolic senescence (i.e. increased βARK1) and symptoms in HF may yield additional understanding of the biological underpinnings of symptoms in HF. Given our limited understanding of the relationship between symptoms and objective markers of heart function, establishing links between HF symptoms and metabolic senescence would begin to move the science of symptom biology in HF forward and pave a path for future inquiry into accelerated biological aging in HF.

Heart failure and frailty. While frailty has been studied extensively in the area of gerontology broadly beginning with seminal work by Bortz (Bortz, 1993) and Walston (Walston & Fried, 1999), it has only recently been examined specifically in HF. In 2001, the Cardiovascular Health Study (CHS) Research Group published landmark work on frailty, including the now universally recognized Frailty Phenotype Criteria (Fried et al., 2001). In a separate CHS analysis, Newman and colleagues showed that frail adults are over six times more likely to have HF compared with those who are non-frail (Newman et al., 2001). These findings subsequently catalyzed research on frailty in HF specifically, and a number of groups have examined various angles of frailty in HF, most observationally (Altimir et al., 2005; R. Boxer, Dauser, Walsh, Hager, & Kenny, 2008; R. Boxer et al., 2010; Cacciatore et al., 2005; Chung et al., 2014; Dominguez-Rodriguez et al., 2015; Dunlay et al., 2014; Gastelurrutia et al., 2014; Kenny, Boxer, Walsh, Hager, & Raisz, 2006; Lupon et al., 2008; McNallan, Chamberlain, et al., 2013; McNallan, Singh, et al., 2013; Sánchez, Vidán, Serra, Fernández-Avilés, & Bueno, 2011; Vidán et al.,

2014). Only one study focused on an intervention directed towards frail adults with HF (Pulignano et al., 2010).

The majority of research of frailty in HF has focused on prevalence and outcomes. The prevalence of frailty among adults with HF has been shown to range from about 15-70%, and upwards of 55% are considered pre-frail. Given these high prevalence rates, it is evident that frailty is a common condition among adults with HF. There is considerable variability in how frailty was measured across these studies, however, and thus, it is a challenge to draw a summative conclusion regarding the overall prevalence of frailty in HF. Frailty in HF has also been associated with worse clinical- and patient-oriented outcomes. Among studies that examined mortality rates, they all found that frail adults with HF had significantly increased risk of death compared with non-frail adults with HF (R. Boxer et al., 2010; Cacciatore et al., 2005; Chung et al., 2014; Dominguez-Rodriguez et al., 2015; Dunlay et al., 2014; Gastelurrutia et al., 2014; Lupon et al., 2008). In relation to healthcare utilization, one study showed that, after adjustment for common covariates, frail adults with HF had a 65% increased risk for being hospitalized and a 92% increased risk for requiring an emergency department (ED) visit (McNallan, Singh, et al., 2013). Even pre-frail adults with HF had a significantly increased risk for hospitalization (22%) and ED visits (60%) in this same study. Furthermore, frail adults with HF had an increased risk for all types of hospitalization, regardless of reason for admission, indicating that these adults may be less capable of managing their conditions – both cardiovascular and noncardiovascular – overall. Finally, only one study has looked at the association of frailty with QOL in HF, and they found that frailty explained a significant amount of variance in QOL after adjusting for known predictors (Buck & Riegel, 2011).

Given the significant intersection between frailty and HF, it behooves us to embark on a critical examination of the role that frailty (particularly physical frailty) plays in the symptom presentation of HF; however, to date, this relationship has not been studied. Two important facets underlie this proposed work: 1) physical frailty and HF are hypothesized to share common biological pathways, such as systemic inflammation, insulin resistance, and neurohormonal activation, and 2) the symptoms of HF often mirror the presentation of physical frailty. Accordingly, as one step towards explaining symptom biology in HF, this program of research examines physical frailty in relation to symptoms in HF, and in the process, sets forth measures of physical frailty in HF that have the potential to standardize our approach to measuring physical frailty in HF in both clinical settings and research.

Theoretical Framework

The theoretical/conceptual framework that underpins this program of research is Lenz's Theory of Unpleasant Symptoms (Lenz, Pugh, Milligan, Gift, & Suppe, 1997; Lenz, Suppe, Gift, Pugh, & Milligan, 1995). Lenz's Theory of Unpleasant Symptoms was chosen because of its focus on symptoms and the three categories of factors (i.e. physiologic, psychological, and situational) that affect one's predisposition to or manifestation of a given symptom (Lenz et al., 1995). This program of research focuses on what Lenz describes as "influential physiologic factors" (i.e. metabolic senescence and physical frailty, in addition to common clinical objective measures) on symptoms experienced by adults living with HF (Lenz et al., 1997; Lenz et al., 1995). Additionally, similar to the conceptualization of unpleasant symptoms in this theory, we consider both physical and affective symptoms as occurring in combination and not in isolation at any

given time. Physical and affective symptoms are also viewed as potentially having similar pathophysiological pathways (C. S. Lee, Gelow, et al., 2014; C. S. Lee, Hiatt, Denfeld, Mudd, et al., 2015). Thus, Lenz's Theory of Unpleasant Symptoms is an appropriate framework for grounding and guiding this program of research and potentially lending evidence to develop this theory in the future.

Purpose/Specific Aims

The overall purpose of this body of work is to broadly elucidate the biological mechanisms underpinning symptoms among adults with HF and to particularly understand the role of accelerated biological aging in HF symptom biology. To accomplish this purpose, five specific aims have been identified and set forth for this program of research with respective manuscripts to address each aim (**Table 1**). In brief, these aims represent the cumulative work of secondary analyses, a systematic review and meta-analysis, and a prospective cross-sectional study all centered on the above purpose.

The first aim is to quantify relationships between objective biomechanical indices of heart function and physical and affective symptoms among adults with HF. This aim is accomplished with a secondary analysis of data from two cohort studies of adults with HF. We examine the effect of objective biomechanical indices (dimensions, contractility, pressures, and flow) on physical and affective symptoms in adults with moderate to advanced HF using generalized linear modeling. Given our limited understanding of the relationship between objective markers of heart function and symptoms in HF, the significant findings from this study advance the literature on symptom biology in HF by demonstrating the relationship between routinely measured cardiac biomechanics and both physical and affective symptoms in HF.

The second aim is to quantify associations among metabolic senescence and symptoms among adults with HF. Using data from two completed studies (Profiling Biobehavioral Responses to Mechanical Support in Advanced Heart Failure (PREMISE), R01NR013492, PI: Lee; and Accelerated Senescence and Symptom Biology in Heart Failure (ASCENSION-HF), ancillary to R01NR013492, PI: Lee), this secondary analysis examines the influence of metabolic senescence on symptoms in HF. βARK1 is measured as a marker of metabolic senescence and integrated with corresponding data on physical symptoms. Generalized linear modeling is used to examine the relationship between physical symptoms and metabolic senescence in HF. This study provides preliminary evidence of the role of accelerated biology in HF symptom biology.

The third aim is to synthesize the literature on the prevalence of frailty in HF and examine the relationship between chronological age and prevalence of frailty in HF. This aim is accomplished with a systematic review and a random-effects meta-analysis of the literature on frailty in HF. The findings from this study significantly advance the science of frailty in HF by quantifying a precise estimate of frailty in HF based on 16 published studies and identifying the relationship between chronological age and prevalence of frailty in HF. In order to move the science of frailty forward in the area of HF we propose assessing physical frailty in HF based on the previous work completed by Fried and colleagues (Fried et al., 2001).

The fourth aim is to characterize physical frailty among adults with HF in a cross-sectional study. A sample of 50 adults with HF scheduled for a right heart catheterization as part of routine care were enrolled in this study. Robust measures of physical frailty (i.e. shrinking, weakness, slowness, physical exhaustion, and low physical activity),

physical symptoms (i.e. dyspnea, sleep-wake disturbances, and pain), and affective symptoms (i.e. depression and anxiety) are combined with corresponding objective markers of heart function (i.e. echocardiographic and cardiopulmonary exercise tests and right heart catheterization parameters of structure, volume, peak exercise capacity, pressure, flow and contractility). As this is one of the first known studies specifically focused on physical frailty in HF using the proposed robust measures to assess each criteria of physical frailty, we generate important findings that will move the science of frailty in HF forward. First, we demonstrate feasibility in the assessment of physical frailty among adults with HF. Second, we provide descriptive findings from this sample that quantify the prevalence of physical frailty in HF. Third, we provide quantitative data that will lay the foundation to determine specific cut points for each of the five dimensions of physical frailty in HF as we move forward with our proposed measures. Finally, we are the first to examine the association between physical frailty and invasive HF hemodynamics as derived by right heart catheterization, which is conducted at the same time point, and other clinical characteristics such as recent echocardiographic and cardiopulmonary exercise tests, laboratory values, and cognitive function. Descriptive and comparative statistics are used in these analyses.

The fifth aim is to quantify associations among measures of physical frailty and physical and affective symptoms among adults with HF. Using the data from the above cross-sectional study, which also concurrently assesses physical and affective symptoms, we quantify the relationship between physical frailty and physical and affective symptoms in HF. Generalized linear modeling is used to examine the relationship between physical frailty and physical and affective symptoms in HF.

Table 1: Outline of Specific Aims and Papers to Address Each Aim

Specific Aim	***Title of Paper***
Aim #1: Quantify relationships between objective biomechanical indices of heart function and physical and psychological symptoms among adults with heart failure. *Hypothesis: There will be significant associations between cardiac biomechanics and physical and psychological symptoms.*	(*Chapter II*) Physical and Psychological Symptom Biomechanics in Moderate to Advanced Heart Failure
Aim #2: Quantify the relationship between metabolic senescence and physical symptoms among adults with HF. *Hypothesis: Increased βARK1 would be significantly associated with worse physical symptoms in HF.*	(*Chapter III*) Explaining Physical Symptoms in Heart Failure with β-Adrenergic Receptor Kinase-1
Aim #3: Synthesize the literature on the prevalence of frailty in heart failure and examine the relationship between chronological age and prevalence of frailty in heart failure.	(*Chapter IV*) The Prevalence of Frailty in Heart Failure: A Meta-Analysis
Aim #4: Quantify the prevalence of physical frailty in moderate to advanced HF, and quantify differences in invasive hemodynamics, along with demographic and clinical characteristics, between physically frail and non-physically frail adults with HF. *Hypothesis: Physical frailty is associated with worse invasive HF hemodynamics compared to non-physically frail.*	(*Chapter V*) Physical Frailty and Invasive Hemodynamics in Heart Failure
Aim #5: Quantify associations among measures of physical frailty and symptoms among adults with HF. *Hypothesis: Those with physical frailty report worse physical and affective HF symptoms compared with those considered not physically frail.*	(*Chapter VI*) The Role of Physical Frailty in Interpreting Heart Failure Symptoms

Implications for Practice

As a result of this cumulative research, there are a number of important implications for practice. First, through the combined work on HF symptom biology from Aims #1, #2, and #5, we will make critical clinical contributions to our broad understanding of the symptom presentation in HF, particularly the relationship of symptoms to objective markers of heart function, markers of senescence, and measures of physical frailty. This body of work will enable nurses, physicians, and other healthcare professionals to more adequately provide and personalize care for patients with HF, including how to manage their symptom burden. By expanding into previously untested frontiers in HF symptom biology with the combined work on senescence and physical frailty, we will elucidate and quantify what patients are experiencing symptomatically. This knowledge, in turn, will benefit patients as this added knowledge may help "validate" the symptom experience in HF.

Second, the theoretical and measurement work on physical frailty in HF derived from this dissertation (Aims #3 and #4) will make significant contributions to multiple areas of inquiry, including theory, measurement, research and practice. Importantly, the testing of the proposed measures of physical frailty in HF will provide evidence of feasibility and rigor that can, in turn, be used in an application to clinical practice. As a by-product of this dissertation, it is hoped that measures of physical frailty will be refined for clinical feasibility and ultimately implemented as part of the physical assessments of patients with HF, both in-patient and out-patient.

Finally, the cumulative effect of this work will highlight the importance of nursing-driven inquiry coupled with an interdisciplinary approach in addressing critical

research questions. This dissertation will demonstrate the need for future nursing research that is grounded in clinical practice and supported by multiple disciplines all centered on the same goal: to improve patient care. Given the complexity of HF, including consideration of it as a "cardiogeriatric syndrome" with its multiple co-occurring chronic geriatric syndromes (Rich, 2001), there is a critical need to attack HF from multiple perspectives, including those from nursing, in an effort to provide adequate clinical treatment, resources, and support to improve both clinical- and patient-oriented outcomes.

Summary

The collective body of work set forth in this program of research addresses and critically studies symptom biology and the role of accelerated biological aging in HF. First, the study on the influence of cardiac biomechanics on physical and affective symptoms is an initial step towards significantly adding to our limited understanding of the relationship between objective markers of heart function and symptoms in HF. Second, advancing what is known about the relationship between objective markers of heart function and symptoms in HF, we quantify the added value of accelerated biological aging (i.e. metabolic senescence) in explaining variability in symptoms in HF. Third, we perform a systematic review and meta-analysis of frailty in HF to synthesize the literature and advance the science of frailty in HF. Fourth, we implement measures of physical frailty as part of a new cross-sectional study that will yield information about the feasibility of assessing physical frailty in HF, provide descriptive findings on the prevalence and characteristics of physical frailty in HF, and quantify the relationship between physical frailty and invasive hemodynamics. Fifth, we quantify the relationship

between physical frailty and symptoms in HF. Cumulatively, this program of research makes several significant advances in HF symptom biology and role of accelerated biological aging in HF and, in turn, enhances our clinical management strategies for one of the most complex conditions we currently face in healthcare.

Chapter II

Physical and Psychological Symptom Biomechanics in Moderate to Advanced Heart Failure

Brief Report

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This manuscript replaces portions of the methods section and results section of the traditional dissertation. Ms. Denfeld was the primary author on this paper, and Dr. Lee was the senior author on this paper. Ms. Denfeld completed the secondary analysis and manuscript preparation under the supervision of Dr. Lee. This article was accepted for publication in the Journal of Cardiovascular Nursing on April 14, 2014. The Journal of Cardiovascular Nursing is an indexed and peer-reviewed journal with an impact factor of 1.809. The readership for this journal includes healthcare personnel, particularly nurses and advanced practice nurses, interested in the physiologic, psychologic, and social needs of cardiovascular patients. This manuscript is in final state.

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Declaration of Conflicting Interests

None Declared

Key Words: Heart Failure; Symptoms; Biomechanics; Hemodynamics

Abstract

Background: There is a common dissociation between objective measures and patient symptomatology in heart failure (HF). **Objective**: To explore the relationship between cardiac biomechanics and physical and psychological symptoms in adults with moderate to advanced HF. **Methods**: We performed a secondary analysis of data from two studies of symptoms among adults with HF. Stepwise regression modeling was performed to examine the influence of cardiac biomechanics (left ventricular internal diastolic diameter (LVIDd), right atrial pressure (RAP), and cardiac index) on symptoms. **Results**: Average age of the sample (n=273) was 57±16 years, 61% were male, and 61% had class III or IV HF. LVIDd (β=4.22±1.63, p=0.011), RAP (β=0.71±0.28, p=0.013), and cardiac index (β=7.11±3.19, p=0.028) were significantly associated with physical symptoms. LVIDd (β=0.10±0.05, p=0.038) and RAP (β=0.03±0.01, p=0.039) were significantly associated with anxiety. There were no significant biomechanical determinants of depression. **Conclusion**: Cardiac biomechanics were related to physical symptoms and anxiety providing preliminary evidence of the biological underpinnings of symptomatology among adults with HF.

Background

It is widely recognized that heart failure (HF) is a complex and heterogeneous disorder (Bleumink et al., 2004; Yancy et al., 2013). Beyond the hallmark physical symptoms like shortness of breath and fatigue (Hauptman et al., 2004), a majority of adults with HF also experience significant psychological symptoms, such as depression and anxiety (Konstam et al., 2005). Pointedly, symptoms are the main progenitor for healthcare utilization (Adams et al., 2005; Moser et al., 2011) and the principal driver of quality-of-life among adults with HF (Zambroski et al., 2005). But, objective measures of HF severity often correlate poorly with HF symptoms (Gottlieb et al., 2009; Guglin et al., 2012; Myers et al., 2006; Rector et al., 2006; Shah et al., 2002). As such, we are largely bereft of insight into the biological underpinnings of symptoms in HF.

However, there are differences in how symptoms were assessed across these few studies on the biological underpinnings of HF symptoms. For example, Guglin, et al. (2012) used data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial in which symptoms were derived from a history and physical examination performed by a provider (details in (Drazner et al., 2008)). Other studies rated only the presence or absence of symptoms (Rector et al., 2006; Shah et al., 2002) or used measures that primarily assess quality of life (Myers et al., 2006; Rector et al., 2006; Shah et al., 2002), and only one study inquired about psychological symptoms (Gottlieb et al., 2009). The primary aim of this study was to quantify relationships between objective biomechanical indices of heart function (dimensions, contractility, pressures, and flow) and physical and psychological symptoms (depression and anxiety) among adults with moderate to advanced HF. We hypothesized

that there would be significant associations between cardiac biomechanics and physical and psychological symptoms.

Methods

We performed a secondary analysis of unique patient data collected during two prospective cohort studies of symptoms among adults with HF (study 1 focused on gender differences in symptoms (C. S. Lee, Gelow, et al., 2014), and study 2 focused on symptom response behaviors (C. S. Lee et al., 2013)). Participants were recruited through a single outpatient HF clinic in the Pacific Northwest between 2010 and 2012. Key inclusion criteria (identical between studies) were age 21 years or greater with New York Heart Association (NYHA) functional class of II-IV HF (i.e. current HF symptoms). Transplantation and mechanical circulatory support were exclusion criteria, as was a diagnosis of major cognitive impairment. Both studies were approved by our institutional review board, and written consent was obtained from all participants.

Measurement

Data on age, gender, marital status, race, and education were obtained using an identical socio-demographic questionnaire in both studies. Functional status (i.e. NYHA) was assessed by an attending HF cardiologist during the same visit as enrollment. History, etiology, and treatment of HF were collected through a review of the electronic medical record. Comorbid conditions were summarized using the Charlson Comorbidity Index (Charlson, Pompei, Ales, & MacKenzie, 1987). Cardiac biomechanical indices were obtained via a review of the medical record including echocardiographic and right heart catheterization reports. Specifically, we collected data on left ventricular internal diastolic diameter (LVIDd) in centimeters, left ventricular ejection fraction (LVEF),

pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), and cardiac index by Fick equation. The median times since right heart catheterization and echocardiography to symptom assessment were 11 and 42 days, respectively.

Physical Symptoms

The Heart Failure Somatic Perception Scale (HFSPS) was designed to measure perceived severity of both nonspecific symptoms (e.g. fatigue and weight gain) and acute symptoms (e.g. orthopnea and dyspnea) in HF (Jurgens, Fain, & Riegel, 2006). Scores on the HFSPS range from 0 to 90, with higher scores indicating worse perceived symptom severity. The HFSPS was chosen over other instruments because it is a physical symptom measure tailored specifically for HF, and not a measure of quality-of-life (Rector, Kubo, & Cohn, 1993) or health status (C. P. Green, Porter, Bresnahan, & Spertus, 2000) that other groups have used as a proxy for physical symptoms. Theta reliability of the original HFSPS was 0.71-0.78 (Jurgens et al., 2006).

Psychological Symptoms

Depression was measured using the 9-Item Patient Health Questionnaire (PHQ9) (Kroenke, Spitzer, & Williams, 2001). The PHQ9 scores each of the 9 related DSM-IV criteria for depression. Scores on the PHQ9 range from 0 to 27 with higher scores indicating worse depression. The PHQ9 is a valid and reliable measure of depression in HF (Hammash et al., 2013). Anxiety was measured using the 6-item Brief Symptom Inventory anxiety scale (BSIANX) (Derogatis & Melisaratos, 1983). Scores on the BSIANX (calculated by adding the ratings and dividing the total by the number of items in the subscale) range from 0 to 4 with higher scores indicating higher anxiety. The BSIANX is a valid and reliable measure of anxiety in HF (Khalil, Hall, Moser, Lennie, &

Frazier, 2011).

Statistical Analysis

All analyses were performed using Stata/MP version 11MP (StataCorp, College Station, TX). Standard descriptive statistics were used to describe the sample. Internal consistency of each measure was quantified using Cronbach's alpha. We used backward stepwise regression modeling ($p<0.20$ retention) to examine the influence of cardiac biomechanical indices on symptom measures and to identify parsimonious multivariate models that were not saturated with non-significant factors. Factors entered into each model were LVIDd, LVEF, PCWP, RAP, cardiac index, ischemic vs. non-ischemic etiology, Charlson Comorbidity Index, months living with HF, treatment with an angiotensin converting enzyme inhibitor/angiotensin receptor blocker and a beta adrenergic blocker, serum sodium, serum hemoglobin, ratio of serum blood urea nitrogen to creatinine, stage 3 or higher chronic kidney disease, atrial fibrillation, gender, age, body mass index, education, and marital status.

Results

The average age of the sample (n=273) was 57 years, 61.2% of participants were male, and 61.2% had NYHA Class III or IV HF (**Table 1**). The sample had enlarged ventricles (average LVIDd = 6.1cm), reduced contractility (mean LVEF = 28.3%), low cardiac output (mean cardiac index = 2.1 L/min/m^2), and high left-and right-sided filling pressures (average PCWP and RAP were 19.0mmHg and 9.6mmHg, respectively). Cronbach's alpha of the HFSPS, PHQ9, and BSIANX were 0.91, 0.88, and 0.85, respectively.

Table 1: Characteristics of the sample (n=273)

	Mean±SD, or n (%)
Patient Characteristics:	
Age (years)	57.3±13.2
Male	167 (61.2%)
Non-Hispanic Caucasian	231 (84.6%)
Education level	
Less than high school	89 (32.6%)
>High school but < college	122 (44.7%)
College degree	62 (22.7%)
Body Mass Index (kg/m^2)	31.0±7.4
Charlson Comorbidity Index (weighted)	2.3±1.4
Atrial Fibrillation	109 (39.9%)
Stage 3 Chronic Kidney Disease	40 (14.7%)
General Heart Failure Characteristics:	
Time with Heart Failure in years: median [IQR]	4.2 [0.8-7.5]
NYHA Functional Class	
Class II	106 (38.8%)
Class III	157 (57.5%)
Class IV	10 (3.7%)
Heart Failure Etiology	
Non-ischemic	174 (63.6%)
Ischemic	99 (36.3%)
Prescribed a β-blocker	246 (90.8%)
Prescribed an ACE-I or ARB	223 (81.6%)
Serum sodium (mEq/L)	137.8±3.3
Serum hematocrit (%)	39.0±5.8
Serum BUN-to-creatinine ratio (mg/dL:1)	20.2±9.5
Cardiac Biomechanics:	
Left ventricular internal end-diastolic diameter (cm)	6.1±1.1
Left ventricular ejection fraction (%)	28.3%±12.4%
Pulmonary capillary wedge pressure (mm/Hg)	19.0±8.5
Right atrial pressure (mm/Hg)	9.6±5.5
Cardiac index ($L/min/m^2$ by Fick equation)	2.1±0.5
Symptomatology:	
Physical symptoms (HFSPS Score; 0-90)	24.6±16.7
Depression (PHQ9; 0-27)	7.2±6.1
Anxiety (BSI; 0-4)	0.53±0.63

Table 1: continued
Abbreviations: ACE-I, Angiotensin Converting Enzyme-Inhibitor; ARB, Angiotensin Receptor Blocker; BSI, Brief Symptom Inventory; HFSPS, Heart Failure Somatic Perception Scale; IQR, interquartile range; NYHA, New York Heart Association; PHQ9, Patient Health Questionnaire; SD, Standard Deviation

Cardiac biomechanics and clinical characteristics explained 17.1% of variance in HFSPS scores (F=3.4, p<0.01), 16.1% of variance in PHQ9 scores (F=6.2, p<0.0001), and 24.1% of variance in BSIANX scores (F=3.5, p<0.001) (**Table 2**). In addition to other clinical characteristics, LVIDd (β=4.22±1.63, p=0.011), RAP (β=0.71±0.28, p=0.013), and cardiac index (β=7.11±3.19, p=0.028) were significant determinants of physical symptoms, and LVIDd (β=0.10±0.05, p=0.038) and RAP (β=0.03±0.01, p=0.039) were significant determinants of anxiety. In other words, greater ventricular dilation and higher right-sided filling pressures were associated with worse physical symptoms and worse anxiety, and higher cardiac output was associated with worse physical symptoms. The ratio of serum blood urea nitrogen to creatinine was the only factor significantly associated with physical symptoms, depression, and anxiety.

Table 2: **Influence of Cardiac Biomechanics and Clinical Characteristics on HF Physical and Psychological Symptoms**

	HFSPS			PHQ9			BSIANX		
	β±SE	*t*	p-value	β±SE	*t*	p-value	β±SE	*t*	p-value
Age (years)				-0.12±0.03	-3.80	<0.001	-0.01±0.01	-3.06	0.003
Male	-8.04±3.58	-2.24	0.027						
> High school but < college							-0.31±0.13	-2.42	0.017
College degree				-2.35±1.09	-2.15	0.033			
Charlson Comorbidity Index				0.92±0.29	3.16	0.002			
Atrial Fibrillation	-6.61±3.15	-2.10	0.038						
LVIDd (cm)	4.22±1.63	2.59	0.011				0.10±0.05	2.10	0.038
RAP (mm/Hg)	0.71±0.28	2.53	0.013				0.03±0.01	2.09	0.039
Cardiac Index (L/min/m^2)	7.11±3.19	2.23	0.028						
BUN/Cr ratio	-0.44±0.17	-2.64	0.009	-0.11±0.04	-2.78	0.006	-0.02±0.01	-2.98	0.004
Beta Adrenergic Blocker							-0.50±0.19	-2.61	0.010
Model R^2/Adjusted R^2	0.171/0.120			0.161/0.135			0.241/0.172		

Abbreviations: BUN/Cr, blood urea nitrogen to creatinine ratio; BSIANX, Brief Symptom Inventory Anxiety Score; HFSPS, Heart Failure Somatic Perception Scale; LVIDd, left ventricular internal diastolic diameter; PHQ9, Patient Health Questionnaire; RAP, right atrial pressure (mm/Hg); SE, standard error.

Note: Results reported were factors retained in backward stepwise models that included left ventricular internal diastolic diameter, left ventricular ejection fraction, pulmonary capillary wedge pressure, right atrial pressure, cardiac index, ischemic vs. non-ischemic etiology, Charlson Comorbidity Index, months living with heart failure, treatment with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, treatment with a beta adrenergic blocker, serum sodium, serum hemoglobin, ratio of serum blood urea nitrogen to creatinine, stage 3 or higher chronic kidney disease, atrial fibrillation, gender, age, body mass index, education and marital status. Only significant factors displayed for economy of presentation.

Discussion

In this sample of 273 patients with moderate to advanced HF, objective cardiac biomechanical indices were significantly related to perceived physical symptoms and anxiety, but not to depression. In several instances, intuitive relationships between biomechanics and symptoms were observed in multivariate models. Larger left ventricular diameter and higher right-sided filling pressures were associated with both worse physical symptoms and anxiety. There were also examples of significant relationships between cardiac biomechanics and symptom perceptions that did not appear intuitive. For example, higher cardiac index was associated with worse physical symptoms. Moreover, and similar to other findings (Guglin et al., 2012), a higher blood urea nitrogen-to-creatinine ratio, which is typically associated with poor prognosis in HF, was associated with lower levels of physical symptoms and lower levels of both depression and anxiety in this sample. Notably, very few other objective clinical characteristics in our model were significantly associated with symptom measures. Thus, although our findings provide insight into symptom biomechanics in HF, there is more to be learned about the intersection between the complex and multidimensional symptoms experienced by persons with HF and underlying pathogenic mechanisms.

Many other groups have reported weak or no relationships between objective measures of HF severity and HF symptoms. One reason why we may have observed significant relationships centers on our choice of symptom measures, including the HFSPS and BSIANX, instead of the investigator-developed scales or quality-of-life/health status measures used by others as proxies for symptoms (Guglin et al., 2012; Myers et al., 2006; Rector et al., 2006; Shah et al., 2002). Because of our choice of

symptom measures, however, we cannot comment on the direct relationship between HF biomechanics and quality-of-life or health status like prior reports (Myers et al., 2006; Rector et al., 2006).

Clinically, our findings indicate that while there were significant relationships between cardiac biomechanics and HF symptoms, one shouldn't be considered surrogate for the other as there is still much to be learned about the complexity of HF symptom pathophysiology. In particular, future studies should examine non-intuitive findings such as the relationship between cardiac index and symptoms as well as the relationship between blood urea nitrogen-to-creatinine ratio and symptoms. Inconsistencies in both objective parameters and symptom measures across related studies hamper our ability to make strong and summative conclusions about the pathogenic underpinnings of symptoms in HF. Methodological approaches chosen to examine symptom biology have also been rather simple (i.e. correlations and linear regression) in contrast to the complexity of symptom pathophysiology. Thus, more advanced statistical methods of integrating multiple objective cardiac parameters and multiple symptoms should be employed in future research. Finally, although findings from this and other cross-sectional studies have contributed to a foundational understanding of HF symptom biology, longitudinal studies are needed to understand the convergence/divergence of changes in HF pathogenesis and physical and psychological symptoms over time.

Limitations

Our sample was relatively young and racially homogenous, and a high proportion had HF of non-ischemic etiology compared with many other HF cohorts. Thus, our findings may not be generalizable to all patients with HF. Furthermore, because of

limitations inherent in cross-sectional research, we cannot comment on the temporality of HF symptoms and cardiac biomechanics, which further supports the need for longitudinal studies. Finally, as our understanding of symptom biology improves we can evolve to testing theoretical models as opposed to simply generating data-driven models as in the results of this study.

Conclusion

Larger left ventricular diameter and higher right-sided filling pressures are associated with worse physical symptoms and anxiety in adults with HF. Longitudinal studies are needed to gain further insight into HF symptom biomechanics in general and the convergence/divergence between objective parameters and symptoms in particular.

References for Chapter II (See Cumulative References)

Chapter III

Explaining Physical Heart Failure Symptoms with β-Adrenergic Receptor Kinase-1

Brief Report

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This manuscript replaces a portion of the literature review (i.e. metabolic senescence) and a portion of the results section of the traditional dissertation. Ms. Denfeld is the primary author on this paper; Dr. Lee is the senior author on this paper. Ms. Denfeld was involved in the conduct of the study (as a research assistant) and performed the statistical analyses under the supervision of Dr. Lee. This paper will be submitted to Journal of Cardiac Failure, which is an indexed and peer-reviewed journal with an impact factor of 3.065. The readership for this journal includes healthcare personnel interested in the pathogenesis, etiology, epidemiology, pathophysiological mechanisms, assessment, prevention, and treatment of heart failure. This manuscript will be ready to submit immediately after the defense of the dissertation.

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Declaration of Conflicting Interests

None Declared

Key Words (MeSH): Heart Failure; Symptoms; Senescence; beta-Adrenergic Receptor Kinase 1

Abstract

Background: Heart failure (HF) is associated with significant physical symptom burden; but exactly how symptoms are related to pathophysiological mechanisms in HF is unclear. To date, no studies have examined the role of metabolic senescence in explaining HF symptoms. **Purpose:** To quantify the relationship between metabolic senescence and physical symptoms among adults with HF. **Methods:** This was a secondary analysis of data collected from a sample of adults with symptomatic HF. Metabolic senescence was measured with β-adrenergic receptor kinase-1 (βARK1). Physical symptoms were measured with the HF Somatic Perception Scale (HFSPS). Generalized linear modeling was used to quantify the relationship between βARK1 and HFSPS scores. **Results:** The average age of the sample (n = 96) was 54.3±13.5 years, 77.1% were male, and a majority (83.3%) of the sample had Class III or IV HF. βARK1 was more explanatory of physical symptoms than common prognostication models. βARK1 was significantly associated with HFSPS scores (β = 0.22±0.1, p = 0.038) after controlling for other predictors of physical symptoms (model R^2 = 0.250, $F(7, 70) = 3.34$, p = 0.004). **Conclusions:** Worse metabolic senescence is associated with worse physical symptoms in HF, providing preliminary evidence of alternative pathophysiologic mechanisms underlying physical symptoms in HF.

Introduction

Many adults with HF experience significant symptom burden, including troublesome physical symptoms such as fatigue and dyspnea (Tsai et al., 2013; Webel et al., 2007), which in turn affect quality-of-life (Zambroski et al., 2005) and prompt seeking care, including hospitalization (Moser et al., 2005). However, we remain deprived of an understanding of the biological underpinnings that give rise to these symptoms in HF based on commonly used objective markers of heart function (Guglin et al., 2012; Rector et al., 2006; Shah et al., 2002), even to the point of a clear mismatch between what patients experience in terms of symptoms and what patients present hemodynamically (C. S. Lee, Hiatt, Denfeld, Mudd, et al., 2015). Hence, it is critical that we explore new frontiers in HF symptom biology by examining other known pathophysiologic mechanisms, such as accelerated biological aging, as potential biological underpinnings of symptoms in HF.

Metabolic senescence is one area within the study of accelerated biological aging in HF and includes the active inquiry into β-adrenergic receptor kinase-1 (βARK1; also called G-protein coupled receptor kinase-2 (GRK2)). β-adrenergic receptors (βARs; part of the family of seven transmembrane receptors or G-protein coupled receptors) are essential molecules in the sympathetic nervous system control of cardiac function and play a major role in neurohormonal activation in HF (C. S. Lee & Tkacs, 2008; Packer, 1992). Upon stimulation with catecholamines (e.g. norepinephrine), βARs couple to stimulatory G-protein (G_s), whose α subunit activates adenylyl cyclase, which then increases cAMP and activates protein kinase A (PKA) resulting in positive increased contractile force and enhanced rate of relaxation (Foster, Roura, Molenaar, & Thomas,

2015). However, evidence has shown large levels of complexity and plasticity in the signaling of βARs that reveals the delicate balance that is necessary in both healthy persons and those with HF (Hasan, 2013). In HF, βAR function is limited by several molecular mechanisms, one of them being βARK1. An increase in βARK1 causes decreased βAR responsiveness (or desensitization) to catecholamines and eventually receptor internalization and dysfunction (Ahmed, 2003; Iaccarino et al., 2005; Santulli & Iaccarino, 2013). Part of this response is thought to be adaptive in that a decrease in βAR signaling reduces energy expenditure, but this limits the heart's capacity to acutely increase output, such as with exercise. In HF, βARK1 is noted to be elevated both in myocardial cells and in lymphocytes (Iaccarino et al., 2005), indicating a loss of βAR responsiveness and increased disease severity. Importantly, βARK1 has been shown to improve (i.e. decrease) among patients implanted with a ventricular assist device (Hata et al., 2006) and following cardiac transplantation (Bonita et al., 2010).

Accordingly, studying metabolic senescence in HF (i.e. βARK1) in relation to physical symptoms in HF may yield additional understanding of the biological underpinnings of symptoms in HF. Therefore, the purpose of this study was to quantify the relationship between metabolic senescence and physical symptoms among adults with HF. We hypothesized that increased βARK1 would be significantly associated with worse physical symptoms in HF.

Methods

Study Design

We performed a secondary analysis of data collected from a case-control study among adults with HF. The details of the primary study are described elsewhere (Lee et

al., 20XX), but will be briefly summarized here. The sample of 96 participants included a cohort of community-dwelling adults with HF (Accelerated Senescence and Symptom Biology in Heart Failure (ASCENSION-HF), ancillary to R01NR013492) who were age-, gender-, HF etiology-, and HF duration-matched with a cohort of adults with advanced HF awaiting left ventricular assist device (LVAD) placement (R01NR013492; Profiling Biobehavioral Responses to Mechanical Support in Advanced Heart Failure (PREMISE)). For the purposes of this analysis, the total sample was analyzed as a whole. The two-arm approach of integrating cross-sectional data from the community-based sample (n = 48) with the baseline sample of PREMISE (n = 48) allowed us to examine the severity of biomarkers tested from blood samples and patient-oriented outcomes across the matched participants.

Formal inclusion criteria for the community-dwelling cohort (ASCENSION) included 1) willing and able to provide informed consent, 2) 18 years or older, 3) confirmed diagnosis of HF by physical exam and echocardiographic evidence, 4) able to read and comprehend 5th grade English or Spanish, and 5) current or past HF symptoms (i.e. New York Heart Association (NYHA) Class I-IV; American Heart Association/American College of Cardiology (AHA/ACC) Stage C or D HF). Potential participants were excluded from the community-dwelling cohort if they had major and uncorrected hearing impairment, diagnosis of cognitive impairment, heart transplantation/mechanical circulatory support prior to enrollment, concomitant terminal illness, major psychiatric illness, or inability to complete the requirements of the study. Formal inclusion criteria for PREMISE (R01NR013492) included: 1) willing and able to provide informed consent, 2) 21 years or older, 3) able to read and comprehend 5th grade

English or Spanish, 4) reachable by telephone, 5) eligible for continuous-flow LVAD implantation as a bridge to transplantation or as destination therapy. Potential participants were excluded from the advanced HF/LVAD cohort if they had major and uncorrected hearing impairment, diagnosis of moderate or severe cognitive dysfunction, heart transplantation prior to enrollment, concomitant terminal illness, major psychiatric illness, or inability to complete the requirements of the study. Both studies were approved by our Institutional Review Board, and written informed consent was obtained from all participants.

Measurement

Sociodemographic and clinical data. Data on age, gender, marital status, race, and education were obtained using a sociodemographic questionnaire. Functional status (i.e. NYHA Class) was assessed by an attending HF cardiologist during the same visit as enrollment. Data on history, etiology, and treatment of HF were collected through an in-depth review of the electronic medical record, including variables required for the Seattle Heart Failure Model (SHFM) (Levy et al., 2006) and elements recommended by the American College of Cardiology/American Association (ACC/AHA) guidelines (Radford et al., 2005). Clinical characteristics, including left ventricular ejection fraction and left ventricular internal end-diastolic diameter (LVIDd) from echocardiographic assessments and pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), and cardiac index (calculated by the Fick equation) from right heart catheterization, were also collected. Comorbid conditions were summarized using the Charlson Comorbidity Index (Charlson et al., 1987). Data collection procedures were identical for both studies.

β-adrenergic receptor kinase-1. ADRB1 ELISA Kits (antibodies-online.com,

Atlanta, GA) were used to quantify βARK1 as an index of metabolic senescence ("Adrenergic, Beta, Receptor Kinase 1 (ADRB1) ELISA Kit Product Details,"). Prior to analysis, samples of blood were centrifuged at 2800rpm for 10 minutes at 5°C to separate plasma. Plasma was aliquoted into 6 x 1.8mL tubes of "Heparin plasma," and 2 x 1.8mL tubes of "Na-citrate plasma." Samples were stored at -80°C. βARK1 was measured using a quantitative sandwich immunoassay technique. An antibody specific for βARK1 was pre-coated onto a microplate; samples were pipetted into the wells and any βARK1 present was bound by the immobilized antibody. A biotin-conjugated antibody specific for βARK1 was then added to the wells after removing any unbound substances. After washing, avidin-conjugated Horseradish Peroxidase (HRP) was added to the wells. Then a substrate solution was added to the wells after a wash to remove any unbound avidin-enzyme reagent, and color developed in proportion to the amount of βARK1 bound in the initial step. The color development was stopped and the intensity of the color was measured. The intra-assay coefficient variation (CV)% is less than 8%, and the inter-assay precision CV% is less than 10%.

Physical symptoms. Physical symptoms were measured with the 18-item HF Somatic Perception Scale (HFSPS) (Jurgens, Lee, & Riegel, 2015). In total, the HFSPS measures perceived severity of both nonspecific symptoms (e.g. fatigue and weight gain) and acute symptoms (e.g. orthopnea and dyspnea) in HF. Scores on the HFSPS range from 0-90 (higher scores indicate worse perceived physical symptoms). The HFSPS is independent in predicting clinical event risk (Jurgens, Lee, et al., 2015). Internal reliability of the HFSPS in our sample was 0.91.

Statistical Analysis

Standard descriptive statistics of frequency, central tendency, and dispersion were used to describe the sample. Raw values of βARK1 were log transformed to achieve normality; both raw values and log transformed values were used in analyses, and raw values are reported to support clinical translation. We used generalized linear modeling to quantify the relationship between βARK1 and physical symptoms. Specifically, we used moderation analysis (Baron & Kenny, 1986) to quantify the interaction of βARK1 and SHFM score in explaining physical symptoms in HF. Stepwise modeling using backward selection ($p < 0.20$ retention) was used to identify significant predictors of physical symptoms. Informed by our prior research (Denfeld et al., 2015), variables added into the model included age, gender, ischemic versus non-ischemic etiology, SHFM score, Charlson Comorbidity Index, atrial fibrillation, treatment with a beta-blocker, treatment with an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor block (ARB), RAP, cardiac index, LVIDd, and blood urea nitrogen to creatinine ratio. All analyses were performed using Stata/MP v.13 (College Station, TX).

Results

Sample characteristics ($n = 96$) are described in **Table 1**. The average age was about 54 years, 77.1% of participants were male, 83.3% had NYHA Class III or IV HF, and 62.5% had non-ischemic HF. In terms of cardiac biomechanics, participants had high filling pressures and low LVEF. The majority of participants were treated with evidence-based therapies, including beta-blockers and ACE-Is or ARBs. The median raw value of βARK1 was 10.7 (IQR [4.2-28.9]) pg/mL, and the range was 0.34 to 126.9 pg/mL.

Table 1: Characteristics of the Sample (*n* = 96)

	M±SD, N(%), or Median [IQR]
Patient Characteristics:	
Age (years)	54.3±13.5
Male	74 (77.1%)
Non-Hispanic Caucasian	79 (82.3%)
Education level	
High school or less	31 (32.3%)
>High school but < college	40 (41.7%)
College degree	25 (26.0%)
Body Mass Index (kg/m^2)	29.9±6.8
Charlson Comorbidity Index (weighted)	2.5±1.6
Atrial Fibrillation	49 (51.0%)
Stage 3 Chronic Kidney Disease	28 (29.2%)
General Heart Failure Characteristics:	
Time with Heart Failure (years)	6.1 [1.5-12.7]
NYHA Functional Class	
Class I	3 (3.1%)
Class II	13 (13.5%)
Class III	55 (57.3%)
Class IV	25 (26.0%)
Non-ischemic Etiology	60 (62.5%)
Prescribed a β-blocker	52 (54.2%)
Prescribed an ACE-I or ARB	71 (74.0%)
Serum sodium (mEq/L)	136.3±4.3
Serum hematocrit (%)	38.7±5.6
Serum BUN/creatinine ratio (mg/dL:1)	20.1 [15.9-25.6]
SHFM Score	2.7±1.2
Left ventricular internal end-diastolic diameter (cm)	6.9±1.3
Left ventricular ejection fraction (%)	23.2±9.7
Pulmonary capillary wedge pressure (mm/Hg)	20.6±9.6
Right atrial pressure (mm/Hg)	8.4±4.4
Cardiac index (L/min/m^2 by Fick equation)	2.0±0.5
Metabolic senescence:	
βARK-1 (raw values; pg/mL)	10.7 [4.2-28.9]
Symptoms:	
Physical symptoms (HFSPS; 0-90)	35.4±18.6

Abbreviations: ACE-I, Angiotensin Converting Enzyme-Inhibitor; ARB, Angiotensin Receptor

Blocker; βARK1, β-adrenergic receptor kinase-1; BUN, blood urea nitrogen; HFSPS, Heart Failure Somatic Perception Scale; IQR, interquartile range; M, mean; NYHA, New York Heart Association; SD, standard deviation; SHFM, Seattle Heart Failure Model; SD, Standard Deviation

Moderation Analysis

In testing the relationship between βARK1 and physical symptoms, we found a significant interaction effect of βARK1 and SHFM scores in explaining HFSPS scores (**Figure 1**). βARK1 (β = 1.42 ± 0.31, p <0.001) and SHFM scores (β = 12.40 ± 1.58, p < 0.001) were significantly related to HFSPS scores, and there was a significant interaction effect of βARK1 and SHFM scores in predicting HFSPS scores (interaction effect: β = -0.42 ± 0.09, p < 0.001; model: $F(3,88) = 87.00$, p < 0.001), indicating that the combination of βARK1 in addition to SHFM scores is significantly better at explaining the gradient of physical symptoms as opposed to SHFM scores alone. For example, patients with the worse physical symptoms had higher levels of βARK1 and not higher SHFM scores per se.

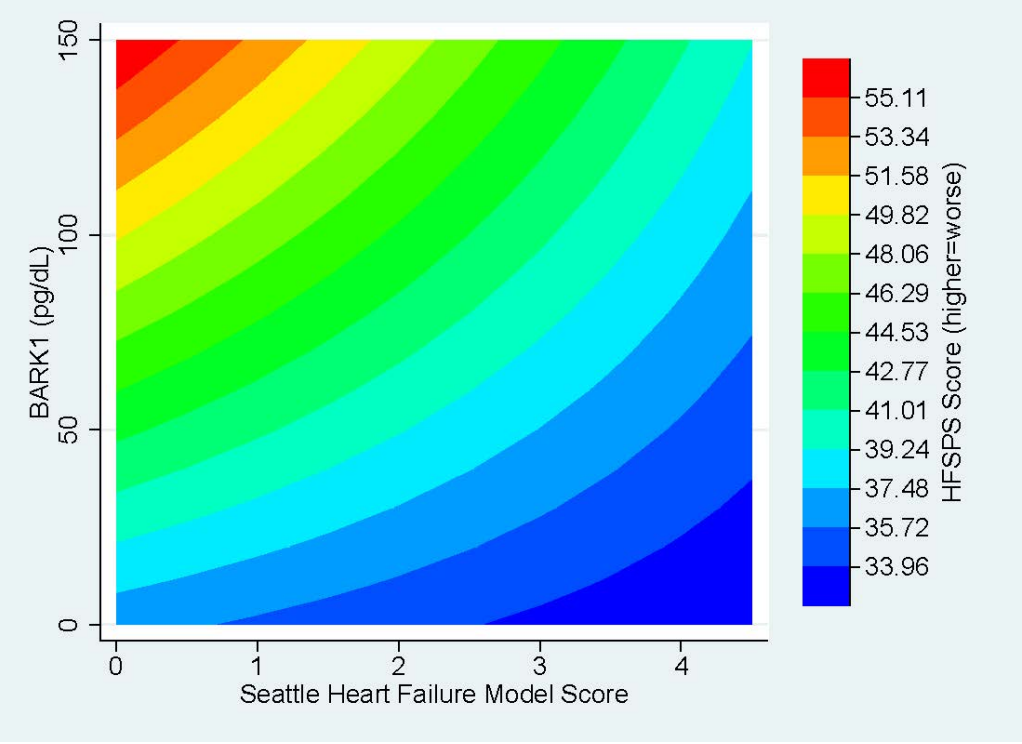

Figure 1. Interaction effect of β-adrenergic receptor kinase-1 (βARK1) and Seattle Heart Failure Model score in explaining physical symptoms.

Stepwise Model

The combination of βARK1 and clinical characteristics, including SHFM scores, significantly explained 25.0% of the variance in HFSPS scores ($F(7, 70) = 3.34$, $p = 0.004$) (**Table 2**). In addition to other clinical characteristics, βARK1 was independently and significantly associated with HFSPS scores ($\beta = 0.21 \pm 0.09$, $p = 0.03$). Substituting the log transformed value of βARK1 demonstrated similar significant results in the model (*data not shown*).

Table 2: Influence of βARK1 and Clinical Characteristics on Physical Symptoms in Heart Failure

	β±SE	***t***	***p***
Male	-9.15±4.54	-2.02	0.048
Age	-0.41±0.15	-2.69	0.009
ACE-I/ARB	10.36±4.64	2.23	0.029
SHFM score	4.93±2.22	2.22	0.03
Right atrial pressure	-1.66±0.50	-3.33	0.001
βARK1	0.22±0.10	2.11	0.038
Model R^2/Adjusted R^2	0.250/0.175		

Results reported were factors retained in stepwise modeling using backward selection that included: age, gender, ischemic versus non-ischemic etiology, Seattle Heart Failure Model score, Charlson Comorbidity Index, atrial fibrillation, treatment with a beta-blocker, treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, right atrial pressure, cardiac index, left ventricular internal end-diastolic diameter, and blood urea nitrogen to creatinine ratio.

Abbreviations: ACE-I, Angiotensin Converting Enzyme-Inhibitor; ARB, Angiotensin Receptor Blocker; βARK1, β-adrenergic receptor kinase-1; SE, standard error; SHFM, Seattle Heart Failure Model.

Discussion

Building on previous symptom biology research in HF, we explored the relationship between metabolic senescence and physical symptoms in an effort to identify the biological underpinnings of symptoms in HF. We are beginning to better understand

the role of βARK1 in the progression of HF (Huang et al., 2014); hence, it is worth exploring βARK1, as a marker of metabolic senescence, in relation to physical symptoms in HF. Our main findings were 1) βARK1 is more helpful than SHFM in differentiating physical symptoms in HF, and 2) adjusting for other clinical characteristics, elevated βARK1 was significantly associated with worse physical symptoms, providing incremental, but meaningful, evidence of the role of metabolic senescence in HF symptom biochemistry.

The interactive effect of βARK1 and SHFM scores indicates it is a combination of metabolic senescence and common prognostication models that tells us more about physical symptoms in HF than either alone. In fact, a gradient in βARK1 more closely followed a gradient in physical symptoms than the range of SHFM scores. Clinically speaking, this indicates if we want to understand physical symptoms in HF we have to look beyond the current list of clinical parameters included in prognostication models and consider alternative pathophysiologic mechanisms such as metabolic senescence.

The significant relationship between βARK1 and physical symptoms in HF provides evidence of the role of metabolic senescence, in explaining the biological underpinnings of physical symptoms in HF. We found that elevated βARK1 is associated with worse physical symptoms. This is the first known study to examine the relationship between metabolic senescence and physical symptoms. Previous work with βARK1 has shown improvements (i.e. decreased βARK1) in patients following ventricular assist device placement (Hata et al., 2006) and heart transplantation (Bonita et al., 2010), suggesting that a decrease in βARK1 would track with improved symptoms. As neurohormonal dysfunction and sympathetic nervous system impairment are hallmarks of

the pathophysiology of HF, it intuitively makes sense that less impairment in these systems would result in better symptoms perhaps through better work capacity or ability to respond to sympathetic nervous system stimulation; however, more research is needed to fully explicate this relationship.

Because we used a global summary score of physical symptoms, we were unable to look at patterns of symptoms that are perhaps different in women versus men or different comparing symptoms attributed to left-sided versus right-sided HF symptoms. Hence, the lack of specificity in symptoms may explain why we observed fewer symptoms in men and in those with higher right-sided filling pressures. For instance, similar to our previous findings (Denfeld et al., 2015), men reported significantly better physical symptoms than women. Also, although others have shown higher right-sided pressures are associated with less symptom burden (Guglin et al., 2012), most have shown limited association between right-sided filling pressures and symptoms in HF (Rector et al., 2006; Shah et al., 2002). Thus, more work is needed to examine these relationships in different patterns of physical symptoms.

An important clinical implication from this study is the identification of a marker of metabolic senescence in HF that helps to explain symptoms, which could potentially provide another "tool in our toolbox" in identifying symptoms in HF. Additionally, βARK1 may provide an amenable target for improving HF symptoms. Finally, this study further supports the inquiry into alternative pathophysiologic mechanisms as potential biological underpinnings of symptoms in HF.

A few limitations are noted with this study. First, we had a relatively small sample that was relatively young, racially homogeneous, and mostly non-ischemic, which limits

the generalizability of our findings to the entire HF population. Second, this was a cross-sectional analysis, and as such, we are unable to draw conclusions about the causal relationship between βARK1 and physical symptoms in HF. Finally, our sample included mostly patients with moderate to advanced HF. As such, future studies should include a larger cross-section of adults with HF that also includes those with relatively stable (i.e. NYHA class I) HF in addition to those with more advanced HF in order to identify varying metabolic senescence at different points in the progression of HF.

Future research is needed to study and integrate multiple measures of metabolic senescence, in addition to βARK1, in order to fully profile the role of metabolic senescence in explaining variations in physical symptoms in HF. Similarly, longitudinal research is needed to understand changes in both βARK1 and symptoms particularly in response to changes in treatment or interventions such as ventricular assist device placement. Finally, the value of βARK1 in predicting clinical events would allow us to further identify the clinical relevance of βARK1 in HF.

Conclusions

Worse metabolic senescence as measured by βARK1 is associated with worse physical symptoms in HF. The need to understand the biological underpinnings of symptoms in HF is underscored by the growing prevalence rate of HF and the associated symptom burden that is carried with it. We have provided preliminary evidence of the role of metabolic senescence in explaining the biological underpinnings of physical symptoms in HF, but more research is needed to fully understand this relationship.

References for Chapter III (See Cumulative References)

Chapter IV

The Prevalence of Frailty in Heart Failure: A Meta-Analysis

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This manuscript replaces portions of the review of the literature (frailty) and results sections of the traditional dissertation. Ms. Denfeld is the primary author on this paper; Dr. Lee is the senior author on this paper. Ms. Denfeld completed the literature review, systematic review, and meta-analysis under the supervision of Dr. Lee. This paper was submitted to and reviewed at Circulation: Heart Failure, which is an indexed and peer-reviewed journal with an impact factor of 5.867, on February 24, 2016. The paper was reviewed but rejected on April 4, 2016 and will be resubmitted immediately after the defense of the dissertation to the Journal of the American College of Cardiology: Heart Failure. The readership for this journal, which is also an indexed and peer-reviewed journal, includes physicians and other healthcare providers who treat patients with cardiovascular disease. There is no available impact factor at this time.

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Declaration of Conflicting Interests

None Declared

Key Words: Heart Failure; Meta-Analysis; Aging; Frailty (suggested, non-MeSH)

Abstract

Background: There is a growing interest in the intersection of heart failure (HF) and frailty; however, estimates of the prevalence of frailty in HF vary widely. The purpose of this paper was to quantitatively synthesize published literature on the prevalence of frailty in HF and to examine the relationship between age and the prevalence of frailty in HF.

Methods and Results: The prevalence of frailty in HF (as operationalized by the Frailty Phenotype and other approaches) was synthesized across published studies using random-effects meta-analysis. Meta-regression was performed to examine the influence of age on the prevalence of frailty. A total of 16 studies involving 4535 patients with HF were included in this meta-analysis. Despite considerable differences across studies, the overall estimated prevalence of frailty in HF was 38.7% (95% Confidence Interval 29.4%-47.9%; $z = 8.22$, $p < 0.001$). The prevalence was slightly lower among studies using the Frailty Phenotype (36.1%, $z = 4.52$, $p < 0.001$) and slightly higher among studies using other approaches (41.7%, $z = 6.96$, $p < 0.001$). There was a significant non-linear relationship (i.e. U-shaped curve) between age and frailty with higher prevalence among younger and older HF patients.

Conclusions: Frailty affects nearly 40% of patients with HF and is most prevalent in the youngest and oldest of patients. Future work should focus on standardizing the measurement of frailty and on broadening the view of frailty beyond a strictly geriatric syndrome in HF.

Introduction

Heart failure (HF) is the leading cause of hospitalization among older adults (Jencks et al., 2009) and is the fastest growing cardiovascular disease in the United States (Heidenreich et al., 2011). In recent years, frailty, often defined as "a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes," (Fried et al., 2001) has emerged as a significant area of research in HF. Given the predictive value of frailty in assigning risk for worse clinical- and patient-oriented outcomes among older adults in general (Fried et al., 2001; Klein, Klein, Knudtson, & Lee, 2005; Woods et al., 2005) and adults with HF in particular (R. Boxer et al., 2010; Buck & Riegel, 2011; Cacciatore et al., 2005; Chung et al., 2014; Dominguez-Rodriguez et al., 2015; Dunlay et al., 2014; Gastelurrutia et al., 2014; McNallan, Singh, et al., 2013), there is now a substantial literature base on frailty in HF. Indeed, HF is associated with accelerated biological aging (L. S. M. Wong et al., 2010) and, as a result, geriatric syndromes like frailty (Afilalo et al., 2014; Dodson & Chaudhry, 2012) are more likely to present irrespective of chronological age. Additionally, recent scientific statements have recommended a formal frailty assessment as a critical element in determining the care of adults with advanced HF in general (Fang et al., 2015), those being listed for heart transplant (Mehra et al., 2016), and those in skilled nursing facilities (Jurgens, Goodlin, et al., 2015).

There are a number of published studies on frailty in HF and several systematic reviews that have provided insight into the overlap between frailty and HF, including proposed pathogenic mechanisms and recommended interventions to prevent or

ameliorate frailty (R. S. Boxer, Shah, & Kenny, 2014; Butts & Gary, 2015; Dodson & Chaudhry, 2012; Flint, Matlock, Lindenfeld, & Allen, 2012; Goldwater & Pinney, 2015; Jha et al., 2015; Murad & Kitzman, 2012; Uchmanowicz, Łoboz-Rudnicka, Szelag, Jankowska-Polańska, & Łoboz-Grudzień, 2014). The overall prevalence and knowledge of factors that influence frailty in HF, however, are reported with considerable inconsistency across studies, and have not been effectively synthesized through prior narrative reviews. A quantitative synthesis of published literature can provide clinicians and researchers alike an estimate of the prevalence of frailty in HF and identify factors that may explain variability in the prevalence of frailty in HF across studies. Accordingly, the purpose of this meta-analysis was to quantitatively synthesize published literature on the prevalence of frailty in HF. In an effort to extend the perspective of frailty in HF beyond a strictly geriatric syndrome, we also examined the relationship between chronological age and prevalence of frailty in HF using meta-regression. This paper concludes with recommendations to harmonize conceptualization and measurement to move forward the science of frailty in HF.

Methods

Data Sources and Study Eligibility

This study was a meta-analysis of published (both full text and abstract) data-based studies on frailty in HF. Studies were considered eligible for inclusion if they met the following criteria: 1) sample or subsample consisted of HF patients, and 2) data on prevalence of frailty in the sample of HF patients was available (any form of frailty measure). Both observational and interventional studies (baseline data) were considered for inclusion. Non-English studies were excluded. We searched OVID Medline (without

revisions, 1946 to September Week 4, 2015) and CINAHL up until September 30, 2015 using the MeSH heading *heart failure* and the keyword *frail**. Abstracts were reviewed for the above criteria and reference lists were hand-searched for additional relevant studies not identified in the search engines. To minimize publication bias, abstracts were screened and known experts in the area of frailty in HF were approached at national meetings to identify potential works-in-progress. Full search strategies are presented within the PRISMA (Moher, Liberati, Tetzlaff, & Altman, 2009) flow diagram (**Figure 1**). Study screening and evaluation for eligibility for this meta-analysis was performed and validated by two members of the research team (Q.E.D. and C.S.L.).

Figure 1. PRISMA Flow Diagram

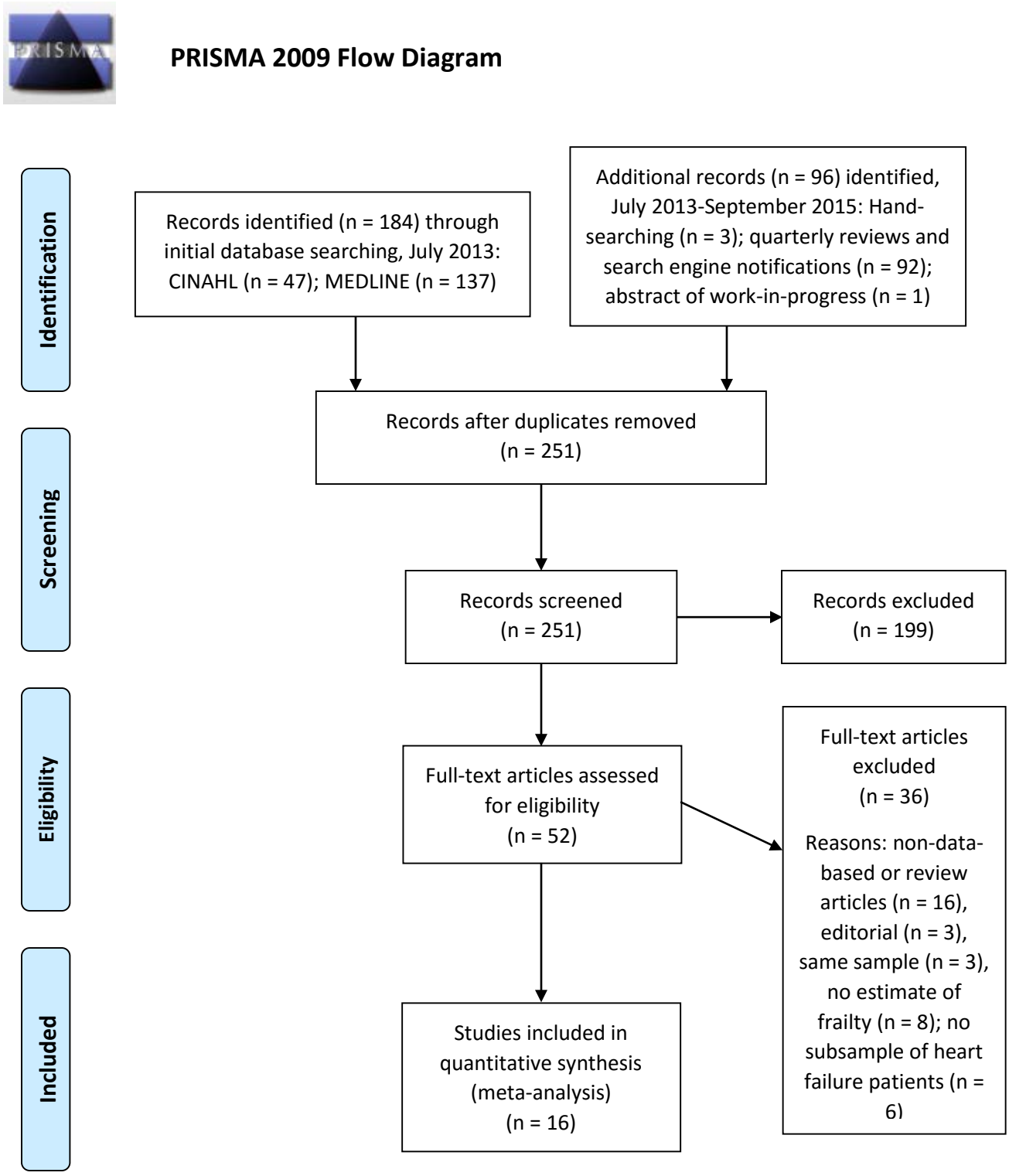

Figure 1. PRISMA flow diagram showing study identification, selection, eligibility, and inclusion. *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit www.prisma-statement.org.

Data Extraction

Data were extracted for the following variables 1) study first author, 2) year of publication, 3) number of HF patients in sample or subsample, 4) description of frailty measure, 5) prevalence of frailty in sample, and 6) mean or median age of sample. If clarification on extracted findings was required, the corresponding author was contacted via electronic mail to request this information and also to query about any known pending work on frailty in HF. Extracted data were independently verified by a research assistant (i.e. double verification). The authors conducted this meta-analysis in concordance with PRISMA standards of quality for reporting meta-analysis(Moher et al., 2009) and the guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (Stroup et al., 2000).

Statistical Analysis

A random-effects meta-analysis was used to quantify the prevalence of frailty in HF because of the considerable heterogeneity across studies in both the measurement of frailty and the samples studied. In random-effects meta-analysis, the effect sizes of observed studies are considered to represent a distribution of possible effects; random-effects meta-analysis incorporates both within-study variance and between-study heterogeneity (Hedges & Vevea, 1998). In this meta-analysis, the summary effect was the

average prevalence of frailty in HF weighted by both within-study variance and between-study heterogeneity using DerSimonian and Laird method (DerSimonian & Laird, 1986). Studies reporting frailty estimates were dichotomized into two groups according to differences in measurement type: “Frailty Phenotype” (Fried et al., 2001) and “Other” (details described below under Results). For transparency, the prevalence of frailty in HF was quantified overall and by measurement type. In addition to weighted estimates, the 95% confidence interval (CI) was reported along with *z* tests (weighted estimate divided by the standard error of the weighted estimate) and associated *p* values as metrics of precision.

Heterogeneity was quantified in this meta-analysis for the overall estimate and estimate by measurement type. Total dispersion in effect sizes across studies (*Q*) and the associated *p* value were calculated. We also calculated I^2 as a “signal-to-noise” ratio of excess dispersion to total dispersion – ranges from 0% (indicating that all of the heterogeneity is spurious) to 100% (indicating that all of the heterogeneity is “real” and requires further examination and explanation) (Higgins, Thompson, Deeks, & Altman, 2003). The bias associated with small study effects, publication bias, and other methodological differences between studies was assessed visually with funnel plots and with Egger’s test (Egger, Smith, Schneider, & Minder, 1997). We performed one-study-removed sensitivity analysis to estimate the influence of extreme estimates.

In an effort to explain significant observed heterogeneity, a random effects meta-regression was performed. Meta-regression assesses the relationship between one or more study-level factors and the effect size (Berkey, Hoaglin, Mosteller, & Colditz, 1995; Knapp & Hartung, 2003); our factor of interest was the average study age because there

was a significant imbalance of age across studies based on preliminary analysis of variance testing. Meta-regression was performed by using the log of the estimate and the standard error of the log of the estimate. Our predictor variable was examined for statistical significance using *p* values along with quantifying the magnitude of the relationship with effect size using R^2. Scatterplots were visually examined and further meta-regression (e.g. using non-linear regression) was performed to refine the relationship between the predictor variable and the effect size. Comprehensive Meta-Analysis V3.3 and Stata MP 13.1 were used for these analyses.

Results

Meta-Analysis

Results of study identification, screening, eligibility, and inclusion are outlined in the PRISMA flow diagram (**Figure 1**). A total of 16 published studies (15 full text and 1 abstract) (Abou-Raya & Abou-Raya, 2009; Altimir et al., 2005; R. Boxer et al., 2008; Cacciatore et al., 2005; Chung et al., 2014; Dominguez-Rodriguez et al., 2015; Dunlay et al., 2014; Gastelurrutia et al., 2014; Joyce et al., 2015; Lupon et al., 2008; McNallan, Chamberlain, et al., 2013; McNallan, Singh, et al., 2013; Pulignano et al., 2010; Sánchez et al., 2011; Uchmanowicz, Wleklik, & Gobbens, 2015; Vidán et al., 2014) involving a total of 4535 patients with HF were considered eligible and included in the meta-analysis (**Table**). Nine studies used either the full Frailty Phenotype measure (Fried et al., 2001) or portions of the Frailty Phenotype measure (e.g. handgrip strength only). Other frailty measurements included the Frailty Index (Mitnitski, Mogilner, & Rockwood, 2001), the Tilburg Frailty Indicator (Gobbens, van Assen, Luijkx, Wijnen-Sponselee, & Schols, 2010), and a geriatric assessment (also termed fragility assessment) that included multiple

geriatric tests such as the Barthel Index (Mahoney & Barthel, 1965) and the Pfeiffer Test (Pfeiffer, 1975).

Table. Characteristics of Studies

First Author (Year)	Sample Size	Frailty Measure	Prevalence of Frailty	Age in years (M±SD)
Abou-Raya (2009) (Abou-Raya & Abou-Raya, 2009)	83 (*HF subsample*)	Modified **Frailty Phenotype** Criteria; 4 criteria	29%	69.9±4.5
Altimir (2005) (Altimir et al., 2005)	360	**Other**; Evaluation using multiple geriatric scales/tests	41.7%	65.2±10.9
Boxer (2008) (R. Boxer et al., 2008)	60	**Frailty Phenotype** Criteria	25%	77±10
Cacciatore (2005) (Cacciatore et al., 2005)	120 (*HF subsample*)	**Other**; Frailty Staging System (*7 domains: disability, mobility, cognitive function, visual function, hearing function, urinary incontinence, and social support*)	15% (*highest frailty grouping*)	75.9±6.7
Chung (2014) (Chung et al., 2014)	72 (*baseline*)	Modified **Frailty Phenotype**; Handgrip strength <25% of total body weight	22%	59±2
Dominguez-Rodriguez (2015) (Dominguez-Rodriguez et al., 2015)	102 (*baseline*)	**Frailty Phenotype** Criteria	28%	73±4
Dunlay (2014) (Dunlay et al., 2014)	99	**Other**; Frailty Index (*31 impairments, disabilities, and comorbidities)*	61.6% (*definition of Frailty Index>0.25*)	65.1±9.4

Gastelurrutia (2014) (Gastelurrutia et al., 2014)	1314	**Other**; Evaluation using multiple geriatric scales/tests	44.2%	66.7±12.4
Joyce (2015; abstract) (Joyce et al., 2015)	88	Modified **Frailty Phenotype**; Handgrip strength	70%	64±16
Lupon (2008) (Lupon et al., 2008)	622	**Other**; Evaluation using multiple geriatric scales/tests	39.9%	68 [29-63] (median [IQR])
McNallan (2013) (McNallan, Singh, et al., 2013)	448	**Frailty Phenotype** Criteria	19%	73.2±13.3
McNallan (2013) (McNallan, Chamberlain, et al., 2013)	223	**Frailty Phenotype** Criteria	21%	71.1±13.9
Pulignano (2010) (Pulignano et al., 2010)	173	**Other**; Modified Frailty Score based on Frailty Index	16.2% (*highest frailty grouping*)	77.4±5.9
Sanchez (2011) (Sánchez et al., 2011)	211	**Frailty Phenotype** Criteria	40.8%	81.6±5
Uchmanowicz (2015) (Uchmanowicz et al., 2015)	110	**Other**; Tilburg Frailty Indicator	75.5%	66±11
Vidan (2014) (Vidán et al., 2014)	450	**Frailty Phenotype** Criteria	70.2%	80.1±6.1

HF indicates heart failure; IQR, interquartile range; M, mean; SD, standard deviation.

The overall estimated prevalence of frailty in HF was 38.7% (95% CI, 29.4%-47.9%; $z = 8.22$; $p < 0.001$) (**Figure 2**). Heterogeneity statistics ($Q = 676.09$; $p < 0.001$, I^2

= 97.8%) indicated that there was significant and substantive variability in the prevalence of frailty in HF across studies. The estimated prevalence of frailty in HF as assessed by the Frailty Phenotype measure was 36.1% (95% CI, 20.5%-51.8%; $z = 4.52$; $p < 0.001$). The estimated prevalence of frailty in HF as assessed by Other measurements was 41.7% (95% CI, 30.0%-53.5%; $z = 6.96$; $p < 0.001$). Effect sizes reported in studies were distributed symmetrically (see **Supplemental Material**), and there was minimal bias from small studies (Egger's test $p = 0.386$). The one-study-removed sensitivity analysis for each subgroup did not significantly refine the prevalence estimate nor significantly reduce the heterogeneity.

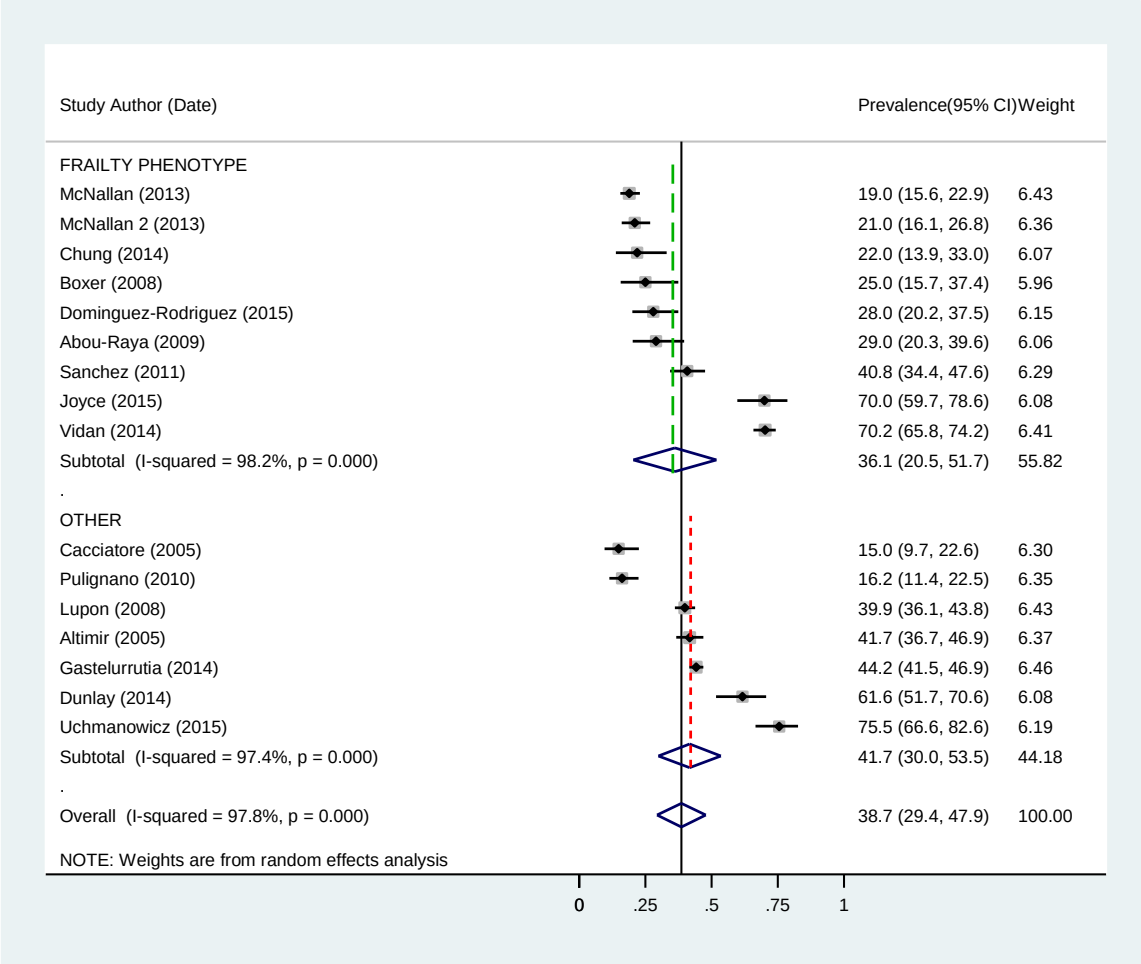

Figure 2. Estimated Prevalence of Frailty in Heart Failure. Random effects meta-

analysis of prevalence of frailty in heart failure by measurement type (Frailty Phenotype ($z = 4.52$, $p < 0.001$) and Other ($z = 6.96$, $p < 0.001$)) and overall ($z = 8.22$, $p < 0.001$). CI indicates confidence interval.

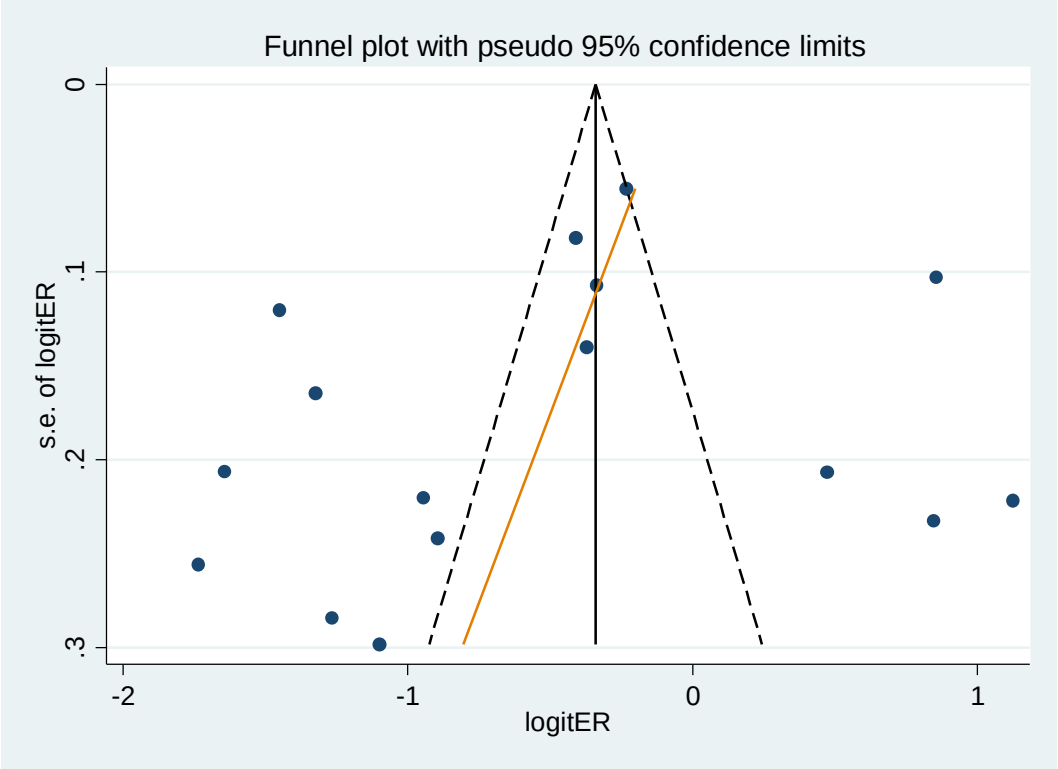

Figure for Supplemental Material. Funnel plot; Egger's test for bias of small studies effects: $t = -0.89$, $p = 0.386$.

Meta-Regression

Average study age was significantly different across the 16 studies ($F = 81.61$, $p < 0.001$) in preliminary analysis; thus, we proceeded with examining age as a predictor variable in explaining variability in the prevalence of frailty in HF. We also observed a parabolic (i.e. U-shaped) relationship between average study age and the prevalence of frailty in our preliminary graphical examination. Hence, we tested the non-linear relationship between average study age and frailty prevalence in HF. After removing one

outlier study (Chung et al.,(Chung et al., 2014) frailty estimate = 22%, mean age 59 years), a quadratic relationship was present between age and prevalence of frailty in HF (**Figure 3**) that explained a significant amount of variance across studies (Model: adjusted R^2 = 60.28%, F = 10.72, $p < 0.01$).

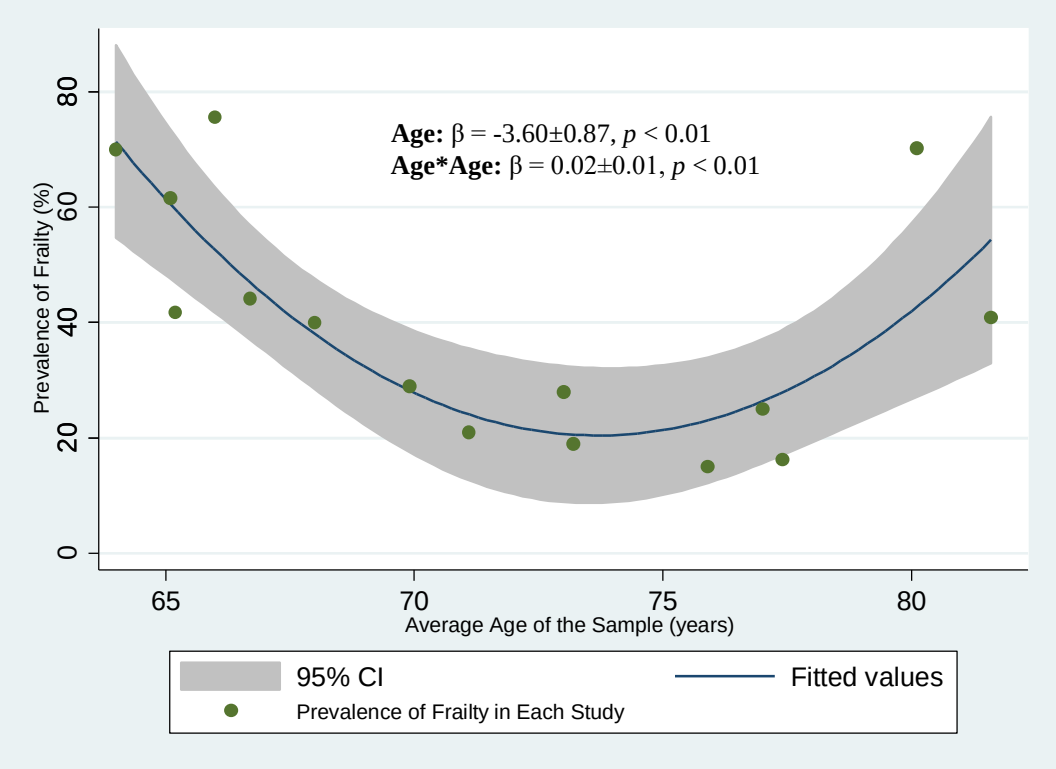

Figure 3. Relationship between Age and Prevalence of Frailty in Heart Failure

Meta-regression of the influence of average study age on prevalence of frailty in heart failure. CI indicates confidence interval.

Discussion

Despite substantial variation across published studies, we derived precise estimates of the prevalence of frailty in HF based on data from 16 published studies involving 4535 patients with HF. In this first known meta-analysis of the prevalence of frailty in HF, it is evident that frailty affects at least one in every three adults with HF.

There is also a prominent U-shaped relationship between chronological age and the prevalence of frailty in HF indicating that frailty is more prevalent among those in the younger and older age range. Finally, based on differences in measurement across studies, it is apparent that there is a small, but meaningful, conceptual divide regarding the best operational definition and corresponding measure that undoubtedly interferes with our ability to capture frailty in HF and integrate frailty into the clinical spectrum.

The high prevalence of frailty in HF indicates that frailty is more common in HF than we may have previously thought, and this has important implications for all practitioners caring for adults with HF, especially as frailty confers worse outcomes both broadly and in HF (R. Boxer et al., 2010; Buck & Riegel, 2011; Cacciatore et al., 2005; Chung et al., 2014; Dominguez-Rodriguez et al., 2015; Dunlay et al., 2014; Fried et al., 2001; Gastelurrutia et al., 2014; Klein et al., 2005; McNallan, Singh, et al., 2013; Woods et al., 2005). In the landmark study by Fried et al. (Fried et al., 2001), overall prevalence of frailty was estimated at about 7% in a large sample of community-dwelling older adults aged 65-101 years. Prevalence of frailty increased with each 5-year age group with an estimate of about 23% in those over 90 years of age. As such, HF is associated with rates of frailty that are substantially higher than what is seen among community-dwelling oldest-old adults.

We identified age as a factor that helps explain the variability of prevalence of frailty in HF across the published literature. The relationship between age and prevalence of frailty was non-linear, indicating that among studies that predominantly included older adults, those in the younger age range (about 65 years) and older age range (over 80 years) had higher prevalence of frailty in HF. This relationship may, in part, be explained

by both the disease-contribution of HF on the likelihood of being frail (the younger group) and the contribution of chronological age on the likelihood of being frail (the older group). As mentioned by previous reviews of frailty in HF (Jha et al., 2015), the high prevalence of frailty in the younger patients indicates that we should consider frailty at all ages, rather than as a strict geriatric syndrome. Hence, frailty can present at any point in the lifespan, and in particular, young, frail patients with HF are an important subset to recognize.

The underlying pathological mechanisms of frailty in HF remain unclear, particularly in relation to the differential contribution of aging and/or the HF condition on frailty. Goldwater and Pinney (Goldwater & Pinney, 2015) recently attempted to explicate a difference between frailty in HF related to primary aging and frailty in HF related to the progression of HF. For example, loss of muscle mass is common among older adults and may predispose older adults to frailty as a function of aging; however, loss of muscle mass and resulting frailty is often seen in HF as well but may be a function of the pathophysiology of HF rather than primary aging. Even though there is noted considerable overlap in pathological mechanisms (e.g. systemic inflammation, oxidative stress) (R. S. Boxer et al., 2014) between aging-related frailty and HF-related frailty, there may be subtle differences in the ability to mitigate frailty in these two groups with interventions such as ventricular assist devices (Flint et al., 2012). Clinically, this indicates that perhaps frailty should be managed differently in that mitigation of disease prevention would potentially ameliorate the frailty seen in younger adults with HF and that age-related decline should be addressed in older adults with HF. However, much more research is needed in this area to understand similar and different pathological

mechanisms and responsiveness to interventions in HF.

One important reason for the significant heterogeneity across HF studies is the variability in measurement of frailty. There are clearly two main perspectives of how frailty in HF is viewed across studies. The definition of frailty set forth by Fried and colleagues (i.e. “a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes”(Fried et al., 2001)) is the most widely cited across studies of frailty in HF (R. Boxer et al., 2008; R. Boxer et al., 2010; Cacciatore et al., 2005; Dominguez-Rodriguez et al., 2015; Dunlay et al., 2014; McNallan, Chamberlain, et al., 2013; McNallan, Singh, et al., 2013). In contrast, other studies incorporated other factors (e.g. social, cognitive, and psychological factors) into their definition and considered frailty to be the cumulative sum of all these factors (Altimir et al., 2005; Gastelurrutia et al., 2014; Lupon et al., 2008). In this meta-analysis we noted that the prevalence of frailty in HF differed by the two perspectives on frailty measurement with a lower prevalence noted among those using the Frailty Phenotype and a higher prevalence noted among those using other frailty measures.

Future Recommendations

Our meta-analysis and review of the current literature highlights several opportunities to improve future research on frailty in HF. First, there is a need to harmonize the definition and measurement of frailty in HF. The major benefit of using a unified definition of frailty in HF is that we can make comparisons across studies, including performing robust meta-analyses and implementing a standardized assessment of frailty in HF. Additionally, more research is needed to rigorously test and refine frailty

measurements to ascertain the most precise and accurate measure of frailty in HF. Based on the preponderance of evidence, we propose that the Frailty Phenotype be adopted as a measure of *physical* frailty in HF as it could be quickly and easily used across research and practice settings at this time. However, much more research is needed to disambiguate the relationships between physical frailty and related concepts such as cognitive function and psychosocial health.

Second, the clinical implications of studying frailty in HF are considerable. Given the finding that younger patients had high prevalence of frailty in HF, we should broaden our view of frailty as a strictly geriatric syndrome to encompass the entire chronological age spectrum in HF. As such, similar to recent guidelines (Fang et al., 2015; Jurgens, Goodlin, et al., 2015; Mehra et al., 2016), we recommend that an assessment of frailty be incorporated into clinical practice for all patients with HF; however, appropriate interventions to mitigate frailty in HF have yet to be determined. Additionally, it would be worthwhile to examine the influence of HF severity on frailty. HF severity was reported inconsistently across studies; hence, we were unable to examine the relationship between HF severity (e.g. New York Heart Association functional classification) and frailty.

Finally, in addition to furthering our understanding of the relationship between age and frailty, there is a need to examine shared biological pathways and manifestations of frailty and HF, including frailty in HF as a result of both primary aging and frailty related to the HF condition. The elucidation of these mechanisms may result in a shift in clinical management in which we treat frailty in HF (as related to aging and/or the HF condition) to improve clinical- and patient-oriented outcomes. Moreover, the

compounded effect of frailty plus HF may allow us to improve prognostication and current risk models (Benbarkat et al., 2012; Levy et al., 2006; Pocock et al., 2013).

Limitations

The findings of this meta-analysis have several limitations. First, due to the integration of studies that used different measures of frailty, our findings demonstrated considerable heterogeneity that should be acknowledged along with our estimate of the prevalence of frailty in HF. Second, although we made every effort to identify completed or on-going studies of frailty in HF, it is possible that we inadvertently missed published or unpublished research in this area. Finally, we did not examine prevalence of pre-frailty in HF as many studies did not provide an estimate of this subgroup. It would be worthwhile, in the future, to include pre-frailty as a subgroup in order to identify adults with HF at risk for frailty.

Conclusions

In this first known meta-analysis of frailty in HF, our findings demonstrated that frailty affects at least one in every three patients with HF and is most prevalent in the youngest and oldest of patients. These results point to the importance of studying frailty in HF across the lifespan and broadening our view of frailty beyond a strictly geriatric syndrome. As such, there is an exigent need to critically examine all aspects of frailty in HF, including standardizing the measurement of frailty in HF, understanding the underlying pathological mechanisms, and mitigating the effects of frailty in HF.

References for Chapter IV (See Cumulative References)

Chapter V

Physical Frailty and Invasive Hemodynamics in Heart Failure

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This manuscript replaces portions of the methods section and the results section of the traditional dissertation. Ms. Denfeld will be the primary author on this paper; Dr. Lee will be the senior author on this paper. Ms. Denfeld conducted the study and analyzed the results of the study under the supervision of Drs. Lee, Mudd (heart failure clinical expert), and Winters-Stone (frailty expert). This paper will be submitted to American Heart Journal, which is an indexed and peer-reviewed journal with an impact factor of 4.463. The readership for this journal includes cardiologists and general practice physicians. This manuscript will be submitted immediately following the defense of the dissertation.

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Declaration of Conflicting Interests

None Declared

Key Words (MeSH): Heart Failure; Hemodynamics; Frail Elderly; Physical Frailty (non-MeSH)

Abstract

Background: Physical frailty is an important prognostic indicator in heart failure (HF); however, few studies have examined the relationship between physical frailty and invasive HF hemodynamics. **Purpose:** To characterize physical frailty in HF in relation to invasive hemodynamics. **Methods:** Fifty adults with New York Heart Association (NYHA) Class II-IV HF were enrolled in a cross-sectional study. Participants were recruited when scheduled for a right heart catheterization (RHC) procedure for clinical purposes. Physical frailty was measured according to the Frailty Phenotype: shrinking, weakness, slowness, physical exhaustion, and low physical activity. Markers of invasive hemodynamics were derived from a formal review of RHC tracings, and projected survival was calculated using the Seattle HF Model (SHFM). **Results:** The mean age of the sample (n = 50) was 57.5±9.7 years, 66% were male, 92% had NYHA Class III/IV HF, and 66% had non-ischemic HF. Physical frailty and pre-frailty were identified in 50% and 48% of participants, respectively. Those with physical frailty had higher pulmonary artery diastolic pressures (p = 0.02), lower mixed venous oxygen (p = 0.02), lower cardiac index by thermodilution (p = 0.02), higher heart rates (p = 0.01), and worse one-year projected survival (p = 0.01) compared with those who were not physically frail. **Conclusions:** Physical frailty is highly prevalent among adults with HF and is associated with worse invasive hemodynamics, providing preliminary evidence of the underlying mechanisms of physical frailty in HF.

Introduction

Heart failure (HF) is an increasingly prevalent condition with approximately 870,000 new cases diagnosed every year (Mozaffarian et al., 2016). The epidemic proportions of HF will be further exacerbated by an aging population, as HF is highly common among older adults (Mozaffarian et al., 2016) and is the most common reason for hospitalization in those over 65 years of age (Jencks et al., 2009; Ross et al., 2010). Additionally, HF is a complex and widely heterogeneous syndrome that requires astute clinical management (Yancy et al., 2013). The rising numbers of adults with HF coupled with the complexity of clinical management highlights the need to pursue new lines of inquiry within the HF condition.

Physical frailty is recognized as a highly prevalent condition generally among older adults (Fried et al., 2001) and specifically among sub-groups of patients such as those with cardiovascular disease (Afilalo et al., 2012; P. Green et al., 2012). As the inquiry into the intersection between physical frailty and HF is becoming more common (Chung et al., 2014; Dominguez-Rodriguez et al., 2015; Dunlay et al., 2014; Gastelurrutia et al., 2014; Jha et al., 2015), there is a need to standardize our approach to measuring physical frailty in HF, conduct more studies specifically centered on physical frailty in HF, and understand the relationship between physical frailty and other commonly used markers in HF. As a way to standardize the measurement of physical frailty in HF and move the science forward, we can begin by assessing *physical* frailty as has been recommended by frailty consensus groups (Morley et al., 2013). Moreover, following recommendations by several HF groups to include an assessment of frailty in HF (Fang et al., 2015; Mehra et al., 2016), there is a critical need to further study all aspects of

physical frailty in HF in order to better understand the relationship between physical frailty and HF. Despite the growing literature on physical frailty in HF, however, physical frailty has not been comprehensively characterized in terms of invasive HF hemodynamics.

Accordingly, the purpose of this study was to characterize physical frailty in HF by: 1) quantifying the prevalence of physical frailty in a sample of adults with moderate to advanced HF, and 2) quantifying differences in invasive hemodynamics, along with demographic and clinical characteristics, between physically frail and non-physically frail adults with HF.

Methods

Study Design

This paper addresses a primary aim of a cross-sectional study entitled Symptom Biology and Accelerated Aging in Heart Failure (SPEED-HF) that involved comprehensive measurements of physical frailty and invasive hemodynamics in HF. The study was conducted between July 2015 and March 2016. A key aspect of the study included assessing physical frailty around the time of a scheduled right heart catheterization (RHC) procedure and thus reducing the time lapse between assessments. After initial screening and approval by the HF cardiologists, potential participants who met the inclusion criteria were approached when scheduled for a RHC as deemed necessary for clinical purposes (e.g. to stage patients for advanced therapies) (**Figure**). Those who agreed to participate were scheduled for a time to meet to provide written informed consent and to complete study requirements. Three physical frailty criteria (grip strength, chair stands, and gait speed) were assessed and symptom questionnaires

(physical and affective symptoms and self-report physical frailty questions) were administered.

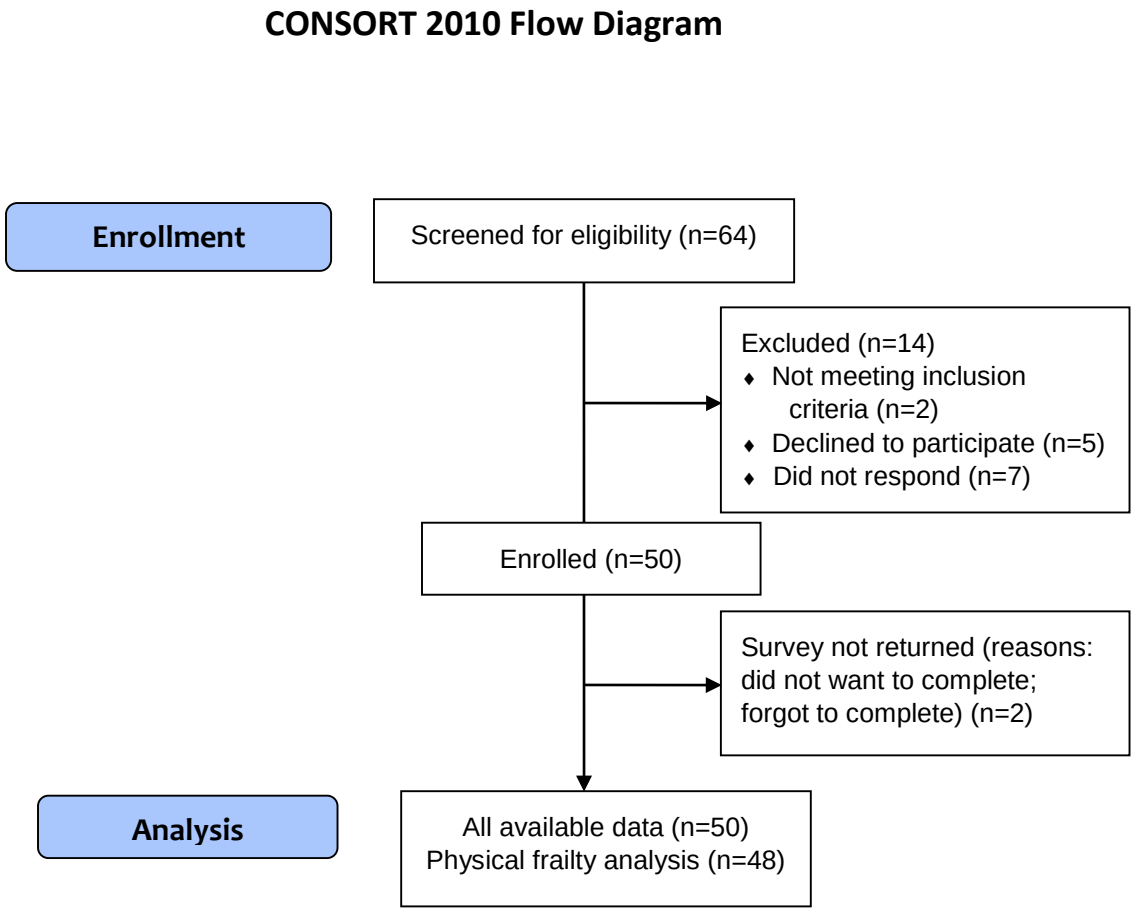

Figure. Enrollment Flow Diagram

Sample

The sampling frame for this study was adult women and men with HF who receive care from a HF practice (out-patient clinic and/or in-patient facilities) at an academic medical center in the Pacific Northwest and who required a RHC for clinical purposes during the study period. Formal inclusion criteria included age ≥ 21 years, ability to read and comprehend 5th grade English, New York Heart Association (NYHA) functional class II-IV (i.e. current HF symptoms) as determined by the attending HF cardiologist, and undergoing RHC for clinical purposes. Participants were excluded if they had previously

had a heart transplant or ventricular assist device placed, had major and uncorrected hearing dysfunction, or were otherwise unable to complete the requirements of the study (e.g. life-threatening illness). This study was approved by the university Institutional Review Board, and written informed consent was obtained from all participants.

Measurement

Data on age, gender, marital status, race, and education were obtained using a socio-demographic questionnaire. Functional status (i.e. NYHA) was assessed by an attending HF cardiologist. Data on history, duration, etiology, and treatment of HF along with clinical characteristics were collected through an in-depth review of the electronic medical record. Comorbid conditions were summarized using the Charlson Comorbidity Index (Charlson et al., 1987).

Invasive hemodynamics. All RHC procedures were performed by either advanced HF cardiologists or interventional cardiologists. Following completion of the RHC procedure, we reviewed the RHC tracings and reports. Specifically, we collected data on pressures based on waveforms, including central venous pressure (CVP; millimeters of mercury (mmHg)); pulmonary artery pressures (PA; mmHg), including PA systolic (PAS) and PA diastolic (PAD) pressures; and pulmonary capillary wedge pressure (PCWP; mmHg). We collected data on flow based on cardiac output (CO; liters/min (L/min) and cardiac index (CI; liters/minute/kilogram (L/min/kg)), both as measured by thermodilution and as calculated by the Fick equation. Mixed venous oxygen (MVO^2; % saturation) was also collected from the RHC. Finally, data on heart rate and aortic blood pressure (systolic (SBP) and diastolic (DBP); mmHg) were collected.

Other objective markers of heart function. Data from the most recent transthoracic echocardiogram were also collected, including left ventricular internal end-diastolic diameter (LVIDd; centimeters (cm)) and visually estimated left ventricular ejection fraction (LVEF; %). Data from recent cardiopulmonary exercise testing were collected, including peak oxygen consumption (peak VO^2; milliliters per kilogram per minute (mL/kg/min)), respiratory quotient (RQ; the ratio of CO^2 eliminated and O^2 consumed), ventilatory equivalent of carbon dioxide (VE/VCO^2) slope coefficient, and peak oxygen consumption at anaerobic threshold (VO^2 at AT; mL/kg/min).

The Seattle HF Model (SHFM) score was calculated based on the model developed by Levy and colleagues (2006) (Levy et al., 2006). In this model, demographic and objective clinical variables and HF treatments are multiplied by respective slope coefficients to generate a single composite risk-prediction score. In addition to the score (range roughly 0 to 4; higher scores = worse survival), SHFM projected one-year survival (%) was calculated.

Mild cognitive dysfunction. Cognitive function was assessed in-person using the MoCA (Nasreddine et al., 2005). The MoCA is a cognitive screening tool, designed for use by first-line clinicians with a cut off score of 26 (i.e. < 26/30) and a sensitivity of 90% and a specificity of 87% to detect mild cognitive dysfunction in adults (Nasreddine et al., 2005). The MoCA has an adjusted algorithm for persons with chronic cardiovascular disease (score < 24/30) that is 100% sensitive to detect amnestic mild cognitive dysfunction (McLennan, Mathias, Brennan, & Stewart, 2011). Thus, a MoCA score of 24 (i.e. < 24/30) was used as the cut off for sub-clinical mild cognitive dysfunction in this study.

Physical frailty. Based on the Frailty Phenotype (Fried et al., 2001), a well-validated measure in older adults, we measured the five criteria of physical frailty: shrinking, weakness, physical exhaustion, slowness, and low physical activity (**Table 1**). To ease practicality and feasibility of assessing physical frailty in a patient population, we selected our measures based on their ability to be assessed in a HF clinical practice.

First, *shrinking* was measured by a self-report of unintentional weight loss of >10 pounds over the last year. Because this dimension is designed to assess loss of muscle and/or fat mass and not fluctuations in fluid, we reviewed the medical record notes to ascertain reason for weight loss. Additionally, those who noted intentional weight loss (e.g. in preparation for bariatric surgery) were not categorized as having unintentional weight loss. A report of having lost more than 10 pounds indicated the presence of shrinking.

Second, *weakness* was measured for both upper and lower extremities. *Weakness of the upper extremities* was measured using a hand-held Smedley III Digital Grip Strength Tester (Takei Scientific Instruments, Japan). Participants were asked to perform standing maximal isometric contraction with each hand three consecutive times with a five-second rest period between each contraction. Weakness was determined using gender and body mass index cut points based on the original Frailty Phenotype (Fried et al., 2001). *Weakness of the lower extremities* was measured using 5-repeat chair stands. Participants were assessed and timed on their ability to rise out of a chair 5 times without using their arms. We used a cut point of > 12 seconds or inability to rise 5 times to define the presence of weakness (Tiedemann, Shimada, Sherrington, Murray, & Lord, 2008).

Third, *slowness* was measured by assessing gait speed by clocking the time (in

seconds) it took a participant to walk 4 meters. Participants were asked to walk at their usual pace, starting at 1 meter before the start line and walking to 1 meter past the 4m finish line. They were permitted to use walking aides such as canes or walkers. Gait speed was calculated by dividing the distance by the time it took to walk the full distance in seconds (in meters per second (m/s)). Numerous cut points have been proposed to identify slow gait speed, including gender and height cut points based on the original Frailty Phenotype Criteria (Fried et al., 2001), 0.8 meters/second (m/s) based on survival among older adults (Studenski et al., 2011), and tertiles based on slow (≤ 0.65 m/s), intermediate (0.66-0.99 m/s), and fast walkers (≥ 1.0 m/s) among adults with HF (Pulignano et al., 2016). Based on a review of these and other studies (Bennett, Winters-Stone, & Nail, 2006), we used a cut point of < 0.9 m/s (for both women and men) to define slowness.

Fourth, *physical exhaustion* was assessed using the 13-item Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F; v.4) (Hjollund, Andersen, & Bech, 2007; Yellen, Cella, Webster, Blendowski, & Kaplan, 1997). The FACIT-F captures self-reported tiredness, weakness, and inability to perform activities of daily living as a result of fatigue over the previous week. The 13 items are rated from 0 (not at all) to 4 (very much); after reverse scoring the necessary items, the items are summed with cumulative scores ranging from 0 to 52 with lower scores indicating more fatigue. The scale has demonstrated good reliability and validity in adults with and without chronic conditions (Cella, Lai, Chang, Peterman, & Slavin, 2002; Hagell et al., 2006). Reliability of the FACIT-F in this sample was 0.92. Based on the application of the FACIT-F in the general population (Cella et al., 2002), we used a cut point of 17 (i.e.

< 17) on the FACIT-F, which corresponds to 2 standard deviations below mean of the general population, to identify those with severe physical exhaustion.

Fifth, *level of physical activity* was measured with the question "During the past week, how much total time did you spend exercising?" Those who reported less than one hour per week (the equivalent of walking about 3 miles per week at an average of 3 miles per hour to approximate expending about 300 kcal per week in physical activity) were classified as having low physical activity. In order to translate this cut point for exercise to functional capacity, we compared responses to this question with the 12-item Duke Activity Status Index (DASI), an instrument of functional capacity that assesses activities related to major aspects of physical function (Hlatky et al., 1989) and has demonstrated good reliability and validity among adults with HF (Fan, Lee, Frazier, Lennie, & Moser, 2015). The DASI scores are converted to metabolic equivalents (METS). Approximately 6.0 METS corresponded to a report of exercising one hour or less per week. Reliability of the DASI in this sample was 0.83.

After completing the measures for each of the five criteria, each participant was classified as either meeting or not meeting the criteria (**Table 1**). The scores were totaled (range 0 to 5), and the level of physical frailty was determined as described by the initial Frailty Phenotype: no criterion = non-frail, 1-2 criteria = pre-frail and ≥3 criteria = frail.

Table 1: Measures to Assess Physical Frailty in Heart Failure

Criteria	*Measurement*	*Heart Failure Nuances*	*Scoring*
Shrinking	Self-reported unintentional weight loss >10 pounds over the past year	Review medical record notes to verify weight loss unrelated to fluid shifts	Yes/No 1 = yes 0 = no
Weakness	Hand-held grip strength dynamometer (upper extremities; cut points by Frailty Phenotype) *and* 5-repeat chair stands (lower extremities; cut point = > 12 sec)	None; should be feasible in HF clinical settings	Chair stand time: 1 = >12 sec 0 = ≤ 12 sec
Slowness	Time it takes to walk 4 meters (cut point = < 0.9 m/s)	None; should be feasible in HF clinical settings	Gait speed: 1 = < 0.9 m/s 0 = ≥ 0.9 m/s
Physical Exhaustion	13-item Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) Scale (cut point = score < 17)	Potential overlap with other causes of physical exhaustion common in HF (e.g. depression, anemia)	FACIT-F score: 1 = < 17 0 = ≥ 17
Low Physical Activity	One question: "During the past two weeks, how much total time did you spend exercising?" (cut point < 1 hour per week) *and* 12-item Duke Activity Status Index	Attempt to capture physical activity levels in adults already extremely limited in their activity	Exercise Question: 1 = < 1 hour per week 0 = ≥ 1 hour per week

Total score = Shrinking + Weakness + Slowness + Physical Exhaustion + Low Physical Activity
Physical frailty = ≥ 3
Pre-frailty = 1-2
Non-frailty = 0

Statistical Analysis

Baseline characteristics were presented using standard descriptive statistics, including measures of central tendency and dispersion. In particular, we were interested in the prevalence rates of physical frailty in HF and proportions of the sample that were identified as physically frail, pre-physically frail, or non-physically frail. Because two symptom surveys were not returned, we were unable to classify physical frailty for two participants (**Figure 1**). And because of the small numbers in the non-frail group ($n = 1$), we combined this group with the pre-frail group ($n = 23$) (i.e. "not physically frail"). Comparative statistics (Student's *t*-, Mann-Whitney *U*, or Fisher exact tests or the Pearson χ^2) were used to determine significant differences in demographic and clinical characteristics between the levels of physical frailty. In particular, we were interested in differences in invasive hemodynamics and SHFM scores and projected one-year survival between the levels of physical frailty. Significance was set at $\alpha < 0.05$. All analyses were performed using Stata/MP version 13MP (StataCorp, College Station, TX).

Results

Characteristics of the sample are presented in **Table 2**. The average age of the total sample enrolled ($n = 50$) was about 57 years (range 27 to 75 years), and the majority were male (66%) and non-Hispanic Caucasian (84%). Most had NYHA Class III or IV HF (92%) and non-ischemic HF (66%), and most were on evidence-based therapies, including beta-blockers (70%) and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (78%). At the time of enrollment and assessment of physical frailty, most (70%) participants were out-patient status.

Table 2: Characteristics of the sample and by level of physical frailty

	M±SD, N (%), or Median [IQR]			
	Total (n=50)	Not Physically Frail (*n* = 24)†	Physically Frail (*n* = 24)	*p* value*
Patient Characteristics:				
Age (years)	57.5±9.7	55.6±11.3	60.1±6.4	0.10
Male	33 (66.0%)	18 (75.0%)	14 (58.3%)	0.22
Non-Hispanic Caucasian	42 (84.0%)	22 (91.7%)	18 (75.0%)	0.25
Education level				0.07
High school or less	18 (37.5%)	5 (20.8%)	13 (54.2%)	
>High school but < college	21 (43.8%)	13 (54.2%)	8 (33.3%)	
College degree	9 (18.8%)	6 (25.0%)	3 (12.5%)	
Body Mass Index (kg/m^2)	30.3±7.6	30.8±8.5	29.5±6.9	0.58
Charlson Comorbidity Index (weighted)	2.3±1.2	2.1±1.2	2.4±1.2	0.47
Atrial Fibrillation	26 (52%)	14 (58.3%)	11 (45.8%)	0.39
Stage 3 Chronic Kidney Disease	10 (20.0%)	3 (12.5%)	6 (25.0%)	0.46
Out-patient (versus in-patient) at enrollment	35 (70%)	19 (79.2%)	14 (58.3%)	0.12
General Heart Failure Characteristics:				
Time with Heart Failure (years)	8.2 [2.4-14.8]	8.7 [4.4-15.5]	8.0 [1.0-13.5]	0.19
NYHA Functional Class				0.01
Class II	4 (8.0%)	4 (16.7%)	0 (0.0%)	
Class III	34 (68.0%)	18 (75.0%)	15 (62.5%)	
Class IV	12 (24.0%)	2 (8.3%)	9 (37.5%)	
Non-ischemic Etiology	33 (66.0%)	18 (75.0%)	14 (58.3%)	0.22
Prescribed a β-blocker	35 (70.0%)	19 (79.2%)	15 (62.5%)	0.20
Prescribed an ACE-I or ARB	39 (78.0%)	20 (83.3%)	18 (75.0%)	0.72
Prescribed an aldosterone antagonist	25 (50.0%)	13 (54.2%)	11 (45.8%)	0.56

Prescribed digoxin	11 (22.0%)	7 (29.2%)	3 (12.5%)	0.29
Prescribed an inotropic medication	8 (16.0%)	4 (16.7%)	4 (16.7%)	1.00
Prescribed a vasodilator (nitrate or hydralazine)	10 (20.0%)	4 (16.7%)	5 (20.8%)	1.00
Serum sodium (mEq/L)	136.9±3.9	138.0±2.9	135.4±4.4	0.02
Serum hemoglobin (g/dL)	13.2±1.6	13.3±1.7	13.2±1.6	0.77
Serum creatinine (mg/dL)	1.2±0.5	1.2±0.4	1.3±0.6	0.49
Left ventricular internal end-diastolic diameter (cm)	6.6±1.0	6.7±1.0	6.4±1.0	0.32
Left ventricular ejection fraction (%)	24.6±9.1	25.4±6.9	23.3±10.7	0.43
Peak VO_2 (mL/kg/min)	15.3±3.5	16.2±3.7	13.6±2.8	0.05
VO_2 at aerobic threshold (mL/kg/min)	12.0±3.4	12.8±3.8	10.2±2.6	0.07
Respiratory quotient	1.1±0.2	1.1±0.2	1.2±0.1	0.55
VE/VCO_2 slope coefficient	32.9±5.2	32.0±4.9	34.5±6.1	0.34
ICD or BiVICD	40 (80%)	22 (91.7%)	16 (66.7%)	0.07
SHFM Score	2.6±0.9	2.2±0.8	2.9±1.0	0.01
SHFM projected one year survival (%)	55.7±25.3	64.7±19.1	46.7±27.6	0.01
Mild cognitive dysfunction (MoCA < 24)	17 (34.0%)	2 (8.3%)	14 (58.3%)	0.001

†Not physically frail includes both non-frail (n = 1) and pre-frail (n = 23)

*p values comparing physically frail versus not physically frail

Abbreviations: ACE-I, Angiotensin Converting Enzyme-Inhibitor; ARB, Angiotensin Receptor Blocker; BiVICD, biventricular implantable cardioverter defibrillator; ICD, implantable cardioverter defibrillator; IQR, interquartile range; M, mean; MoCA, Montreal Cognitive Assessment; NYHA, New York Heart Association; SD, standard deviation; SHFM, Seattle Heart Failure Model; VE/VCO^2, ventilatory equivalent of carbon dioxide slope coefficient; VO_2, peak oxygen consumption.

Table 3: Physical frailty characteristics of the sample and by level of physical frailty

	M±SD, N (%), or Median [IQR]			
	Total (*n* = 50)	Not Physically Frail (*n* = 24)†	Physically Frail (*n* = 24)	*p* value*
Physical Frailty Measures:				
Unintentional weight loss	17 (34.0%)	6 (24.0%)	11 (45.8%)	0.13
Weakness by handgrip strength (kg)				
Women	24.1±9.3	30.6±10.5	20.1±6.0	0.06
Men	41.0±7.8	42.1±8.8	39.8±6.8	0.42
Weakness by chair stands (sec)	14.6 [12.0-21.3]	12.3 [11.0-15.1]	20.3 [14.7-25.7]	<0.001
Slowness (m/s)	0.9±0.2	1.1±0.2	0.7±0.2	<0.001
Physical exhaustion (FACIT-F; 0-52)	24.3±10.6	29.1±9.3	19.5±9.8	0.001
Low physical activity	32 (66.7%)	11 (45.8%)	21 (87.5%)	0.002
Duke Activity Status Index (METS)	5.9±1.6	6.8±1.4	5.1±1.3	<0.001

†Not physically frail includes both non-frail (*n* = 1) and pre-frail (*n* = 23)
**p* values comparing physically frail versus not physically frail
Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue Scale; IQR, interquartile range; M, mean; SD, standard deviation.

Table 4: Invasive hemodynamic characteristics of the sample and by level of physical frailty

	M±SD			
	Total (*n* = 50)	Not Physically Frail (*n* = 24)†	Physically Frail (*n* = 24)	*p* value*
Right Heart Catheterization Hemodynamics:				
Right atrial pressure (mm/Hg)	8.2±4.2	8.0±4.0	8.5±4.5	0.69
Pulmonary artery systolic pressure (mm/Hg)	41±15.1	37.2±13.4	44.6±15.7	0.09
Pulmonary artery diastolic pressure (mm/Hg)	18.8±17.9	16.4±7.0	21.4±7.9	0.02
Pulmonary capillary wedge pressure (mm/Hg)	18.6±8.2	17.0±7.2	20.4±9.0	0.16
Mixed venous oxygen saturation (%)	61.9±7.3	64.2±6.8	59.2±7.1	0.02
Cardiac output (L/min by thermodilution)	4.8±1.5	5.3±1.6	4.2±1.1	0.01
Cardiac index (L/min/m^2 by thermodilution)	2.3±0.6	2.5±0.6	2.1±0.5	0.02
Cardiac output (L/min by Fick equation)	4.0±1.1	4.3±1.1	3.7±1.0	0.04
Cardiac index (L/min/m^2 by Fick equation)	2.0±0.5	2.1±0.4	1.9±0.5	0.16
Aortic systolic blood pressure (mm/Hg)	110.5±18.1	114.9±16.0	105.8±19.6	0.10
Aortic diastolic blood pressure (mm/Hg)	69.7±8.5	69.0±7.5	70.3±9.9	0.61
Heart rate (beats per minute)	78.7±16.1	73.1±12.9	84.8±17.6	0.01

†Not physically frail includes both non-frail (*n* = 1) and pre-frail (*n* = 23)

**p* values comparing physically frail versus not physically frail

Abbreviations: L/min, liters per minute; L/min/kg, liters per minute per kilogram; M, mean; mmHg, millimeters of mercury; SD, standard deviation.

Prevalence of Physical Frailty in Heart Failure

Physical frailty was identified in 50% (*n* = 24) of the sample, and pre-physical frailty was identified in 47.9% (*n* = 23) of the sample (**Table 3**). Only 1 was considered non-frail. In the entire sample, about one-third had unintentional weight loss, 10% were considered weak by handgrip, 80% were considered weak by 5-repeat chair stands, almost half were considered slow, one-third reported severe physical exhaustion, and two-thirds had low physical activity. Notably, seven participants were unable to complete 5 chair stands and two participants were unable to complete the gait speed assessment. Reported unintentional weight loss and weakness by grip strength were not significantly different between physical frailty levels (**Table 3**).

Demographic and Clinical Characteristics of Physical Frailty in Heart Failure

Compared with those who were not physically frail, those physically frail were significantly more likely to be in NYHA Class IV, have lower serum sodium levels, and lower VO_2 Max (**Table 2**), indicating physical frailty among adults with HF was associated with more functional impairment and more advanced stages of HF than those not physically frail. Those physically frail also had significantly higher proportions of mild cognitive dysfunction than those not physically frail. Finally, those with physical frailty had significantly higher SHFM scores and worse one-year projected survival than those not physically frail. There were no significant differences between many other socio-demographic and clinical characteristics, indicating physical frailty in HF is not age- nor gender-dependent and manifests across the spectrum of the HF clinical presentation (i.e. varied etiologies, co-morbidities, and ejection fractions).

Invasive Hemodynamics and Physical Frailty in Heart Failure

Multiple measures of invasive hemodynamics were significantly different comparing those physically frail versus those not physically frail (**Table 4**). Those with physical frailty had significantly higher pulmonary artery diastolic pressures, lower mixed venous oxygen saturations, lower cardiac output (thermodilution and Fick), lower cardiac index (thermodilution only), and higher heart rates. Additionally, those with physical frailty had numeric differences in aortic systolic blood pressure, pulmonary artery systolic pressure, and PCWP compared with those who were not physically frail, although not significantly different.

Discussion

The results from this study have generated several novel findings. First, using comprehensive and clinically applicable physical frailty measures, we have provided evidence that physical frailty is highly prevalent among adults with moderate to advanced HF, indicating a large number of adults with HF have some combination of shrinking, weakness, slowness, physical exhaustion, and low physical activity. Second, the characterization of physical frailty in HF based on demographic and clinical characteristics demonstrates that physical frailty presents across the spectrum of HF in terms of age, gender, etiology, and duration of HF; although physical frailty was associated with more advanced stages of HF and mild cognitive dysfunction. Finally, we are the first known study to show that multiple invasive hemodynamics are significantly worse in those physically frail compared with those not physically frail.

In comparing our findings with other HF studies using the Frailty Phenotype, we observed higher prevalence rates of physical frailty in this sample and similar rates of pre-frailty (R. Boxer et al., 2008; Dominguez-Rodriguez et al., 2015; McNallan, Singh, et

al., 2013; Sánchez et al., 2011; Vidán et al., 2014). Our rates of physical frailty could be higher as a result of the more advanced state of this sample (i.e. all participants required a RHC). Additionally, we enrolled from both hospital and community settings in order to capture a wide cross-section of adults with HF. Almost one-third of the sample was in-patient at the time of enrollment; however, in-patient status was not significantly associated with physical frailty.

Importantly, the findings of this study illustrate that physically frail adults with HF are sicker in regards to functional status, serum sodium levels, cognitive function, and projected survival. It is not surprising that all of the physically frail adults with HF had either Class III or IV functional classification. The inability to rise from a chair and walk down the hall, much less engage in modest levels of physical activity, is characteristic of impaired function in HF. Additionally, the finding that those with physical frailty had worse cognitive function in the presence of lower sodium indicates that the presence of physical frailty may be a signal of advancing illness in HF. Impaired cognitive function is often linked with frailty broadly (Canevelli, Cesari, & van Kan, 2014; Halil, Cemal Kizilarslanoglu, Emin Kuyumcu, Yesil, & Cruz Jentoft, 2014). Along with other studies in HF (Cacciatore et al., 2005; Jha et al., 2016), there is strong evidence that cognitive function is significantly worse among those with physical frailty in HF. Finally, the significant difference in projected survival is in line with other studies that have demonstrated worse survival in adults with HF who are also frail (Cacciatore et al., 2005; Jha et al., 2016; Lupon et al., 2008).

This was the first study to comprehensively examine the relationship between physical frailty and invasive hemodynamics among adults with HF. We found that

physically frail adults with HF had higher pulmonary artery diastolic pressures, lower mixed venous oxygen, lower cardiac outputs and indexes, and higher heart rates. Our results confirm the findings from the one other study to examine this relationship in HF. Among HF patients referred for heart transplantation, Jha et al. (2016) found significant differences in RAP, wedge pressure, and cardiac index between nonfrail and frail patients using the Frailty Phenotype. The low mixed venous oxygen saturation and cardiac output (i.e. flow) at rest coupled with low peak VO^2 and elevated VE/CO^2 during exercise provides evidence that perhaps physical frailty may, in part, be a manifestation of low-output HF. It also aligns with the cycle of physical frailty, which is conceptualized as decreased physiological reserves resulting from the cumulative decline across physiologic systems (Fried et al., 2001; Fried et al., 2009; Walston & Fried, 1999). Physical frailty is evidence that the body is slowing down for a multitude of reasons (e.g. accelerated aging, poor nutrition, and inactivity); in HF, the body is slowing down because HF, by nature, is an inability of the heart to adequately perfuse the tissues. Thus, the findings from this study provide preliminary evidence of some of the pathophysiologic mechanisms of physical frailty in HF.

The design of this study demonstrates the feasibility of assessing physical frailty in HF and provides evidence for the measurement of physical frailty based on the Frailty Phenotype (Fried et al., 2001). The measures of physical frailty were easily assessed in about 5-7 minutes in both the out-patient and in-patient settings with only minor adaptations required. First, asking patients about changes in their weight over the past year was informative as most patients were able to distinguish weight loss as a result of fluid shifts versus weight loss as a result of loss of muscle and/or fat. Second, we

assessed weakness in both the upper and lower extremities and found that both assessments were feasible in a multitude of settings with only minor adaptations required (e.g. performing the handgrip test in a seated position). This is the first study to incorporate 5-repeat chair stands as a measure of lower extremity weakness as part of an assessment of physical frailty in HF. In the future, we would recommend using 5-repeat chair stands as this was more informative than grip strength, better captured a function that most adults with HF encounter every day (e.g. rising from a chair or toilet), and has been shown to predict falls (Tiedemann et al., 2008). Third, timing gait speed was simple to conduct and easily understood by participants. Fourth, physical exhaustion was assessed using a well-validated tool; however, a specific cut point to identify those with severe physical exhaustion was difficult to ascertain, especially since exhaustion/fatigue is one of the cardinal symptoms in HF. We used a cut point based on the distribution of fatigue in the general population, but future psychometric research on the FACIT-F is needed in HF. Finally, low physical activity was easily captured with one question about exercise, which corresponded to reduced functional capacity as assessed by the DASI.

A number of clinical implications can be drawn based on these results. First, our assessment of physical frailty using the five criteria was feasible and can easily be adapted for both out-patient and in-patient clinical settings. The five criteria together are informative in a comprehensive and additive manner, and we would recommend using all five criteria when assessing physical frailty. Second, the significant differences in several invasive hemodynamic measures imply that the presence of physical frailty in a patient with HF could be an indicator of low-output HF. Finally, based on the collective significant differences in functional classification, objective markers, and cognitive

dysfunction between the physical frailty classes, we have demonstrated that physical frailty is revealing advanced stages of HF.

This study has a few limitations. First, we had a limited sample size, and thus, we may have been underpowered to detect some differences. Second, this was a cross-sectional study, and we are unable to draw conclusions about the temporal nature of physical frailty in HF. Finally, our sample was comprised of mostly young, Non-Hispanic Caucasian adults with moderate to advanced HF who were requiring a RHC for clinical purposes, such as staging for advanced therapies; hence, these results may not be generalizable to all adults with HF.

In addition to the recommendations described above, future research should focus on continuing to test the five criteria of the Frailty Phenotype in HF patients and examine cut points for each of the five criteria in the HF population, especially for weakness, gait speed, and physical exhaustion. The intentionality of weight loss is a point to be considered in future research. In this study, some participants noted intentional weight loss in preparation for bariatric surgery or in an effort to ease shortness of breath. As weight loss is used as a proxy for muscle loss, the application of an additional measure to validate shrinking, such as other anthropometrics or a dual-energy X-ray absorptiometry scan, could be studied. Also, assessing physical activity through the use of accelerometers could be a way to validate the level of physical activity in HF patients. Finally, more research is needed to further explicate the relationship between physical frailty and HF, particularly related to physical frailty as a manifestation of low-output HF. One way to do this, as described by Flint and colleagues (2012), is to distinguish physical frailty that is responsive to mechanical circulatory support (MCS) from physical

frailty that is not responsive to MCS (Flint et al., 2012). Studying physical frailty in patients receiving MCS presents a unique opportunity to dissect the similarities and differences between physical frailty and HF and also better understand the etiological causes of physical frailty in HF.

Conclusions

Our study demonstrates that in a sample of adults with moderate to advanced HF, half are considered physically frail and that physical frailty is associated with worse functional and cognitive status and risk prognostication scores. Importantly, our findings indicate that an assessment of physical frailty is associated with worse invasive hemodynamics and possibly signifies low-output HF. Given the ease of an assessment of physical frailty, we would recommend incorporating physical frailty in the clinical management of HF.

References for Chapter V (see Cumulative References)

Chapter VI

The Role of Physical Frailty in Interpreting Heart Failure Symptoms

Brief Report

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This manuscript replaces a portion of the results section of the traditional dissertation. Ms. Denfeld will be the primary author on this paper; Dr. Lee will be the senior author on this paper. Ms. Denfeld conducted the study and performed the statistical analyses under the supervision of Dr. Lee. Drs. Winters-Stone and Mudd provided critical expertise on frailty and heart failure clinical applicability. This paper will be submitted to European Journal of Cardiovascular Nursing, which is an indexed and peer-reviewed journal with an impact factor of 1.876. The readership for this journal includes healthcare personnel interested in all aspects of cardiovascular care, including research and patient care. This manuscript will be ready to submit immediately following the defense of the dissertation.

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Declaration of Conflicting Interests

None Declared

Key Words (MeSH): Heart Failure; Symptoms; Frail Elderly; Physical Frailty (non-MeSH)

Abstract

Background: Heart failure (HF) is a complex clinical syndrome associated with significant symptom burden; however, our understanding of the relationship between symptoms and physical frailty in HF is limited. **Purpose:** To quantify associations among measures of physical frailty and symptoms among adults with HF. **Methods:** A sample of adults with symptomatic HF were enrolled in a cross-sectional study. Physical frailty was measured according to the five dimensions of the Frailty Phenotype Criteria: shrinking, weakness, slowness, physical exhaustion and low physical activity. Physical symptoms were measured with the HF Somatic Perception Scale-Dyspnea subscale, the Epworth Sleepiness Scale, and the Brief Pain Inventory short form. Affective symptoms were measured with the Patient Health Questionnaire-9 and the Brief Symptom Inventory-Anxiety scale. Comparative statistics and generalized linear modeling were used to quantify associations between physical frailty and symptoms, controlling for Seattle HF Model score. **Results:** The mean age of the sample (n = 50) was 57.5±9.7 years, 66% were male, 92% had New York Heart Association class III/IV HF, and 66% had non-ischemic etiology. Those physically frail had more than twice the level of dyspnea (p = 0.001), 73% worse wake disturbances ($p < 0.001$), and 86% worse depressive symptoms (p = 0.001) compared with those not physically frail. There were no differences in pain or anxiety. **Conclusions:** Physically frail adults with HF have considerably worse dyspnea, wake disturbances, and depression. Targeting physical frailty may help identify and improve physical and affective symptoms in HF.

Introduction

As a common end-point of many cardiovascular conditions such as hypertension and coronary artery disease (Ford et al., 2007; Ong et al., 2007), heart failure (HF) is a highly prevalent and complex clinical syndrome. For the millions of Americans living with HF, the syndrome of HF is highly burdensome symptomatically (Moser et al., 2005; Westlake et al., 2005) and difficult to manage clinically (Yancy et al., 2013). Given the little-to-no association between symptoms in HF and traditional objective markers of heart function (Gottlieb et al., 2009; Guglin et al., 2012; Shah et al., 2002), we are severely hampered in our ability to reduce symptom burden. As a new frontier in HF symptom biology, the relationship between HF and common geriatric syndromes may help us better understand symptoms in HF.

Physical frailty, a common geriatric syndrome, is considered an indicator of biological aging (Fried et al., 2001) and has become a high priority in cardiovascular disease (Afilalo et al., 2014; Gary, 2012). Among adults living with HF, physical frailty has been shown to be highly prevalent and associated with worse clinical- and patient-oriented outcomes (R. Boxer et al., 2008; Cacciatore et al., 2005; Chung et al., 2014; Dominguez-Rodriguez et al., 2015; Dunlay et al., 2014; Gastelurrutia et al., 2014; Jha et al., 2016; Lupon et al., 2008; McNallan, Chamberlain, et al., 2013; Pulignano et al., 2016; Uchmanowicz et al., 2015; Vidán et al., 2014). Furthermore, it is thought that both physical frailty and HF share common pathophysiological mechanisms (R. S. Boxer et al., 2014), and it is logical that the symptoms of HF would mirror physical frailty. A few studies have found that frail adults with HF have worse depression (Jha et al., 2016; McNallan, Chamberlain, et al., 2013), and only one study (Uchmanowicz & Gobbens,

2015) has examined the relationship between frailty and anxiety in HF. No studies, however, have examined the relationship between physical frailty – as assessed by the Frailty Phenotype (Fried et al., 2001) – and both physical and affective symptoms in HF. Accordingly, the purpose of this paper is to quantify associations among measures of physical frailty and symptoms among adults with HF. We hypothesized that those physically frail would report worse physical and affective HF symptoms compared with those considered not physically frail.

Methods

This article addresses a primary aim of a cross-sectional study on physical frailty in HF conducted by a single group of HF investigators from July 2015 to March 2016. The design of the study is described elsewhere (Denfeld et al., 20XX), but key aspects of the study included assessing physical frailty and symptoms in patients scheduled for a right heart catheterization (RHC) procedure. Participants were recruited from a HF practice (out-patient clinic and/or in-patient facilities) at an academic medical center in the Pacific Northwest. Formal inclusion criteria included: age ≥ 21 years of age, ability to read and comprehend 5th grade English, New York Heart Association (NYHA) functional classification II-IV (as determined by the HF cardiologist), and scheduled for a RHC *for clinical purposes only*. Potential participants were excluded if they had had a previous heart transplant or ventricular assist device, had major uncorrected hearing dysfunction, or were otherwise unable to complete the requirements of the study (e.g. life-threatening illness). Written informed consent was obtained by study staff not directly involved in patient care. This study was approved by our Institutional Review Board and conforms to the principles set forth in the Declaration of Helsinski (Rickham, 1964).

Measurement

Data on age, gender, marital status, race, and education were obtained using a socio-demographic questionnaire. Functional status (i.e. NYHA) was assessed by an attending HF cardiologist. Data on history, duration, etiology, and treatment of HF along with clinical characteristics were collected through an in-depth review of the electronic medical record. Comorbid conditions were summarized using the Charlson Comorbidity Index (Charlson et al., 1987). Objective markers of heart function included reports and waveform tracings derived from the RHC procedure and recent echocardiographic and cardiopulmonary exercise test reports. The Seattle HF Model (SHFM) score was calculated based on the model developed by Levy and colleagues (2006) (Levy et al., 2006). In this model, demographic and objective clinical variables and HF treatment are multiplied by respective slope coefficients to generate a single composite risk-prediction score.

Mild cognitive dysfunction. Cognitive function was assessed in-person using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). The MoCA is a cognitive screening tool, designed for use by first-line clinicians, with a cut off score of 26 (i.e. < 26/30) and a sensitivity of 90% and a specificity of 87% to detect mild cognitive dysfunction in adults (Nasreddine et al., 2005). The MoCA has an adjusted algorithm for persons with chronic cardiovascular disease (< 24/30) that is 100% sensitive to detect amnestic mild cognitive dysfunction (McLennan et al., 2011). Thus, a MoCA score of 24 (i.e. < 24/30) was used as the cut-off for sub-clinical mild cognitive dysfunction in this study.

Physical frailty. Using the Frailty Phenotype (Fried et al., 2001), a well-validated

measure in older adults, we measured the five criteria of physical frailty: shrinking, weakness, slowness, physical exhaustion, and low physical activity. To ease practicality and feasibility of assessing physical frailty in a patient population, we selected our measures based on their ability to be assessed in clinical practice. The details of each measure are presented elsewhere (Denfeld et al., 20XX) but are summarized here.

Shrinking was measured by a self-report of unintentional weight loss of >10 pounds over the last year. *Weakness* was measured using 5-repeat chair stands. Participants were assessed and timed on their ability to rise out of a chair 5 times without using their arms. A cutoff of > 12 seconds or inability to rise 5 times was used to define weakness (Tiedemann et al., 2008). *Slowness* was measured by assessing gait speed by clocking the time (in seconds) it took a participant to walk 4 meters (in m/s). We defined slowness as < 0.9 (m/s) based on a review of previous studies (Bennett et al., 2006; Pulignano et al., 2016; Studenski et al., 2011). *Physical exhaustion* was assessed using the 13-item Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F; v.4) (Hjollund et al., 2007; Yellen et al., 1997). Based on the application of the FACIT-F in the general population (Cella et al., 2002), we used a cut point of 17 on the FACIT-F, which corresponds to 2 standard deviations below the mean of the general population, to identify those with severe physical exhaustion. *Level of physical activity* was measured by the participants' response to a single question "During the past week, how much total time did you spend exercising?" Those who reported less than one hour per week were classified as having low physical activity.

After completing the assessments for each of the five criteria, each participant was classified as either meeting (score = 1) or not meeting (score = 0) the criteria. The

scores were totaled (range 0 to 5), and the level of physical frailty was determined as described by the Frailty Phenotype: no criterion = non-frail, 1-2 criteria = pre-frail and ≥ 3 criteria = frail.

Physical symptoms. Physical HF symptoms were measured with the 18-item Heart Failure Somatic Perception Scale (HFSPS) (Jurgens, Lee, et al., 2015). In total, the HFSPS measures perceived severity of both nonspecific symptoms (e.g. fatigue and weight gain) and acute symptoms (e.g. orthopnea and dyspnea) in HF. However, for the purposes of this study and to avoid measurement overlap with the physical frailty measures, the 6-item subscale for dyspnea (HFSPS-D) was used. Scores on the HFSPS-D range from 0 to 30, with higher scores indicating worse perceived dyspnea. Reliability and predictive validity of the HFSPS-D has recently been demonstrated (Jurgens, Lee, et al., 2015). The reliability of the HFSPS-D in our sample was 0.94.

Sleep-wake disturbances were measured with the Epworth Sleepiness Scale (ESS) (Johns, 1991). The ESS asks respondents to rate how likely they would be to doze off in 8 different situations by choosing response options that range from 0 (would never doze) to 3 (high chance). Scores on the ESS range from 0 to 24, with higher scores indicating worse wake disturbances; a cutoff score greater than 10 (i.e. ≥ 11) indicates excessive wake disturbances. The reliability of the ESS in our sample was 0.86.

The Brief Pain Inventory (BPI) Short Form (Cleeland & Ryan, 1994) was used as an assessment of pain intensity and interference. The BPI consists of 4 questions about pain severity (BPI Severity) and 7 questions about pain interference (BPI Interference). Respondents rate their worst, least, average, and current pain intensity and also rate the degree to which pain interferes with domains of functioning on a scale of 0 (no pain or

does not interfere) to 10 (as bad as you could imagine or interferes completely). Scores for each scale are summed and averaged; total scores for both scales range from 0 to 10. The reliability of the BPI Severity and Interference scales in our sample was 0.92 and 0.92, respectively.

Affective symptoms. The 9-Item Patient Health Questionnaire (PHQ9) (Kroenke et al., 2001) was used to assess depression. The PHQ9 scores each of the 9 related DSM-IV criteria for depression. Scores on the PHQ9 range from 0 to 27 with higher scores indicating worse depression; a cutoff score of 10 or higher (i.e. ≥ 10) indicates moderate or greater depression. The PHQ9 is a valid and reliable measure of depression in HF (Hammash et al., 2013). The reliability of the PHQ-9 in our sample was 0.85.

Anxiety was measured using the 6-item Brief Symptom Inventory anxiety scale (BSIANX) (Derogatis & Melisaratos, 1983). Scores on the BSIANX (calculated by adding the ratings and dividing the total by the number of items in the subscale) range from 0 to 4 with higher scores indicating worse anxiety. The BSIANX is a valid and reliable measure of anxiety in HF (Khalil et al., 2011). The reliability of the BSIANX in our sample was 0.84.

Statistical Analysis

Internal consistency of each measure was quantified using Cronbach's alpha. Standard descriptive statistics of frequency, central tendency, and dispersion were used to describe the sample. Because only one participant was considered non-frail, we combined non-frail and pre-frail into one category, "not physically frail." Two participants did not return surveys, and thus, we were unable to classify physical frailty status for these two participants reducing our physical frailty analysis to $n = 48$. Comparative statistics,

including Student's *t*-, Mann-Whitney *U*, or Fisher exact tests or Pearson χ^2, were used to compare demographic and clinical characteristics and symptoms between those considered physically frail and those not physically frail. We used generalized linear modeling to generate proportional differences in symptoms comparing those with physical frailty to those not physically frail, adjusting for SHFM score. All analyses were performed using Stata/MP version 13MP (StataCorp, College Station, TX).

Results

Sample characteristics are described in **Table 1**. The average age of the total sample enrolled (n = 50) was about 57 years, and the majority were male (66%) and non-Hispanic Caucasian (84%). Most had NYHA Class III or IV (92%) and non-ischemic HF (66%), and most were on evidence-based therapies, including beta-blockers (70%) and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (78%). At the time of enrollment and assessment of physical frailty, 35 (70%) participants were out-patient status. Half of the participants were physically frail (n = 24) and nearly the rest of the sample were considered pre-frail (n = 23). Those physically frail had significantly worse one-year projected survival and peak VO^2 and had significantly higher proportions of NYHA Class IV functional classification and mild cognitive dysfunction than those not physically frail.

Table 1: Characteristics of the sample and by level of physical frailty

	M±SD, N (%), or Median [IQR]			
	Total (*n* = 50)	Not Physically Frail (*n* = 24)†	Physically Frail (*n* = 24)	*p* value*
Patient Characteristics:				
Age (years)	57.5±9.7	55.6±11.3	60.1±6.4	0.10
Male	33 (66.0%)	18 (75.0%)	14 (58.3%)	0.22
Non-Hispanic Caucasian	42 (84.0%)	22 (91.7%)	18 (75.0%)	0.25
Education level				0.07
High school or less	18 (37.5%)	5 (20.8%)	13 (54.2%)	
>High school but < college	21 (43.8%)	13 (54.2%)	8 (33.3%)	
College degree	9 (18.8%)	6 (25.0%)	3 (12.5%)	
Charlson Comorbidity Index (weighted)	2.3±1.2	2.1±1.2	2.4±1.2	0.47
Atrial Fibrillation	26 (52%)	14 (58.3%)	11 (45.8%)	0.39
Stage 3 Chronic Kidney Disease	10 (20.0%)	3 (12.5%)	6 (25.0%)	0.46
Out-patient (versus in-patient) at enrollment	35 (70%)	19 (79.2%)	14 (58.3%)	0.12
General Heart Failure Characteristics:				
Time with Heart Failure (years)	8.2 [2.4-14.8]	8.7 [4.4-15.5]	8.0 [1.0-13.5]	0.19
NYHA Functional Class				0.01
Class II	4 (8.0%)	4 (16.7%)	0 (0.0%)	
Class III	34 (68.0%)	18 (75.0%)	15 (62.5%)	
Class IV	12 (24.0%)	2 (8.3%)	9 (37.5%)	
Non-ischemic Etiology	33 (66.0%)	18 (75.0%)	14 (58.3%)	0.22
Prescribed a β-blocker	35 (70.0%)	19 (79.2%)	15 (62.5%)	0.20
Prescribed an ACE-I or ARB	39 (78.0%)	20 (83.3%)	18 (75.0%)	0.72
Left ventricular ejection fraction (%)	24.6±9.1	25.4±6.9	23.3±10.7	0.43
Peak VO_2 (mL/min/kg)	15.3±3.5	16.2±3.7	13.6±2.8	0.05

SHFM Score	2.6±0.9	2.2±0.8	2.9±1.0	0.01
SHFM projected one year survival (%)	55.7±25.3	64.7±19.1	46.7±27.6	0.01
Mild cognitive dysfunction (MoCA < 24)	17 (34.0%)	2 (8.3%)	14 (58.3%)	<0.001

†Not physically frail includes both non-frail (*n* = 1) and pre-frail (*n* = 23)
**p* values comparing physically frail versus not physically frail
Abbreviations: ACE-I, Angiotensin Converting Enzyme-Inhibitor; ARB, Angiotensin Receptor Blocker; BPI, Brief Pain Inventory; IQR, interquartile range; M, mean; MoCA, Montreal Cognitive Assessment; NYHA, New York Heart Association; SD, standard deviation; SHFM, Seattle Heart Failure Model;

Table 2: Symptom characteristics of the sample and by level of physical frailty

	M±SD or N (%)			
	Total (*n* = 50)	Not Physically Frail (*n* = 24)†	Physically Frail (*n* = 24)	*p* value*
Symptomatology:				
Dyspnea (HFSPS-D; 0-30)	12.2±9.0	7.7±5.8	16.7±9.5	<0.001
Pain severity (BPI; 0-10)	3.0±2.3	2.7±1.9	3.4±2.6	0.28
Pain interference (BPI; 0-10)	3.6±2.7	3.1±2.5	4.0±2.8	0.24
Excessive wake disturbances (ESS score > 10)	19 (39.6%)	3 (12.5%)	16 (66.7%)	<0.001
Moderate depression (PHQ9 score ≥ 10)	25 (52.1%)	7 (29.2%)	18 (75.0%)	<0.001
Anxiety (BSI; 0-4)	0.76±0.75	0.61±0.64	0.91±0.83	0.16

†Not physically frail includes both non-frail (*n* = 1) and pre-frail (*n* = 23)
**p* values comparing physically frail versus not physically frail
Abbreviations: BPI, Brief Pain Inventory; BSI, Brief Symptom Inventory; ESS, Epworth Sleepiness Scale; HFSPS-D, Heart Failure Somatic Perception Scale-Dyspnea Subscale; IQR, interquartile range; M, mean; PHQ9, Patient Health Questionnaire; SD, standard deviation.

Physical symptoms. Those physically frail had significantly worse dyspnea and had higher rates of excessive wake disturbances compared with those not physically frail (**Table 2**). There was no significant difference in reported pain severity or interference. After adjusting for SHFM score, those physically frail were more than two times as dyspneic and had 73% worse wake disturbance symptoms than those not physically frail (**Table 3**).

Affective symptoms. Those physically frail had significantly higher rates of moderate or greater depression compared with those not physically frail (**Table 2**). There was no significant difference in reported anxiety. After adjusting for SHFM score, those physically frail had 86% more depressive symptoms than those not physically frail (**Table 3**).

Table 3: Proportional differences in physical and affective symptoms among physically frail adults with heart failure

	% difference (%±SE)	*p* value
HFSPS-D scores†	128.6±55.1	0.001
ESS scores†	72.8±25.8	<0.001
PHQ9 scores†	85.9±36.1	0.001

† after adjusting for Seattle Heart Failure Model score
Abbreviations: CI, confidence interval; ESS, Epworth Sleepiness Scale; HFSPS-D, Heart Failure Somatic Perception Scale-Dyspnea Subscale; PHQ9, Patient Health Questionnaire

Discussion

The purpose of this study was to quantify associations among measures of physical frailty and symptoms among adults with HF. The main finding from this study is that those physically frail have significantly worse dyspnea, wake disturbances, and depression compared with those not physically frail. These results demonstrate that 1) physical frailty tells us more about symptoms in HF than traditional risk prognostication scores, and 2) a phenotype of physical frailty mirrors some of the burdensome symptoms

experienced by adults with HF.

Since our understanding of the biological underpinnings of symptoms in HF is limited, our finding of a significant association between physical frailty and both physical and affective symptoms may help elucidate the pathophysiological mechanisms giving rise to symptoms in HF. The general disconnect between symptoms and objective markers of heart function (C. S. Lee, Hiatt, Denfeld, Mudd, et al., 2015) indicates symptoms are not necessarily a function of traditional invasive hemodynamic or echocardiographic assessments. Even though the biological mechanisms of physical frailty continue to be unraveled (Fedarko, 2011), the most common areas of dysregulation involve the endocrine, immune, and hormonal symptoms (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013). Hence, symptoms in HF may be manifestations of dysregulation in these systems rather than as a purely hemodynamic dysregulation. In turn, a better understanding of the pathophysiological mechanisms of symptoms in HF may help us better understand the mechanisms underlying physical frailty.

The results from this study confirm that physical frailty and symptoms mirror each other in HF. In essence, those adults with HF who have some combination of shrinking, weakness, slowness, physical exhaustion, and/or low physical activity have significantly worse dyspnea, wake disturbances, and depression. Even though others have provided evidence that frail adults with HF have worse depression (Jha et al., 2016; McNallan, Chamberlain, et al., 2013), this is the first known study to examine both physical and affective symptoms in HF. Furthermore, towards a strength of this study, we chose measures that would minimize overlap between symptoms and physical frailty as opposed to studies that have used depression questionnaires to assess physical

exhaustion. Our intent was to capture *physical frailty* that is distinct from, but also complementary to, common symptoms in HF. Clinically speaking, these findings indicate that a simple physical frailty assessment, which takes about 5-7 minutes and can easily be run by trained personnel such as a medical assistant, could provide much needed interpretation into both physical and affective symptoms experienced by patients with HF. And vice versa, worse physical and affective symptoms could be a signal that patients are concurrently physically frail. Finally, the mirroring of physical frailty and symptoms in HF demonstrates that dyspnea, wake disturbances, and depression may be part of the etiology and manifestation of physical frailty in HF.

The limitations of this study should be noted. This was a cross-sectional study that was not designed to address causal mechanisms, and thus, we were only able to report associations and not examine causal relationships. Additionally, this was a small, young, racially homogenous, and predominantly non-ischemic sample, and the results may not be generalizable to the entire HF population at large. Finally, all but one of the participants were physically frail or pre-frail (most likely due to the more advanced stage of these patients (i.e. they all required a RHC)), and thus, we did not fully capture the spectrum of frailty as originally designed by Fried and colleagues (Fried et al., 2001). The lack of a non-frail group as a comparison group limits our findings, but also highlights the significant intersection between physical frailty and HF, as previously explicated (Afilalo et al., 2014; R. S. Boxer et al., 2014) (Denfeld et al, Ch. IV & V).

There is a need for future research in this area. First, longitudinal research is needed to understand how physical frailty changes over time among adults with HF and how this change tracks with symptoms. Second, targeted interventions are needed to

address physical frailty in HF that may, in turn, help improve symptoms in HF. Finally, the pathophysiological mechanisms underlying the parallel relationship between physical frailty and symptoms in HF have yet to be teased apart.

Conclusions

In summary, adults with HF who are considered physically frail have significantly and clinically worse dyspnea, wake disturbances, and depression than adults with HF who are not physically frail. Using measures based the Frailty Phenotype, these findings demonstrate an assessment of physical frailty tells us more about symptoms experienced by adults with HF than other traditional measures such as objective markers of heart function. Therefore, incorporating an assessment of physical frailty may help clinicians in interpreting and targeting the burdensome symptoms in HF.

References for Chapter VI (See Cumulative References)

Chapter VII

Discussion, Summary, & Implications

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Discussion

Heart failure (HF) is a growing problem in the United States and worldwide (Mozaffarian et al., 2016). The epidemic of HF will be further exacerbated by an aging population (Jencks et al., 2009; Najafi et al., 2009) and improved treatments for common antecedents of HF such as coronary artery disease (Ford et al., 2007) and hypertension (Ong et al., 2007). Unfortunately for both the patient and healthcare system, the syndrome of HF confers enormous burden as physical and affective symptoms are the main drivers of quality of life (Zambroski et al., 2005) and prompt patients to seek care and hospitalization (Moser et al., 2011). Given the importance of symptoms in HF, however, we have a limited understanding of the biological mechanisms underpinning symptoms in HF, including the role of accelerated biological aging.

Accordingly, the purpose of this program of research was to broadly elucidate the biological mechanisms underpinning symptoms among adults with HF and to particularly understand the role of accelerated biological aging, including metabolic senescence and physical frailty, in HF symptom biology. Cumulatively, this program of research has made incremental and meaningful contributions to the bodies of literature on HF symptom biology and accelerated biological aging in HF, particularly the intersection between physical frailty and HF. Hence, this discussion presents a summary of the findings, along with an integration with previous research, centered on three areas: 1) HF symptom biology, 2) accelerated biological aging in HF, and 3) physical frailty in HF. Following this, in the section on summary and implications, we summarize the program of research, describe theoretical, methodological, and clinical implications, and suggest directions for future research in the above three areas.

Heart Failure Symptom Biology

The first area to which this program of research has contributed is "HF symptom biology," a key line of inquiry our group has been instrumental in forging (C. S. Lee, Hiatt, Denfeld, Chien, et al., 2015; C. S. Lee, Hiatt, Denfeld, Mudd, et al., 2015). In Chapter II, we provided evidence that two objective markers of heart function were significantly associated with both physical symptoms and anxiety in HF. Greater ventricular dilation and higher right-sided filling pressures were associated with both worse physical symptoms and anxiety, providing evidence of potential cardiac biomechanical underpinnings of symptoms that we have coined previously as "symptom biomechanics" (Denfeld et al., 2015). Despite explaining a significant amount of variance in these symptoms based on cardiac biomechanics, there was still a large amount of unexplained variance, indicating that additional lines of inquiry were needed in HF symptom biology, such as those related to accelerated biological aging.

In Chapter III, we found that one indicator of accelerated biological aging, metabolic senescence (as measured by β-adrenergic receptor kinase-1 (βARK1)), was more explanatory of physical symptoms than a common prognostication model (i.e. the Seattle HF Model (SHFM)). Simply put, our findings showed it is more about differences in βARK1 than differences in SHFM scores in explaining the spectrum of physical symptoms in HF. We also found βARK1 was independently and significantly related to physical symptoms in HF, and together with other clinical characteristics, explained a significant amount of variance in physical symptoms. Clinically speaking, this indicates if we want to understand physical symptoms in HF, we have to look beyond the current list of clinical parameters included in prognostication models and/or other traditional

clinical characteristics and consider alternative pathophysiological mechanisms such as metabolic senescence. Thus, we provided additional evidence of potential cardiac biochemical changes underpinning symptoms in HF that our group has coined previously as “symptom biochemistry” (C. S. Lee, Mudd, et al., 2014).

In Chapter VI, we demonstrated those physically frail had significantly worse physical and affective symptoms compared with those not physically frail. In summary, those physically frail had over two times worse dyspnea, 73% worse wake disturbances, and 86% worse depression. These findings indicate symptoms in HF are paralleling or mirroring physical frailty, providing evidence that both symptoms and physical frailty may have common underlying pathophysiological mechanisms that give rise to them concurrently. Thus, given these significant associations, we have provided evidence of potential biodynamics as underpinning symptoms in HF, what our group is coining as “symptom biodynamics.” Together, these three studies have provided preliminary evidence to support new lines of inquiry into symptom biomechanics, symptom biochemistry, and symptom biodynamics in HF.

Improvements to heart failure symptom biology research. Across these chapters, we have made improvements to the growing research on HF symptom biology. First, since symptoms in HF have been measured in a myriad of ways in the literature, we selected symptom measures that would capture the patient’s symptoms in a robust manner. In contrast to previous studies (Bhardwaj et al., 2012; Guglin et al., 2012; Rector et al., 2006; Shah et al., 2002), we did not use providers’ subjective assessment of symptoms or quality of life/health status measures as proxies for a patient’s assessment of their symptoms. Instead, inventories of symptoms were carefully selected in order to

capture the spectrum of both physical and affective symptoms in HF and to avoid measurement overlap, particularly with the physical frailty measures. Furthermore, based on the theory framing this study (Lenz et al., 1997), we considered physical and affective symptoms as occurring concurrently (C. S. Lee, Gelow, et al., 2014). As such, we assessed symptoms in both domains using general measures well-validated in the HF population and well-validated measures specific to the HF population.

Second, in order to avoid time lapses between objective and subjective measures, we performed assessments and administered surveys within a short time frame. Given that symptoms can fluctuate (Moser et al., 2011; Webel et al., 2007), particularly in response to treatment, we carefully designed the studies so that measures were captured at approximately the same time, particularly for the study on physical frailty in HF. This allowed us to generate a "snapshot" of symptoms in relation to objective markers that potentially signal underlying pathophysiological mechanisms.

Further areas for refinement. Despite these strengths and significant findings, we also found a few results that will require further research. First, we found that higher flow (as measured by the cardiac index) and better renal function (as measured by the blood urea nitrogen-creatinine ratio) were associated with worse physical symptoms in Chapter II; and in Chapter III, we noted that women and those with lower right atrial filling pressures had worse physical symptoms. Non-intuitive findings in the symptom biology in HF literature is a common theme as others (Guglin et al., 2012) have found non-intuitive relationships between renal function and physical symptoms (i.e. better renal function = worse physical symptom) and right atrial size and physical symptoms (i.e. decreased right atrial size = worse physical symptoms). Because we used a global

summary score of physical symptoms for both Chapters II and III, we were unable to look at patterns of symptoms that are perhaps different in women versus men or different in those attributed to left-sided versus right-sided HF symptoms. Hence, the lack of specificity and lack of patterns of symptoms may explain our observed findings. Our group has begun examining HF symptom biology based on either known groups, such as gender (C. S. Lee, Hiatt, Denfeld, Chien, et al., 2015), or newly identified groups based on symptom-hemodynamic profile (C. S. Lee, Hiatt, Denfeld, Mudd, et al., 2015). Future research is needed to understand these nuanced differences, especially considering the heterogeneous and complex nature of HF.

The need for heart failure symptom biology research. In our quest to identify the biological underpinnings of symptoms, we must ask ourselves "why is this knowledge needed?" If we already have a variable to assess (e.g. "is the patient dyspneic?"), is there a need for an objective marker as a surrogate to assess each particular symptom? And by knowing this information, how does it benefit the patient? The short answer to these questions is that because HF is a complex, burdensome, and highly variable syndrome, the more knowledge we have, the better. As Jurgens (2016) explained in the associated commentary to the manuscript in Chapter II: 1) it is necessary to understand symptoms because they are the driving forces behind quality of life, self-care behaviors, and hospitalizations, and they predict survival (Ekman et al., 2005; C. S. Lee, Gelow, et al., 2014); 2) reported symptoms vary considerably between and within patients depending on many factors so it is necessary to adequately capture symptoms in relation to physiological changes; and 3) the pathophysiology of HF is complex (Jurgens, 2016). To add to this, understanding symptom biology in HF also validates a patient's

symptoms, it pinpoints pathophysiological processes to target in an effort to improve symptoms, and it provides additive information for the clinician, potentially alerting providers of worsening symptom burden.

Summary. Collectively, we have demonstrated that multiple markers of pathophysiological mechanisms in HF, some commonly used and some novel, are related to physical and affective symptoms in HF. Given that the world's literature preceding this program of research has shown little-to-no association between traditional markers of heart function and HF symptoms (Guglin et al., 2012; Rector et al., 2006; Shah et al., 2002), these findings have made meaningful and incremental steps towards a better understanding of HF symptom biology and development of targeted interventions to ameliorate burdensome symptoms in HF. However, there is much more to be learned and more objective markers to study in order to advance our understanding of HF symptom biology.

Accelerated Biological Aging in Heart Failure

The second area to which this program of research has contributed is accelerated biological aging in HF. Broadly speaking, accelerated biological aging is known to occur irrespective of chronological age (Kirkwood, 2005) and is particularly evident in cardiovascular disease (Samani & Van Der Harst, 2008). Both metabolic senescence and physical frailty are considered indicators of accelerated biological aging: metabolic senescence identifies, in part, the cellular phenotype and physical frailty identifies, in part, the clinical phenotype of accelerated biological aging.

In Chapter III, we showed that metabolic senescence, as measured by βARK1, could play an important role in the clinical management of HF through its association

with physical symptoms. Metabolic senescence involves premature aging at a molecular and cellular level in relation to basic metabolic functions such as adrenergic response. Although metabolic senescence, or altered adrenergic response, has been studied before broadly (Rockman, Koch, & Lefkowitz, 2002) and in relation to βARK1 (Huang et al., 2014; Iaccarino et al., 2005) in HF, the relationship between metabolic senescence and symptoms in HF has not been studied to date. Thus, the results from this study (as described above in detail) advance the science by demonstrating the clinical relevance of accelerated biological aging in HF.

In Chapter IV, in addition to generating a precise estimate of the prevalence of frailty in HF, we demonstrated that there is a distinct U-shaped relationship between age and the prevalence of frailty in HF, indicating that those studies who had relatively "younger" samples (about age 65) and those who had "older" samples (about age 80+) had higher prevalence rates of frailty in HF. This relationship may, in part, be explained by both the disease-contribution of HF on the likelihood of being frail (the younger group) and the contribution of chronological age on the likelihood of being frail (the older group). Even though very few studies had samples with average ages below age 65, we can extrapolate the non-linear relationship to younger adults with HF (those in their 20s, 30s, 40s, and 50s) and postulate that frailty is likely to manifest at chronologically younger ages. As mentioned by previous reviews of frailty in HF (Jha et al., 2015), the high prevalence of frailty in the younger patients indicates that we should consider frailty at all ages, rather than as a strict geriatric syndrome. Hence, frailty, as an indicator of accelerated biological aging, can present at any point in the lifespan, and in particular, young, frail patients with HF are an important subset to recognize.

In Chapter V, we showed that physical frailty is associated with more advanced stages of HF. Physical frailty was associated with worse New York Heart Association (NYHA) functional classification, lower sodium levels, lower peak oxygen consumption during exercise, and mild cognitive dysfunction. Furthermore, those physically frail had worse flow and worse mixed venous oxygen saturation by right heart catheterization than those not physically frail, indicating that physical frailty is identifying those with low-output HF. This possibly indicates that physical frailty is manifesting in advanced HF patients when they surpass the threshold for physiological decline as a result of reduced flow and oxygen delivery to the peripheral tissues. It is also important to note that these findings were irrespective of chronological age, providing evidence of accelerated biological aging in HF across the lifespan.

Chronological versus biological age. Old age is typically defined as greater than or equal to 65 years. This cutoff is based on socioeconomic policies in which old age is reached when someone is eligible for retirement or pension plans ((WHO)). Old age beginning at age 65 years, however, assumes that one has followed a “normal” aging trajectory biologically-, physiologically-, and clinically-speaking. For adults with HF, aging often takes place at an accelerated rate (L. S. M. Wong et al., 2010), which in turn accelerates the point of inability to actively contribute to daily life; as such, it is increasingly important to identify one’s biological age. Based on the findings from our studies, we can start to assemble a profile of biological age for individual HF patients.

Accelerated biological aging has traditionally been associated with replicative senescence (e.g. telomere length and telomerase) (de Jesus & Blasco, 2012; L. S. Wong, de Boer, Samani, van Veldhuisen, & van der Harst, 2008) and inflammation (Franceschi

& Campisi, 2014). A profile of accelerated biological aging in HF, however, must look beyond these traditional biomarkers. Metabolic senescence, as measured by βARK1, is more closely associated with myocardial stretch, as measured by N-terminal pro-B-type natriuretic peptide ($r = 0.41$, $p = 0.001$) than with replicative senescence, as measured by telomerase ($r = 0.19$, $p = 1.00$), or inflammation, as measured by soluble tumor necrosis factor alpha receptor 1 ($r = 0.18$, $p = 1.00$). Furthermore, metabolic senescence is reflected in other markers such as adiponectin ($r = 0.33$, $p = 0.03$), indicating that if we want to start understanding accelerated biological aging in HF, we must look beyond the traditional biomarkers. Although a few markers of senescence have been identified (de Jesus & Blasco, 2012), and we have proposed additional markers, one single marker cannot be used to quantify senescence; hence, moving forward, a multimarker strategy will be necessary in order to assess biological age, which may also include clinical phenotypes such as physical frailty.

Summary. Taken together, the findings across these manuscripts show that two indicators of accelerated biological aging – metabolic senescence and physical frailty – are manifesting in HF. Beyond the challenges presented to us as a result of higher prevalence of HF among chronologically older adults generally (Jugdutt, 2010), there is demonstrated accelerated biological aging in HF. Based on our results, we can draw a few conclusions: 1) accelerated biological aging, particularly among younger adults with HF, is important to recognize, 2) coupled with other traditional indicators of advanced HF (Fang et al., 2015), the presence of metabolic senescence and/or physical frailty should alert clinicians to possible impending advanced stages of HF, and 3) more work is needed ascertain which additional markers comprise accelerated biological aging in HF.

Physical Frailty in Heart Failure

The third area this program of research has contributed to is physical frailty in HF. Beyond the contributions described above in terms of understanding physical frailty in HF as an indicator of accelerated biological aging, this presented body of work advances the field of physical frailty in HF through a synthesis of the literature, a robust application of physical frailty measures specifically in HF, and recommendations for future work on physical frailty in HF.

In Chapter IV, based on a meta-analysis of 16 studies involving 4535 adults with HF, we showed that about one in three adults with HF are classified as frail. In this paper, we summarized the state of the science of frailty in HF, highlighting the areas of weakness and offering suggestions for improvement and advancement of the field. The significant heterogeneity in relation to the myriad of measures used to assess frailty, or physical frailty, in HF underscores the point that we and others make in regards to the lack of cohesion in the frailty literature (Afilalo et al., 2014; Morley et al., 2013).

In Chapters V and VI, we conducted a study to quantify the prevalence of frailty in a sample of 50 adults with moderate to advanced HF and to quantify the relationships between physical frailty and both objective markers of heart function and HF symptoms. Ours was the first known study to quantify these important relationships as a step towards understanding the intersection of physical frailty and HF. As described above, we found that physical frailty is identifying those adults with low-output and possible advanced stages of HF, functionally, hemodynamically, cognitively, and symptomatically.

The state of frailty in heart failure literature. At this time, the literature on frailty in HF is small but exponentially growing. The work on frailty in HF preceding this

body of work, however, has been marked by high variability and heterogeneity in both the definition and measurement of frailty. To broadly summarize the disarray of the frailty literature: 1) there are upwards of 20 measures of frailty, 2) measurement overlap is a common theme (e.g. many studies, including the original Frailty Phenotype, have used depression questionnaires to assess physical exhaustion), and 3) there is no consensus regarding inclusion of mood disorders and cognitive function in a definition of frailty (Bergman et al., 2007; Halil et al., 2014). This has, unfortunately, made it difficult to advance the science of frailty in HF. Because of the sheer commitment to addressing frailty in HF, however, publications on frailty in HF continue to emerge, albeit with the same multitude of frailty measures. As such, our zeal for frailty in HF is, in fact, hindering our ability to truly advance the science.

Our study, however, will hopefully move this science forward as we selected comprehensive and clinically appropriate measures to capture physical frailty in HF. Using the Frailty Phenotype as a framework, we identified measures that would capture how much weight the person lost, how weak they were, how slow they were, how physically exhausted they were, and how much they participate in physical activity. What this paper brings to the science is a well-researched and clinically applicable assessment of physical frailty that can be used in future studies on frailty in HF. Additionally, this study revealed two unique aspects of physical frailty in HF: 1) physical frailty is reflecting low-output HF, and 2) physical frailty and symptom presentations mirror each other.

Physical frailty as a result of heart failure and/or aging. There is discussion in the literature surrounding the differentiation of frailty related to the condition of HF and

frailty related simply to the aging process (Goldwater & Pinney, 2015). Physical frailty and HF share common risk factors such as loss of muscle mass, reduced endurance, and low physical activity. Thus, it has been difficult to unravel the mechanisms that give rise to physical frailty in HF and explicitly define how this is similar to or different from the independent progression of HF.

What we have demonstrated in this body of work is that physical frailty is reflecting low-output HF and is also a manifestation of advancing stages of HF in terms of poor hemodynamics at rest and during exercise, worse functional status, cognitive dysfunction, and worsening symptoms. What this means is that broadly speaking, physical frailty may be improved through common HF interventions that improve flow, such as mechanical circulatory support, including left ventricular assist devices (LVAD). As has been well-described by Flint and colleagues, LVADs offer a unique opportunity to dissect physical frailty that is HF-related from physical frailty that is related to other causes (Flint et al., 2012). Although our study of 50 adults with HF was not powered to look at differences within the physical frailty group, we suspect that the overlap between physical frailty and HF is more prominent for some than others. For example, one patient may have physical frailty that is almost entirely driven by HF. As such, interventions to improve HF, such as LVAD, would theoretically reverse most of the physical frailty. On the other hand, another patient may have physical frailty that is primarily driven by other causes such as comorbidities or aging. Hence, interventions would need to target these other causes and not just low-output HF.

What this also means is that exercise and nutrition interventions, which are commonly used to target physical frailty, may only work for a subset of HF patients or

may only work after mitigating the effects of low-output HF. Furthermore, the findings from this study may help explain why exercise trials, such as HF-ACTION (O'Connor et al., 2009), have had only modest results, indicating we may have to treat the low-output HF first before using exercise. Thus, at this time, we have made a small contribution towards understanding how physical frailty develops in the HF condition, and more importantly, identified targets to ameliorate physical frailty in HF.

Summary. Taken together, through a robust systematic review and meta-analysis and a well-designed cross-sectional study centered on physical frailty in HF, this program of research significantly advances the science of physical frailty in HF. Given the high prevalence of physical frailty in HF as identified in both the meta-analysis and our study and the significant relationships of physical frailty with hemodynamics and symptoms, it is clear that physical frailty in HF is not to be ignored. Although more research is needed, we have provided preliminary evidence of physical frailty as an important indicator of worsening HF.

Summary and Implications

In summary, the care of adults with HF is complex, complicated, and burdensome to both the patient and to the healthcare system. Inherently, the syndrome of HF is heterogeneous, and because of this, we as researchers are charged with a difficult task of understanding the variability and root causes of symptoms in HF. The collective body of work set forth in this program of research addressed and critically examined HF symptom biology and the role of accelerated biological aging, including metabolic senescence and physical frailty, in HF (**Figure 1**). First, the study on the influence of cardiac biomechanics on physical and affective symptoms was a preliminary step towards our

understanding of the relationship between objective markers of heart function and symptoms in HF. Second, we provided preliminary evidence of the role of metabolic senescence in explaining physical symptoms in HF. Third, the systematic review and meta-analysis of frailty in HF revealed that frailty is highly prevalent in HF and that there is a U-shaped relationship between age and prevalence of frailty in HF. Fourth, based on a cross-sectional study on physical frailty in HF, we provided evidence of significant associations between physical frailty and several invasive hemodynamic measures. Fifth, we demonstrated that those with physical frailty have significantly worse physical and affective symptoms. Cumulatively, this program of research has made several significant advances in symptom biology and role of accelerated biological aging in HF and, in turn, enhanced our clinical management strategies for one of the most complex conditions we currently face in healthcare.

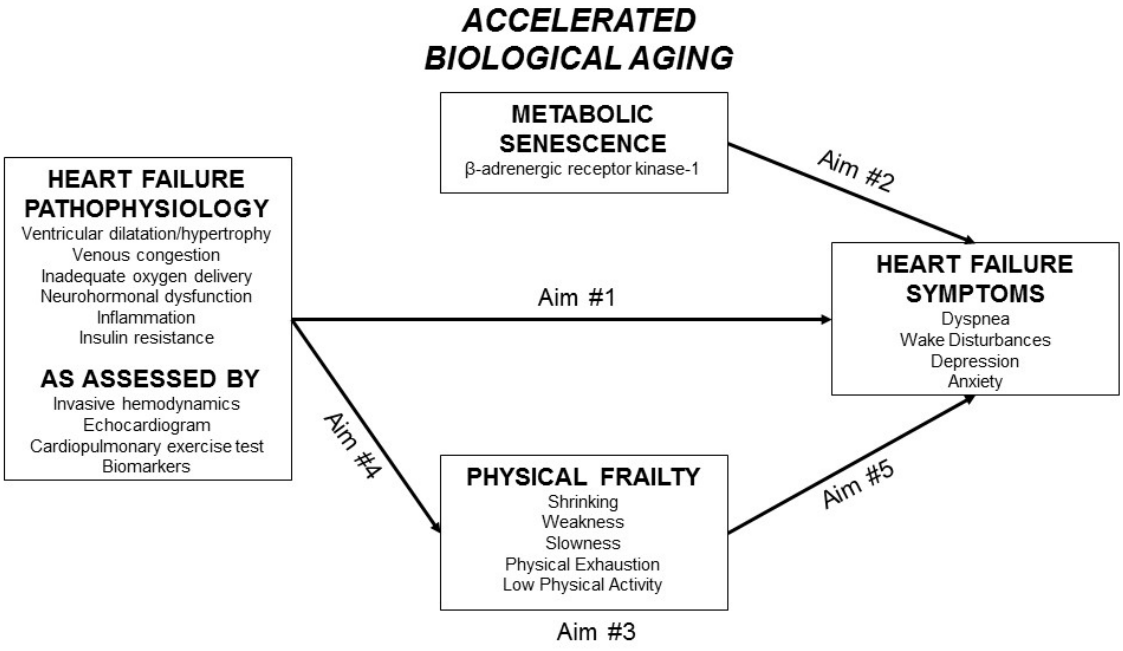

Figure 1. Program of research framework for understanding symptom biology and accelerated biological aging in heart failure.

Implications

Theoretical Implications. The cumulative results from this program of research support prior theories and frameworks. In particular, this work supports and adds to Lenz's Theory of Unpleasant Symptoms (Lenz et al., 1997) lending evidence of multiple physiological factors as contributors to unpleasant symptoms in a chronic illness. Specifically, our work in HF symptom biology provided evidence of hemodynamic and echocardiographic assessment data, metabolic senescence, and physical frailty as physiologic factors related to symptoms in HF. Additionally, by incorporating multiple symptoms from both physical and affective domains, we have supported one of the main tenets of the theory by demonstrating symptoms in chronic illness must be considered in combination. Finally, our assessment of physical frailty and the association of physical frailty with invasive hemodynamics shows how physiological factors can affect performance (e.g. rising out of a chair and walking down the hallway).

Methodological Implications. This body of work builds on a well-validated measure of frailty, the Frailty Phenotype (Fried et al., 2001), by adapting and improving the five measures of the Frailty Phenotype as they are applied to adults with HF. In our assessment of physical frailty, we showed that shrinking (i.e. unintentional weight loss) as a result of loss of muscle and/or fat was, for the most part, distinguishable from weight loss as a result of fluid shifts. Unintentional weight loss, as originally described by Fried et al. (2001), is used as a proxy to assess shrinking or wasting among frail adults. An issue in HF specifically is how to distinguish various iterations of weight loss: intentional weight loss due to diet/exercise, intentional weight loss due to increase in diuretic usage, or unintentional weight loss due to inadequate nutrition and/or loss of muscle mass. One

question moving forward is to ascertain if intentional weight loss due to diet/exercise is also reflective of shrinking in HF. Additionally, since unintentional weight loss was not significantly different between the physical frailty levels, removal of this criteria may be necessary as others have done (Ensrud et al., 2009).

We also showed that 5-repeat chair stands were a more informative measure of weakness than grip strength. Grip strength is one of the most common measures of weakness in studies of frailty in HF and is sometimes used as a sole indicator of frailty in HF (Chung et al., 2014). One of the problems with using grip strength is the multitude of cut points from which to define weakness. Moreover, and more importantly, we found that grip strength was a poor surrogate of strength (or weakness) as many participants could maximally squeeze a hand-grip dynamometer above and beyond the cut point but simply could not rise from chair without using their arms. By measuring ability to rise from a chair, we more adequately captured a function that adults – with or without HF – perform every day (e.g. rise from a chair or toilet). Furthermore, we used a well-known functional mobility test that predicts falls in older adults (Tiedemann et al., 2008). Grip strength, however, was moderately correlated with the 5-repeat chair stand time (r = -0.34, p = 0.03), indicating both measures are capturing some degree of weakness from both upper and lower extremities (of note, this excludes those who were unable to rise out of a chair). But, given the lack of a strong correlation, no significant difference in grip strength between the two physical frailty levels (presented in Chapter V), and limited functional interpretability, we recommend using 5-repeat chair stands as a measure of weakness in the future.

Finally, the measurement of physical exhaustion and low physical activity was a

challenge in relation to specific cut points to define both of these criteria. Both physical exhaustion and low physical activity are common findings in HF. Fatigue is a cardinal symptom and many adults with HF reduce their level of physical activity, in part, due to fatigue and shortness of breath. Deriving HF-specific cut points is not a valid approach because it would skew the results and would make comparisons across populations difficult. Thus, we chose to use a distribution among the general population to define severe physical exhaustion (i.e. less than 2 standard deviations from the mean) and aligned our physical activity criteria with approximations in expended energy per week as originally specified in the Frailty Phenotype (Fried et al., 2001).

Clinical Implications. Finally, this program of research has provided evidence to support clinical practice. Our collective findings from our studies on the biological underpinnings of symptoms could inform conversations in clinical settings, especially when eliciting information regarding daily symptom burden. In clinical settings, patients may have a report bias and perhaps a tendency to underreport their symptoms when asked by a provider, but the collective information provided from an assessment of traditional objective markers coupled with physical frailty, and potentially markers of accelerated biological aging in the future, would assist providers in ascertaining symptom burden.

Additionally, one approach to take when assessing a patient with HF is to consider multiple angles: the symptoms, the objective markers of heart function, and the physical frailty measures. What is appealing about the physical frailty measures is that they could be considered an intermediary between symptoms and objective markers of heart function. In essence, the physical frailty measures (e.g. chair stands) could adequately capture the symptoms (e.g. shortness of breath after 10 seconds of activity) in

an objective fashion that also reflects invasive hemodynamics.

Strengths. This program of research has a number of strengths. First, as described above, we selected robust measures of symptoms that are either general measures well-validated in the HF population (e.g. the Patient Health Questionnaire-9) or well-validated measures specific to the HF population (e.g. the HF Somatic Perception Scale). Second, we applied measures based on the well-validated Frailty Phenotype to the HF population that would be clinically translatable and capture physical frailty in a comprehensive fashion in this population. Third, we used a variety of statistical approaches, including generalized linear modeling and meta-analytic approaches, as appropriate, to advance the science of HF symptom biology and accelerated aging in HF. Moreover, we presented the data in a manner that would be easily translated in a clinical practice, such as using proportional differences to quantify worse symptomatology among physically frail adults with HF. Finally, this program of research identified areas of research in symptom biology, accelerated biological aging, and physical frailty in HF that had limited evidence to support clinical practice. By targeting these areas for research, we have brought to the forefront recommendations for improving both clinical practice and research among adults with HF.

Limitations. The limitations of this program of research should be noted. First, all analyses were performed on cross-sectional data, and thus, we are unable to draw any conclusions regarding the temporal relationship between the variables studied. At this time, we can only speculate on causal relationships; as such, future longitudinal research is necessary to fully explicate these relationships. Second, with the exception of the meta-analysis, the samples for our analyses (from four studies in total) were drawn from a

population of moderate to advanced HF patients who received care from a single practice at a university-affiliated academic medical center, many of whom were seeking advanced HF therapies. Hence, our findings are limited to this subgroup of HF patients, and this may explain why we had a large percentage of physically frail adults with HF. Finally, the broad literature on frailty is plagued by significant heterogeneity and conceptual and practical inconsistencies in both the definition and measurement of frailty. Hence, the state of the frailty literature at this time complicates a comprehensive literature review and meta-analysis and hinders the consistent application of frailty measures to the HF population. Thus, this program of research made every attempt to begin "cleaning up" the frailty in HF literature specifically by synthesizing the literature and providing the basis for future assessments of physical frailty in HF.

Future Research. Despite the significant and meaningful contributions made by this program of research, there remains a critical need for further research in HF symptom biology and accelerated biological aging in HF. Specific areas of research are outlined in **Table 1** and **Figure 2**. Broadly speaking, more work is needed to address changes in these variables over time, examine multiple markers of accelerated biological aging in one study to understand them as a single process, identify patterns/clusters of these variables in patients with HF based on known groups (e.g. gender) and yet-unidentified profiles, and understand the underlying pathophysiologic mechanisms, especially various facets of the aging process from molecular to cellular to physiological to clinical phenotypes. Additionally, across all future research, more advanced statistical approaches such as latent growth mixture modeling should be used to answer these research questions, as appropriate. Finally, the clinical relevance of the findings should

be considered when designing and conducting all future research.

Table 1: Future Research in Symptom Biology, Accelerated Biological Aging, and Physical Frailty in Heart Failure	
Heart Failure Symptom Biology	• Longitudinal research to examine changes in symptoms and objective markers over time • Relationship between patterns and/or clusters of symptoms and pathophysiologic mechanisms of heart failure • Relationship between other novel biomarkers (i.e. soluble ST2) and symptoms
Accelerated Biological Aging in Heart Failure	• Better understand the role of βARK1 in the pathophysiology of heart failure through comparison with other known markers • Study changes in βARK1 longitudinally in all heart failure patients (NYHA class I to IV) and in those following mechanical circulatory support (e.g. LVAD) • Quantify the predictive value of βARK1 • Identify other markers of accelerated biological aging through proteomics research
Physical Frailty in Heart Failure	• Validate cut points for each criteria • Further refine shrinking criteria through self-report and/or objective measure of loss of lean muscle mass • Further refine assessment of physical activity in heart failure through self-report and/or objective measure of physical activity • Temporal progression of physical frailty in heart failure • Ascertain changes in physical frailty following mechanical circulatory support (e.g. LVAD) • Study other outcomes, such as falls and disability

Abbreviations: βARK1, β-adrenergic receptor kinase-1; LVAD, left ventricular assist device; NYHA, New York Heart Association; ST2, interleukin-1 receptor-like-1 precursor

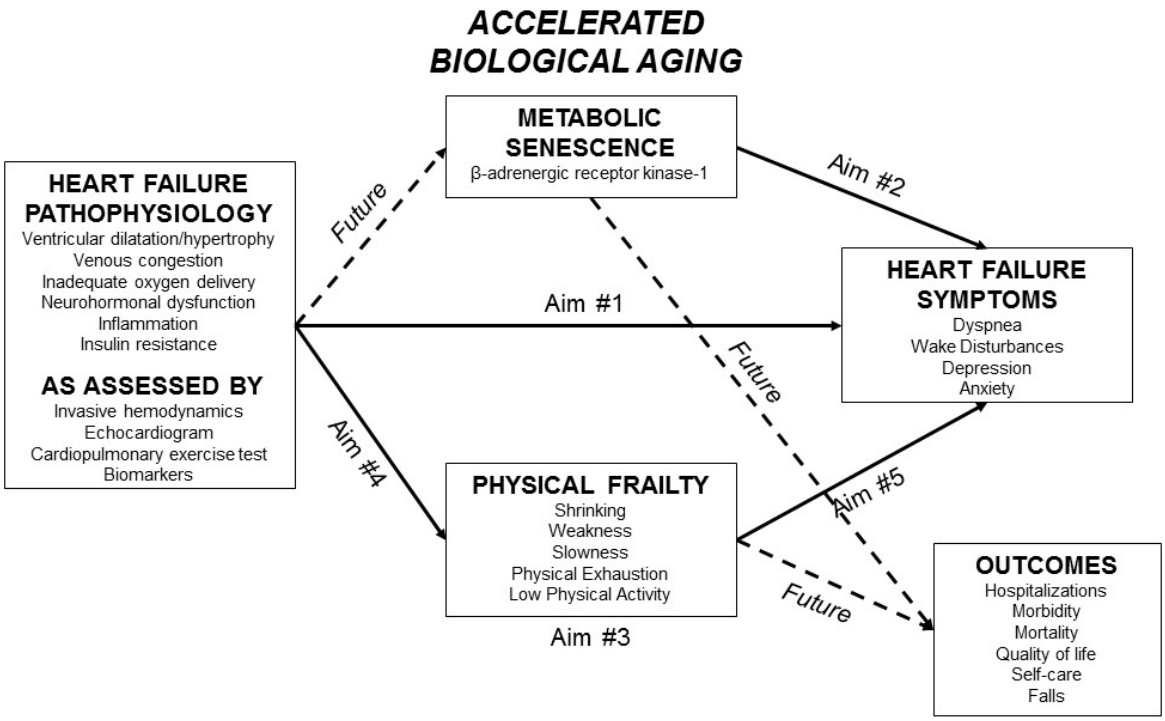

Figure 2. Future research (denoted by dashed lines) in symptom biology and accelerated biological aging in heart failure.

Conclusions

In conclusion, this program of research has made incremental and meaningful contributions to the science of HF symptom biology and the role of accelerated biological aging in HF. The body of work presented here demonstrates significant advances in these areas along with important theoretical, methodological, and clinical implications. There is a need for further research, however, to continue expanding our understanding of HF symptom biology and subsequently our clinical management of HF.

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