Symptoms and Self-care Behaviors: A Biobehavioral Study in Heart Failure

By

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Abstract

Background: Heart failure (HF) is a growing syndrome characterized by burdensome symptoms and poor quality of life. Engagement in self-care behaviors is important to effectively manage symptom. **Objective:** 1) To gain new knowledge regarding the biologic underpinnings of HF symptoms and the associations of HF symptoms with self-care behaviors, particularly over time. 2) To enhance our understanding of how an objective marker of worsening HF and self-care behaviors influence health-related quality of life (HRQOL). **Methods:** This manuscript dissertation uses multiple data sources in cross-sectional and longitudinal study design to address three aims. First, primary data from an observational study quantifies the relationship between a marker of cardiopulmonary congestion and HF symptom and HRQOL over 3 months. Second, using cross-sectional secondary data, self-care is tested as a moderator of the association between HF symptoms and HRQOL. Last, using longitudinal secondary data, patterns of HF symptoms and self-care behaviors are examined over 6 months. **Conclusions:** As a whole, this dissertation contributes to the science of symptom biology and self-care by providing new information regarding the biological underpinnings of HF symptoms and enhancing our understanding of self-care behaviors.

MeSH Keywords: Heart Failure, Symptoms, Self-care, Quality of Life

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Chapter I

Introduction

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Background and Significance

Heart failure (HF) is the fastest growing cardiac disorder affecting nearly 6 million people in the US and is associated with distressing symptoms that negatively influence a patient's quality of life (Heidenreich et al., 2013; Heo et al., 2013; Mozaffarian et al., 2016). Common signs and symptoms in HF such as dyspnea, fatigue and edema, are indicators of vascular or systemic congestion resulting from elevated pressure within the chambers of the heart and pulmonary system. Symptoms associated with pulmonary congestion (dyspnea and orthopnea) are a frequent reason patients with HF are hospitalized (Gheorghiade, Abraham, Albert, & et al., 2006; Nohria et al., 2003). Currently, clinicians rely on self-report of symptoms to diagnose HF, assess the severity of symptom burden and to adjust treatment regimens (C.S. Lee & Auld, 2015; Yancy et al., 2013). Although symptoms have an essential role in HF, many patients with HF struggle to recognize and communicate to providers worsening symptoms (Jurgens, 2006; Jurgens, Hoke, Byrnes, & Riegel, 2009). Complicating the ability for clinicians to predict who will experience worse symptoms, is that there are few objective markers of HF associated with symptoms. While hemodynamic measures and other pathological markers of HF are well correlated with outcome measures such a mortality and hospitalization, the objective indices of heart function have poor correlations with hallmark HF symptoms such as dyspnea and fatigue (Guglin, Patel, & Darbinyan, 2012; Rector, Anand, & Cohn, 2006; Shah et al., 2002). Identifying objective markers of worsening HF associated with self-reports of symptoms may allow earlier intervention for patients, reducing symptom burden and improving patient quality of life.

In addition to clinician-directed management of heart failure, patients' ability to engage in better HF self-management behaviors is associated with better outcomes such as improved survival and better quality of life (C. S. Lee, Moser, Lennie, & Riegel, 2011; C. S. Lee et al., 2014). The mechanism for how self-management behaviors may incur these benefits for patients is not well understood. One hypothesis is that better self-management reduces the severity of symptoms leading to better outcomes (Graven, Grant, Vance, et al., 2015; Riegel, Dickson, & Faulkner, 2015b). Although this hypothesis makes intuitive sense, a number of studies have demonstrated that better self-management behaviors are associated with worse symptom severity or that better self-management over time is not associated with changes in HF symptoms (C. S. Lee, Gelow, et al., 2015; C. S. Lee et al., 2014). One reason the relationship between self-reported symptoms, self-management behaviors and outcomes remains difficult to interpret is a reliance on self-reported symptoms. The difficulty many patients have in recognizing and reporting symptoms may contribute to the difficulty in detecting relationships between symptoms, self-management behaviors and outcomes. Identifying whether self-management behaviors influence HF symptoms and HRQOL may provide new insights to develop tailored interventions that integrate self-management behaviors and objective metrics of HF to improve key outcomes for patients.

The studies presented in this Dissertation will examine 1) whether pulmonary congestion detected with bio-impedance can serve as an objective HF-related metric associated with patient-reported outcomes and 2) the extent to which self-management behaviors are associated with HF symptoms and HRQOL, particularly over time.

Literature Review

Heart Failure

Heart failure is the fastest growing cardiovascular disorder affecting about 6.5 million people in the United States and approximately 40 million people worldwide (Benjamin et al., 2017; Mozaffarian et al., 2016). Heart failure is the most common reason for hospital admission in the US for those older than 65 years of age and it is estimated that the prevalence of HF will increase 46% over the next 15 years with approximately 8 million people living with HF in 2030 (Mozaffarian et al., 2016). In the US, nearly 1 in 9 deaths are attributed to HF, with a higher incidence as age increases (Mozaffarian et al., 2016). Additionally, costs associated with treatment of HF are projected to increase 3-fold by 2030 to $70 billion (Heidenreich et al., 2013). The number of deaths and hospitalizations associated with HF have changed little between 1995 and 2013 suggesting novel avenues to improve outcomes for people with HF are needed (Mozaffarian et al., 2016).

Heart failure is a complex syndrome involving multiple body systems and is the result of many cardiovascular disorders such as hypertension, myocardial infarction, valve disorders, diabetes mellitus and various cardiomyopathies (C.S. Lee & Auld, 2015). Heart failure occurs when ventricular ejection and/or filling of blood is impaired, generally (although not exclusively) resulting in diminished cardiac output. Low blood flow and oxygen delivery stimulates the sympathetic nervous system; increasing heart rate, strengthening cardiac contractions and increasing blood pressure (C.S. Lee & Auld, 2015). Specialized cells in the kidneys respond to decreased blood flow by increasing the release of hormones that potentiate vascular constriction and retention of sodium and water. The end result of this compensatory response is a viscous cycle with elevating blood pressure, a rapid heart rate, increased systemic inflammation and remodeling of the myocardium which further comprises the ability of the weakened heart to eject blood. The inability of the heart to effectively empty the ventricles cause blood to back up into the pulmonary and systemic vasculature precipitating the distressing symptoms such as dyspnea, fatigue and edema.

Patient Outcomes in HF

Heart failure is a progressive syndrome punctuated by episodes of rapidly worsening cardiac dysfunction contributing to debilitating symptoms and high utilization of healthcare resources (Mentz & O'Connor, 2015). As a result of frequent symptoms and hospitalizations, people with HF have significantly poorer physical and mental quality of life compared to those without HF (Heo, Moser, Lennie, Zambroski, & Chung, 2007). In additional to poor quality of life, individuals with HF have a rate of mortality that exceeds many types of cancers (Stewart, MacIntyre, Hole, Capewell, & McMurry, 2001). In spite of advances in medications and technology to treat HF over the last 30 years, survival with HF remains unacceptably low. Approximately 50% of people with heart failure will die within the first 5 years of diagnosis (Benjamin et al., 2017).

Symptoms in Heart Failure

Symptoms are a subjective perception of a physiologic change within the body and they play an essential role in the diagnosis, treatment and patient response to HF (Yancy et al., 2013). Heart failure is, in part, diagnosed by the presence of symptoms such as dyspnea and lower extremity edema (C.S. Lee & Auld, 2015; Yancy et al., 2013). Clinicians often rely on self-report of symptoms to modify treatment regimens and evaluate progression of HF. There are many symptoms associated with HF including physical and psychological domains. The physical domain includes symptoms like dyspnea, fatigue, edema, nausea, loss of appetite and pain (Zambroski, Moser, Bhat, & Ziegler, 2005). Psychological symptoms are commonly related to depression and anxiety (Bekelman et al., 2007). Exacerbation of physical symptoms are a common reason patients seek care and are hospitalized (Gheorghiade, Abraham, et al., 2006; Nohria et al., 2003). Experiencing frequent symptoms like dyspnea, fatigue, edema, and depression results in poor quality of life (Zambroski et al., 2005) and higher clinical event risk including death, hospitalization, ventricular assist device implantation and heart transplantation (C. S. Lee et al., 2013). In sum, self-reported HF symptoms are a key indicator of HF progression and provide essential information about how well patients are living with HF. Worsening symptoms are often an important sign more aggressive intervention is required to quell the rapid decline in cardiac function and to prevent subsequent reduction in quality of life.

The study of symptoms in HF has primarily focused on self-reported symptom severity and frequency. While self-reported symptoms are essential to the effective management of HF, patients often have a difficult time recognizing and communicating the physiologic changes that signal worsening hemodynamic function and escalation of HF symptoms (Friedman, 1997; Jurgens et al., 2009). Jurgens et al. (2009) and others have shown that patients delay seeking care up to 7 days or longer after the detection of a distressing symptom (L. S. Evangelista, Dracup, & Doering, 2000; Jurgens, 2006; Jurgens et al., 2009). Reasons for delay provided by patients include; not recognizing symptoms as related to their heart (but rather a sign of aging or other co-morbidity), the often gradual onset of symptoms and difficulty in recognizing changes in homeostasis due to inactivity or subtle changes in cognitive function (Jurgens et al., 2009). Regardless of the reason, it is clear that many patients struggle with perceiving and interpreting physiologic changes in their baseline functioning often leading to preventable hospitalizations and further functional decline. The identification of objective markers of HF symptomology may provide additional information to alert patients and clinicians of physiologic changes that may result in exacerbation of HF symptoms.

Discordance between Objective Markers of HF and Symptoms

Hindering the development of strategies to incorporate objective signs of symptoms into clinical management of HF, is the lack of association between known objective physiologic factors of heart failure and subjective indicators of HF, namely HF symptoms and HRQOL. For example there are few significant relationships between markers of cardiac function such as ejection fraction, left ventricular diameter, systolic and diastolic blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure and the hallmark HF symptoms of dyspnea and fatigue or measures of HRQOL (Denfeld et al., 2015; Guglin et al., 2012; C. S. Lee, Hiatt, Denfeld, Mudd, et al., 2015; Rector et al., 2006; Shah et al., 2002). The few relationships that have been observed are of a small magnitude and have questionable clinical significance (Guglin et al., 2012).

The lack of strong association between objective markers of heart function and subjective reports of symptoms suggests the perception of symptoms may be determined by factors other than measures of cardiac function typically used to assess HF (Guglin et al., 2012). Symptoms in HF are complex, involving multiple systems within the body (Gheorghiade, Filippatos, De Luca, & Burnett, 2006; Parrinello et al., 2015). Current HF research suggests incorporating additional cardiopulmonary metrics and markers of other body systems involving the vascular, skeletal, immune and central nervous systems may provide additional objective markers of HF symptoms (Ceunen, Vlaeyen, & Van Diest, 2016; Seongkum Heo et al., 2014; Shimiaie et al., 2015; Yu et al., 2005). For example, Heo et al. (2014) recently showed markers of inflammation associated with physical HF symptoms, however, only in those without depression. Shimiaie et al. (2015) demonstrated exercise intolerance due to fatigue or shortness of breath in patients with HF was associated with both cardiac and peripheral factors using a combination of metrics obtained from echocardiography and cardiopulmonary stress testing. Lastly, numerous studies regarding the subjective perception of the internal body state, known as interoception, have shown specific neural pathways that respond to internal physiologic states are connected to regions of the brain associated with sensation, emotion and decision-making (Ceunen et al., 2016; Craig, 2003). This intriguing area of study suggests the ability to detect and respond to physiologic changes within the body (i.e. symptoms) is related to the function of structures within the nervous system (Ceunen et al., 2016). In summary, few objective markers typically used to assess HF are related to the subjective experience of HF symptoms or HRQOL. A more complex and multifaceted approach involving metrics from additional physiologic or behavioral sources are likely needed to more accurately predict symptom severity and quality of life.

Pulmonary Congestion in HF

Pulmonary congestion or increased fluid in the lungs results from elevated intracardiac pressures that increase as ventricular function declines in HF (Gheorghiade, Filippatos, et al., 2006). Increased ventricular pressures exert back pressure on the pulmonary veins causing elevated pulmonary venous pressures and pulmonary vascular congestion. Pulmonary congestion, in addition to decreased cardiac output in HF, has been associated with decreased lung compliance, ventilation-perfusion mismatch and impaired gas exchanged that hamper the ease of breathing resulting in the sensation of dyspnea (Parrinello et al., 2015). Furthermore, pulmonary congestion is associated with poorer survival and higher readmission rates compared to HF patients without congestion (Gheorghiade, Abraham, et al., 2006).

Due to the importance of pulmonary congestion as a marker of worsening HF and contributor to symptoms such as dyspnea and edema, alleviation of pulmonary congestions and dyspnea has typically relied on treatment with diuretics and fluid restrictions. Diuretic treatment has been shown to lower ventricular and pulmonary pressures and reduce dyspnea (Bayliss, Norell, Canepa-Anson, Sutton, & Poole-Wilson, 1987). Pulmonary congestion, however, often begins days to weeks before being detected by patients as increased difficulty breathing. By the time pulmonary congestion is identified, aggressive treatment with diuretics is often needed to rapidly reduce cardiopulmonary pressures and dyspnea. In combination with low cardiac output and reduced renal perfusion, the aggressive use of diuretics may contribute to further neurohormonal stimulation, kidney dysfunction and dehydration which further complicates HF treatment (Hasselblad et al., 2007). Earlier detection of pulmonary congestion may allow for less aggressive diuretic treatment and less dyspnea mitigating HF progression and kidney dysfunction leading to improvements in functional ability and quality of life.

In order to more effectively identify pulmonary congestion, many researchers have begun to focus on remote non-invasive technologies to objectively evaluate changes in physiology that may signal increasing pulmonary congestion. Bio-impedance has emerged as one method by which fluid in the lung and pulmonary vasculature can be monitored (Tang, Warman, Johnson, Small, & Heywood, 2012; Ypenburg, Bax, van der Wall, Schalij, & van Erven, 2007; Yu et al., 2005). Bio-impedance involves using a device, such as those within implanted cardiodefibrilaltors/pacemakers, to send a high frequency, low amperage, alternating current through the chest to measure changes in electronic resistance. Increasing congestion within the lungs results in a reduction in the resistance/impedance to the electronic current (Wang, 2007). Changes in impedance have superior sensitivity (76%) over weight gain (23%) in predicting clinical events, and lower false detection event rates than weight gain (1.9 vs. 4.3/patient-year) (Abraham et al., 2011). Moreover, changes in impedance indicating worse congestion are associated with a greater risk of hospitalization for HF and worse HF self-management behaviors (Rathman, Lee, Sarkar, & Small, 2011; Sharma et al., 2015; Small et al., 2009). Bio-impedance can be measured in many current models of implantable ICDs and pacemakers. An important gap in our understanding of this device-detected pulmonary congestion is whether changes in bio-impedance is related to symptoms in HF. This is an important gap to address, especially given that pulmonary congestion may begin days to weeks before patients are able to detect physiological changes and the difficulty patients have in sensing these changes. Early detection of pulmonary congestion may lead to earlier intervention, resulting in fewer symptoms, less utilization of healthcare resources, improved survival and better quality of life.

Management of HF

In order to slow the progression of heart failure and improve patient outcomes such as symptom burden, quality of life and survival, clinicians and patients with HF engage in a variety of HF management practices. Management of HF can be thought of as having two separate loci of control, clinician-directed management and patient – or self-directed management also known as HF self-care.

Clinician-directed Management. Clinician – directed management entails specific guideline-based recommendations for treatment of HF typically regarding pharmacological and non-pharmacological interventions. Pharmacological therapy involves treatment with medications that aim to mitigate the sympathetic response (beta-adrenergic blockade) and to block adverse effects of the renal response to chronic low cardiac output (angiotensin converting enzyme and aldosterone inhibitors) (Yancy et al., 2013). Additionally, device therapy for either primary or secondary prevention is recommended for some patients to improve symptoms and prevent sudden death (Yancy et al., 2013). Non-pharmacological recommendations typically include general health promotion activities (e.g. regular exercise, a healthy diet, maintaining a healthy weight, regular follow-up with primary care and management of comorbidities, keeping current with vaccinations, ect.), symptom prevention and monitoring behaviors (e. g. taking medications as directed, daily weights, sodium and fluid restrictions), symptom response behaviors (e. g. taking additional diuretics, contacting healthcare providers) and seeking out and maintaining systems of social support (Riegel, Moser, et al., 2009; Yancy et al., 2013).

HF Self-care. An essential aspect of HF management is how well patients engage in the recommended behaviors to treat their cardiac dysfunction and to prevent, detect and manage HF symptoms (Riegel & Weaver, 2009). Self-care behaviors are consistently categorized as adherence behaviors that focus on the prevention and monitoring of HF symptoms (Riegel et al., 2015b) and as decision-making behaviors which focus on managing symptoms after they have been detected (Riegel et al., 2015b). Adherence behaviors, also known as self-care maintenance, include taking medications as prescribed, limiting fluid intake, daily weighing and attending regularly scheduled appointments with HF providers (Riegel et al., 2015b). Decision-making behaviors, often described as self-care management, involve appraisal of the symptoms and making decisions about the best way to manage symptoms such as taking additional diuretics or contacting a healthcare provider (Riegel et al., 2015b). Better self-care in HF has been shown to be associated with improved survival (C. S. Lee, Moser, Lennie, & Riegel, 2011) and better quality of life (C. S. Lee et al., 2014). Self-care behaviors in patients with HF, however, are generally poor (Debra K. Moser et al., 2012).

There is evidence that engaging in better self-care behaviors is associated with reduced levels of HF biomarkers and that better adherence behaviors are association with less device-detected pulmonary congestion (C. S. Lee, Moser, Lennie, Tkacs, et al., 2011; Rathman et al., 2011). These studies suggest HF self-care behaviors may be able to influence HF pathophysiology leading to less severe HF, fewer symptoms and better quality of life. Significant gaps in our understanding of HF self-care are how these behaviors are associated with patient-reported outcomes of symptoms and HRQOL. Recent cross-sectional studies have shown HF self-care behaviors associated with both worse and better HF symptoms while other studies have shown HRQOL to be either positively or negatively associated with self-care behaviors (C. S. Lee et al., 2014; Peters-Klimm et al., 2013). An important limitation in the literature regarding the role of self-care behaviors in affecting symptoms and HRQOL is the lack of longitudinal study designs. Current models describing the influence of HF physiology or self-care behaviors on outcomes has relied primarily on cross-sectional designs preventing the elucidation of temporal associations. Identifying a HF-related physiologic change associated with patient-reported outcomes may provide important information to address symptoms earlier. The association of HF self-care management with symptoms, especially over time, may provide additional insight to facilitate more tailored interventions to reduce symptoms and improve patient HRQOL.

Theoretical Framework

The research presented in this dissertation is guided by two theoretical models; 1). Lenz et al.'s Theory of Unpleasant Symptoms (TOUS)(1997) and 2) Riegel et al.'s the Situation Specific Theory of Heart Failure Self-care (2015a). The TOUS is a middle range theory which posits that there are 3 main factors driving the patient experience of symptoms; physiologic, psychological and situational. The symptom experience then influences patient performance such as functional status and physical performance (Lenz et al., 1997). In addition, the TOUS posits that symptoms can occur in clusters to influence outcomes. This dissertation is focused on the relationships between HF physiology in patients, multiple symptoms occurring together and health-related quality of life as the performance metric.

The Situation Specific Theory of HF Self-care describes three central aspects of self-care in patients with heart failure; self-care maintenance (adherence and symptom monitoring), symptom perception, and self-care management (the response to symptom perception) (Riegel et al., 2015a). These constructs are linked sequentially starting with self-care maintenance leading to symptom perception and perception of symptoms being required for self-care management to occur. The Situation specific Theory of HF self-care is rooted in process of naturalistic decision making that stresses individual experience and context influences engagement in HF self-management behaviors (Riegel et al., 2015a). The Situation Specific Theory of HF Self-care has informed a middle-range theory of Self-care of Chronic illness which also has a central proposition that self-care behaviors influence outcomes such as quality of life (Riegel, Jaarsma, & Stromberg, 2012).

While each theoretical model provides insight into distinct constructs (Symptoms, HRQOL or HF Self-management), there are significant gaps in the models that limit their use to predict symptoms and quality of life in patients with HF. For example, the TOUS does not include patient behaviors that have been proposed to be associated with outcomes in chronic illness (Riegel et al., 2012). On the other hand, the theory of HF self-care lacks a clear description of the relationship between the self-care, symptoms and outcomes. Lastly, neither theory provides guidance about how symptoms, self-care behaviors and outcomes such as HRQOL may change or influence one another over time. Thus, this dissertation will examine the relationships between physiological indicators of patient-reported symptoms and HRQOL. In addition, HF self-management behaviors will be tested as moderators of the relationship between HF symptoms and HRQOL. Finally, the dissertation will aid the understanding how these constructs may change and affect one another over 6 months, building upon and extending the existing theories.

Dissertation Purpose and Aims

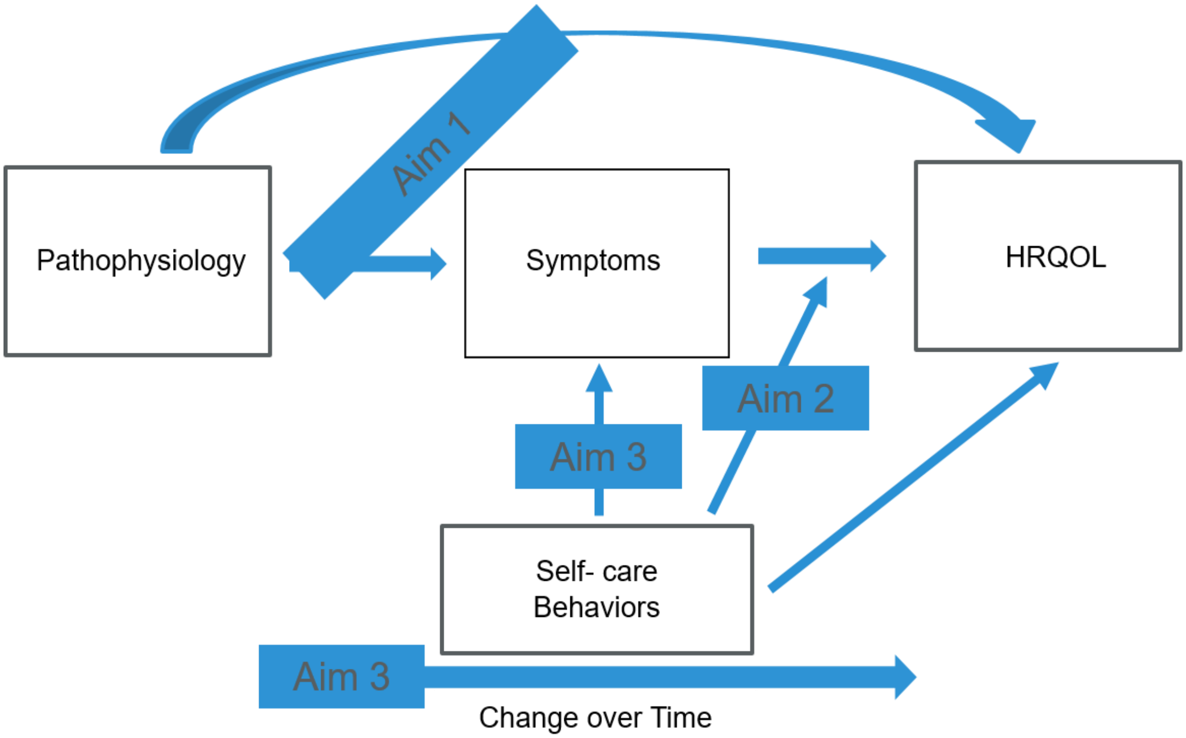
The overall purpose of this dissertation is to gain new knowledge regarding the biologic underpinnings of HF symptoms and the associations of HF symptoms with self-care behaviors, particularly over time. In addition, this dissertation aims to enhance our understanding of how an objective marker of worsening HF and self-care behaviors influence HRQOL. A better understanding of how HF pathophysiology and behaviors, influence patient-reported symptoms and HRQOL, may reveal new avenues of inquiry to integrate multiple sources of data including biological and behavioral information to better identify patients at risk for worsening symptoms and poor HRQOL.

Table 1: Manuscripts and Specific Aims

Chapter: Title of Paper	Specific Aim
Chapter 2: An Objective Marker of Heart Failure associated with Patient-reported Outcomes over 6 months.	Aim 1: Quantify associations between device-detected congestion with both patient reported HF symptoms and health-related quality of life over time. *Hypothesis 1.1: Greater frequency and duration of episodes of congestion will be associated significantly with worse physical HF symptoms.* *Hypothesis 1.2: Greater frequency and duration of episodes of congestion will be associated significantly with worse HRQOL.*
Chapter 3: Self-care Moderates the Relationship between Symptoms and Health-related Quality of Life in Heart Failure	Aim 2: Determine whether Self-management behaviors moderate the relationship between patient-reported HF symptoms and HRQOL. *Hypothesis 2.1: Self-care management behaviors will moderate the relationship between symptoms and HRQOL such that better self-care management behaviors will be associated with less symptoms severity and better HRQOL.*

Chapter 4: Patterns of symptoms are associated with self-care behaviors over 6 months in heart failure.	Aim 3: Identify naturally-occurring patterns of change in heart failure symptoms over 6 months and determine whether patterns in symptom change is associated with self-care behaviors. *Hypothesis 3.1: Changes in heart failure symptoms will be significantly associated with changes in self-management behaviors over 6 months.*

Figure 1. Intergrated Theoretical Framework



Aim 1. The first aim will be completed using a cross-sectional study design quantifying the relationship between device-detected pulmonary congestion (an objective marker of HF pathophysiology), HF symptoms and HRQOL over 3 months. The results of this study will provide novel information about whether pulmonary congestion detected through bio-impedance can serve as marker of hallmark HF symptoms and HRQOL. By showing how impedance data is related to an important patient-related outcome such as HRQOL, the clinical application of this technology may be more clearly elucidated.

Hypothesis 1.1: Greater frequency and duration of episodes of congestion will be associated significantly with worse physical and psychological HF symptoms.

Hypothesis 1.2: Greater frequency and duration of episodes of congestion will be associated significantly with worse HRQOL.

Aim 2. The second aim examines the influence of HF self-management behaviors in moderating the relationship between patient-reported symptoms and HRQOL. The study will be conducted as a secondary analysis of 101 men and 101 women with symptomatic HF. The analysis was developed to examine whether self-management behaviors may be an important factor in understanding the relationship between patient-reported outcomes of HF symptoms and HRQOL.

Hypothesis 2.1: Self-care management behaviors will moderate the relationship between symptoms and HRQOL such that better self-care management behaviors will be associated with less symptoms severity and better HRQOL.

Aim 3. The third aim will determine whether changes in self-reported HF symptoms are associated with self-management behaviors over 6 months. As suggested by the study described in aim 2, self-management behaviors and symptoms together may provide important information about how well people are living with HF. It has yet to be shown whether changes in symptoms over time are associated with changes in HF self-management behaviors. To address this gap, a secondary analysis will be conducted on longitudinal data that examines trajectories in HF symptom over 6 months and association with self-management behaviors.

Hypothesis 3.1: Changes in heart failure symptoms will be significantly associated with changes in self-management behaviors over 6 months.

Implications

The proposed dissertaiton has several important implications for clinicians and researchers of patients with HF. First, as described by Aim 1, identifying a commonly available marker of symtpoms and HRQOL may allow earlier detection of worsening HF, promoting earlier intervention to prevent a escalating symptoms and declines in HRQOL. Aim 2 may provide evidence that engagement in self-management behaviors moderate how symptoms affect HRQOL. Incorporating the assessment of symptoms and self-manangement behaviors into clinic practice may enhance the identification of patient at risk for poor HRQOL. Aim 3 enhances our understanding of how self management behaviors may be associated with patient-reported symptom burden over time. More information regarding the importance of self-management behaviors in affecting patient-reported outcomes of symptoms severity and HRQOL may allow more targeted self-management interventions that integrate objective and subjective data to more effectively imporve outcomes for patienst with HF.

Summary

Heart failure is a debilitating disorder characterized by a heavy burden of symptoms, poor quality of life and poor survival. Symptoms in HF are one of the primary indicators of illness progression and how well patients are living with HF. Yet, many patient struggle to effectively perceive and respond to symptoms increasing their risk of experiencing poor quality of life. Currently, there are few objective markers of hallmark symtpoms in HF which makes the detection of adverse physiologic changes difficult for patients and clinicians. A better understanding of the bioligical underpinnins of subjective metrics of HF and of symptoms and self-care behaviors will provide new insights into how biology, behaviors and outcomes can be integrated to influence patient-oriented outcomes.

References for Chapter I (See Cumulative References)

CHAPTER II

An Objective Measure of Worsening Heart Failure is Associated with Patient-reported Outcomes in Heart Failure

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This manuscript represents a significant contribution to the Dissertation work. Mr. Auld is the primary author on this paper, and Dr. Lee is the senior author on this paper. This manuscript will be submitted to Heart and Lung. Heart and Lung reports on research advancing the science and care of acute and critical chronic cardiac or pulmonary illnesses. As of 2016, the publication has an impact factor of 1.657.

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Abstract

Background: Congestion is primary cause of symptoms in HF. Yet, intrathoracic impedance, an objective marker of cardiopulmonary congestion, has not been examined in relation to hallmark HF symptoms. **Objective:** To quantify the relationship between physical and psychological symptoms, HRQOL and device-detected cardiopulmonary congestion in patients with HF over 3 months. **Methods:** In a cohort of adults with moderate to advanced HF, multivariate generalized linear modeling was used to quantify the association of cardiopulmonary congestion (Optivol® Index exceeding 60 **Ω** threshold) with HRQOL (9-item Kansas City Cardiomyopathy Questionnaire) and physical (Functional Assessment of Chronic Illness Therapy-Fatigue Scale; HF Somatic Perception Scale Dyspnea and Early and Subtle Symptoms subscales) and psychological symptoms (9-item Patient Health Questionnaire; 6-item Patient-Reported Outcomes Measurement Information System Anxiety Scale). **Results**: The mean age of the sample (n=49) was 62 years old, 43% were women, and 63% had NYHA class III/IV HF. Adjusted analysis with GLM demonstrated that Optivol Index threshold crossings were significantly associated with increases in dyspnea (p=0.017), early and subtle symptoms (p=0.029), depressive symptoms(p=0.003) and anxiety (p=0.028). Having an Optivol Index threshold crossing in the previous 90 days was also significantly associated with worse HRQOL (p=0.02). **Conclusions:** Intrathoracic impedance measured with the Optivol Index can provide additional information regarding the patient experience of hallmark physical and psychological HF symptoms over 3 months.

Background

Heart failure (HF) is a devastating cardiovascular syndrome that is continuing to increase in prevalence in the US. Currently, 6.5 million Americans are diagnosed with HF and that number is projected to increase by 46% by 2030 (Benjamin et al., 2017). Heart failure is the leading cause of hospital admission for older adults and in spite of recent improvements in medical management and technological advances in the treatment of HF, patients with HF continue to experience poor quality of life due to distressing symptoms such as dyspnea, fatigue, depression and anxiety (Heo et al., 2007; Jencks, Williams, & Coleman, 2009; Zambroski et al., 2005).

Cardiopulmonary congestion resulting from fluid overload and elevated pressures in the heart is a common cause of symptoms and it is a primary reason for HF hospitalization (Adams et al., 2005; Negi et al., 2014; Parrinello et al., 2015). Remote monitoring of pulmonary congestion has recently been introduced into implantable defibrillator/pacemakers many patients with HF receive and device-detected congestion events are associated with higher rates of HF and worse mortality (Small et al., 2014; Tang et al., 2012). One area that has yet to be studied with this technology is the association between device-detected cardiopulmonary congestion and patients' experience of HF symptoms. Patient-reported symptoms in HF are key drivers for healthcare utilization and quality of life (Negi et al., 2014; Schwarz & Elman, 2003; Zambroski et al., 2005). However, patients are often limited in their ability to recognize and respond to symptoms (i.e. self-care management)(Jurgens, 2006; C. S. Lee, Gelow, et al., 2015). These limitations include 1) difficulty in identifying the symptoms as related to HF especially in the presence of multiple co-morbidities (Darling et al., 2013), 2) symptoms that are subtle and difficult to detected (Jurgens et al., 2009) and 3) late recognition of symptoms (Jurgens, 2006).

Further complicating the identification of symptoms for patients and clinicians is a dearth of objective markers of heart function related to patient HF symptoms (Bhardwaj et al., 2012; Guglin et al., 2012; Lewis et al., 2007; Rector et al., 2006; Shah et al., 2002). For patients, daily weights are poorly associated with clinical deterioration (Abraham et al., 2011) and for clinicians few hemodynamic indicators of HF are related to symptoms (Guglin et al., 2012). In a recent study, Lee et al. (2015) describes multiple groups with differing profiles of hemodynamic-symptoms mismatch. One group of HF patients experienced very poor hemodynamics with only moderate levels of symptom burden and exhibited an increased clinical event risk compared to patients whose hemodynamics and symptoms were congruent. This study, along with evidence of patient difficulty identifying and managing symptoms, highlights the need to find better methods to monitor symptoms both as an indicator of progressing HF and as a means to improve patient-reported outcomes such as symptom and HRQOL. The purpose of this study is to quantify the relationship between symptoms, HRQOL and device-detected cardiopulmonary congestion in patients with HF over 3 months. A better understanding how an objective measure of worsening HF is associated with changes in symptoms and HRQOL may enhance more patient-specific interventions; reducing costly readmission and improving quality of life.

Materials and Methods

This was an observational study examining 3 months of device-detected cardiopulmonary congestion data in 49 patients with symptomatic HF. In brief, patients from a HF clinic associated with an academic medical center in the Pacific Northwest were identified by their cardiologist as having symptomatic HF (NYHA Class II-IV) and an Optivol® (Medtronic, Minneapolis) enabled device. Between January 2017 and December 2017, identified patients were approached at a pacemaker/ICD clinic visit by a member of the research team not directly involved with HF care for participation in the study. The study was approved by the medical center institutional review board and all participants provided written and informed consent. At enrollment, the prior 3 months of device data was downloaded and a questionnaire was completed either during the visit or by mail per the participants' preference. The questionnaire collected data on demographic, socioeconomics and information asking patients to evaluate their HF symptoms and HRQOL over the past 3 months. In addition, an assessment of mild cognitive function was administered at the time of enrollment. Clinical information regarding the patient's HF treatment and co-morbidities were obtained from an in-depth review of the participants' medical record at the time of enrollment.

Measurement

Device-detected cardiopulmonary congestion

Cardiopulmonary congestion was quantified using data that is already generated and stored in patients' implanted Optivol® (Medtronic, Minneapolis) therapeutic devices. Briefly, devices send a high frequency, low amperage, alternating current from the device generator to the right ventricular coil, tip, or ring electrode to measure changes in electronic resistance. Increasing congestion within the lungs results in a reduction in the

Figure 1. Device-detected Cardiopulmonary Congestion with Optivol® Index.

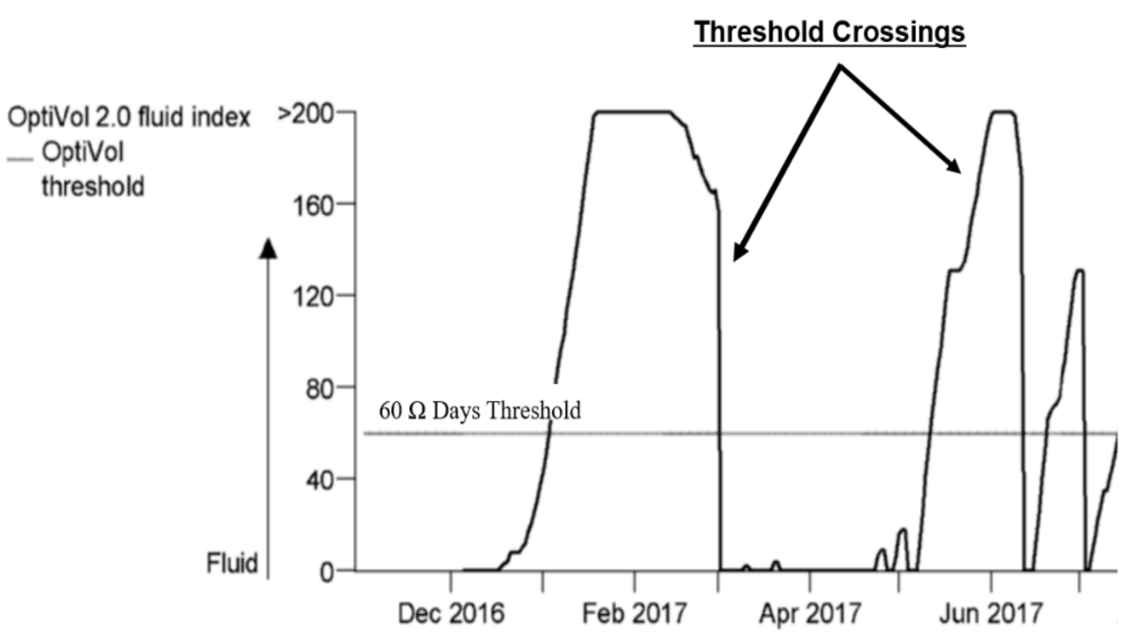

Figure 1: Optivol fluid index threshold crossings occur when Optivol fluid index exceeds 60 Ω days. Threshold crossings are indications of a cardiopulmonary congestion event. The precise number and duration of the threshold crossings were determined.

resistance/impedance to the electronic current (Ypenburg et al., 2007; Yu et al., 2005). Average raw daily impedance is quantified and stored in the device computer; raw average daily impedance is calculated in an identical fashion among all commercially-available Optivol® devices. Post-hoc, several metrics of congestion are calculated including the Optivol® ® fluid index, which represents day-to-day differences between impedance and a reference impedance threshold of 60 Ω days (**Figure 1**). In our study as well as others (Rathman et al., 2011; Small et al., 2009), an Optivol® Index exceeding the 60 Ω threshold constitutes a “threshold crossing”, an indicator of a cardiopulmonary congestion event. The data extracted from the devices included the frequency and duration of all threshold crossings in the previous 3 months. Device data is collected beginning 34 days after implantation as pocket healing interferes with impedance. Major surgical procedures within 6 weeks may interfere with impedance; hence, this is an important exclusion criterion.

Physical HF Symptoms

Fatigue was measures using the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) (v. 4) (Yellen, Cella, Webster, Blendowski, & Kaplan, 1997). The FACIT-F assesses patients' tiredness, weakness, and difficulty conducting usual activities due to fatigue (Hjollund, Andersen, & Bech, 2007; Yellen et al., 1997). Scores of the 13 items range from 0-52 with higher scores indicating more fatigue. The FACIT-F has excellent concordant validity with the Piper fatigue scale (r = 0.83) and Profile of Mood States fatigue scale (r =0.77) (D. Cella et al., 2005). The scale has also good reliability and validity in adults (David Cella, Lai, Chang, Peterman, & Slavin, 2002).

Dyspnea was measured with the 6-item dyspnea subscale of the Heart Failure Somatic Perception Scale (HFSPS Dyspnea) (Jurgens, Fain, & Riegel, 2006). The HFSPS is rooted in the Theory of Unpleasant Symptom which posits that the patient's physiology and multiple symptoms are important factors in the symptom experience (Jurgens, Lee, & Riegel, 2015). The HFSPS asks about how much the participant was bothered by HF symptoms related to shortness of breath or other breathing difficulties and provides six response options ranging from 0 (not at all) to 5 (extremely bothersome). The HFSPS dyspnea has excellent internal consistency (alpha = 0.89) concordant validity with the KCCQ functional limitations scale (r = 0.53) and independently predicts HF-related clinical events (per point HR = 1.031, p=0.031) (Jurgens et al., 2015).

Early and Subtle symptoms were measured with the 7-item early and subtle subscale of the HFSPS (HFSPS E&S) (Jurgens et al., 2015). The HFSPS asks about how much the participant was bothered by HF symptoms that can occur prior to more noticeable symptoms such as dyspnea and fatigue. For example, the HFSPS E&S asks patients to rate how much they were bothered by tight clothing, stomach ache, waking to urinate and needing more rest during the day. The HFSPS E&S provides six response options ranging from 0 (not at all) to 5 (extremely bothersome).36 The HFSPS E&S has good internal consistency (alpha = 0.75) moderate concordant validity with the KCCQ functional limitations scale (r = 0.39) and independently predicts HF-related clinical events (per point HR = 1.030, p=0.028) (Jurgens et al., 2015).

Psychological HF Symptoms

Depressive symptoms were measured using the 9-item Patient Health Questionnaire (PHQ9). The PHQ9 has 4 response options ranging from 0 (not at all) to 3 (nearly every day) (Spitzer, Kroenke, & Williams, 1999). Higher scores (range 0-27) indicate more depression. The PHQ9 has been validated in the HF population. The PHQ9 is 87% sensitive and 76% specific in detecting depressive disorder in the general population (Kroenke, Spitzer, & Willaims, 2001).

Symptoms of anxiety were measured with the 6-item patient reported outcomes measurement information system (PROMIS) short form anxiety scale. The PROMIS anxiety SF-6 asks respondents to rate level of fear, anxiousness and worry with 5 response options of never, rarely, sometimes, often, always (scale of 1 -5). A raw score is calculated by summing the 6-items with a range of 6-30. Raw scores correspond to T-scores based on large nationally representative samples (Pilkonis et al., 2011).

Mild Cognitive Dysfunction

Mild cognitive dysfunction was measured with the Montreal Cognitive Assessment (MoCA). The MoCA assesses a number of cognitive functions including short-term verbal memory recall, visuospatial ability, executive function, attention, concentration, working memory, language, and orientation. The MoCA has been shown to be sensitive and specific to mild cognitive function with a cut-off score of <26 and has been used in patients with HF (Harkness et al., 2014; Nasreddine et al., 2005). The MoCA was assessed in person following the detailed instructions.

Health-Related Quality-of-Life

Heart failure-specific health-related quality of life was measured with the Kansas City Cardiomyopathy Questionnaire Short Version (KCCQ-12). The KCCQ-12 is a 12-item Likert scale comprised of 4 sub-scales; symptom frequency, physical and social function and quality-of-life. Scores range from 0-100 with higher scores reflecting better function. A KCCQ-12 summary score is created by calculating the mean of the 4 sub-scores. The KCCQ-12 has excellent concordant validity (0.93-0.99) with the original well-validated and reliable item measure and good test-re-test reliability (0.76-0.92) (Spertus & Jones, 2015).

Statistical Procedure

Means, standard deviations, frequency, and percentages were used to describe the sample using Stata/IC v14.2 (Texas). The Student’s t test, Mann-Whitney U, analysis of variance (ANOVA), Kruskal-Wallis test, Chi-square or Fischer’s exact tests were used to examine differences between participants with no threshold crossings and those with varying frequency and duration of threshold crossings over the previous 3 months. Two different variables were created to describe the Optivol threshold crossings in this study. One described the presence (or not) of a threshold crossing in the previous 90 days and the second was created by dividing the sample into tertiles with the first group having no days above threshold and the following two groups split by the median days above the Optivol index threshold. Given some of the symptom and HRQOL variables were modestly skewed, both parametric and non-parametric tests were used to evaluate the

Table 1. Characteristics of the Sample (n= 49)

		-----------Threshold (TH) Crossings -----------		
	Sample (n = 49)	+TH Crossing (n= 22)	−TH Crossing(n = 27)	p value
Age (in years)	62.4 ± 13.5	63.0 ± 13.1	62.0 ± 14.0	0.801
Female	21 (42.9)	10 (45.5)	11 (40.7)	0.740
Educational Status				
High School or less	15 (31.9)	6 (27.3)	9 (33.3)	0.659
Financial Status				
More than enough	8 (17.4)	3 (13.6)	5 (18.5)	0.429
Marital Status				
Married or living with partner	31 (63.3)	14 (63.6)	17 (63.0)	0.961
Charlson Co-morbidity category				
low (score of 1 or 2)	27 (55.1)	9 (40.9)	18 (66.7)	
medium (score of 3 or 4)	17 (34.7)	10 (45.5)	7 (25.9)	
high (score of 5 or more)	5 (10.2)	3 (13.6)	2 (7.4)	0.174
BMI	30.9 ± 6.7	31.0 ± 5.6	30.8 ± 7.6	0.914
MOCA	25.8 ± 2.3	25.5 ± 2.6	26.0 ± 2.2	0.473
Heart Failure Characteristics:				
NYHA III/IV	31 (63.3)	15 (68.2)	16 (59.2)	0.519
Ejection Fraction %	33.8 ± 14.2	29.4 ± 14.1	37.4 ± 13.4	**0.048**
LVID	5.8 ± 1.2	5.9 ± 1.1	5.8± 1.3	0.856
Primary Etiology				
Ischemic	10 (20.4)	7 (31.8)	3 (11.1)	0.090
Systolic BP	113.6 ± 15.3	112.9 ± 13.9	114.2 ± 16.6	0.763
Aldosterone Antagonist	28 (57.1)	11 (50.0)	17 (63.0)	0.362
Diuretic	39 (79.6)	19 (86.4)	20 (74.1)	0.288
ACE/ARB	43 (87.8)	17 (77.3)	26 (96.3)	0.077
Beta Blocker	46 (93.9)	20 (90.9)	26 (96.3)	0.581
Hemoglobin	13.3 ± 2.0	13.5 ± 1.8	13.1± 2.1	0.722
Serum Sodium	138.0 ± 3.1	138.5 ± 3.0	137.5 ± 3.2	0.143
Years with HF				
>7 years	24 (49.0)	15 (68.2)	10 (37.0)	**0.030**

Table 1 Legend: Sample characteristics comparing those with a threshold crossing (+) to those with no threshold crossings in the previous 90 days (-). Threshold crossing = exceeding the 60 Ω Opitvol Index threshold in the 3 months prior to study enrollment. Abbreviations – BMI – body mass index, MOCA – montreal cognitive assessment, NYHA- New York heart association functional class, LVID- left ventricular internal diameter, ACE/ARB- angiotensin converting enzyme inhibitor/angiotensin receptor blocker, HF-heart failure

differences between the frequency and duration of threshold crossings. Since the levels of significance between the parametric and non-parametric tests were similar, the parametric tests (t tests and ANOVA) were used to describe the differences in symptoms and HRQOL. Hedge's g was calculated to determine effect sizes between the presence or duration of threshold crossing and symptoms and HRQOL. Generalized linear modeling using either a gamma or normal distribution was used to quantify the association of cardiopulmonary congestion (Optivol® Index exceeding 60 Ω threshold) with HRQOL and physical and psychological symptoms. The log likelihood, AIC and BIC were used to compare models with lower values indicative of better fit. A p-value <0.5 was considered significant. For HRQOL models, estimates are in units of the KCCQ summary scale. In order to facilitate comparisons across symptoms, the relative difference in symptoms are reported for differing levels of the frequency and duration of threshold crossings. The relative differences are reported as a percentage increase or decrease in the symptom score compared to the referent (0 threshold crossings and 0 days above threshold).

Covariates were identified using an empirical/theoretical approach. Covariates significantly different between those with threshold crossing and none (empirical) as well as other variables shown to be significantly associated with HRQOL or symptoms from the literature were included to adjust the analyses. Specifically, NYHA Class for HRQOL models and comorbidities for symptom models were used as the theoretical covariates.

Results

Participants in the study were on average 62 ± 13.5 years old, predominantly white (93.5%) and married or living with their partners (63%) (**Table 1**). Women

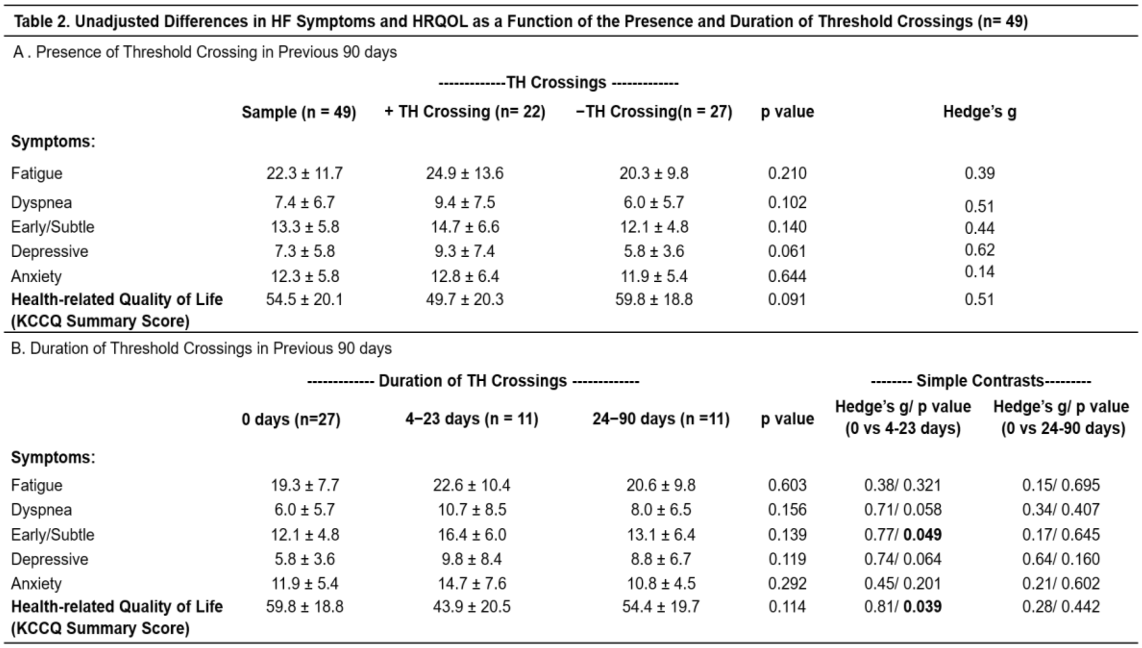

Table 2. Unadjusted Differences in HF Symptoms and HRQOL as a Function of the Presence and Duration of Threshold Crossings (n= 49)

A . Presence of Threshold Crossing in Previous 90 days

		-------------TH Crossings -------------			
	Sample (n = 49)	**+ TH Crossing (n= 22)**	**−TH Crossing(n = 27)**	**p value**	**Hedge's g**
Symptoms:					
Fatigue	22.3 ± 11.7	24.9 ± 13.6	20.3 ± 9.8	0.210	0.39
Dyspnea	7.4 ± 6.7	9.4 ± 7.5	6.0 ± 5.7	0.102	0.51
Early/Subtle	13.3 ± 5.8	14.7 ± 6.6	12.1 ± 4.8	0.140	0.44
Depressive	7.3 ± 5.8	9.3 ± 7.4	5.8 ± 3.6	0.061	0.62
Anxiety	12.3 ± 5.8	12.8 ± 6.4	11.9 ± 5.4	0.644	0.14
Health-related Quality of Life (KCCQ Summary Score)	54.5 ± 20.1	49.7 ± 20.3	59.8 ± 18.8	0.091	0.51

B. Duration of Threshold Crossings in Previous 90 days

		------------- Duration of TH Crossings -------------			-------- Simple Contrasts---------	
	0 days (n=27)	**4−23 days (n = 11)**	**24−90 days (n =11)**	**p value**	**Hedge's g/ p value (0 vs 4-23 days)**	**Hedge's g/ p value (0 vs 24-90 days)**
Symptoms:						
Fatigue	19.3 ± 7.7	22.6 ± 10.4	20.6 ± 9.8	0.603	0.38/ 0.321	0.15/ 0.695
Dyspnea	6.0 ± 5.7	10.7 ± 8.5	8.0 ± 6.5	0.156	0.71/ 0.058	0.34/ 0.407
Early/Subtle	12.1 ± 4.8	16.4 ± 6.0	13.1 ± 6.4	0.139	0.77/ **0.049**	0.17/ 0.645
Depressive	5.8 ± 3.6	9.8 ± 8.4	8.8 ± 6.7	0.119	0.74/ 0.064	0.64/ 0.160
Anxiety	11.9 ± 5.4	14.7 ± 7.6	10.8 ± 4.5	0.292	0.45/ 0.201	0.21/ 0.602
Health-related Quality of Life (KCCQ Summary Score)	59.8 ± 18.8	43.9 ± 20.5	54.4 ± 19.7	0.114	0.81/ **0.039**	0.28/ 0.442

Table 2 Legend: Simple Contrasts show the level of significance for the mean comparisons between 0 days above threshold and 4-23 days above threshold and 0 days above threshold and 24-90 days above threshold conducted post-hoc analysis of variance. Threshold crossing = exceeding the 60 Ω Opitvol Index threshold in the 3 months prior to study enrollment.

comprised 43% of the sample. Most participants had moderate to severe functional limitation due to HF (63 % NYHA III/IV) and a non-ischemic HF etiology (80%).

A slight majority (55%) of the sample did not have a threshold crossing in the previous three months. Having ≥ one threshold crossing in the previous three months was significantly associated with lower ejection fraction and longer duration of HF (**Table 1**). 4-23 days above threshold had significantly worse HRQOL and early and subtle symptoms compared with participants with no days above threshold (**Table 2B**).

In multivariate models, worse HRQOL was significantly associated with the presence of at least one threshold crossing and a duration of 4-23 days above threshold (**Table 3**). Adjusted multivariate models of symptoms (**Table 4**) showed that dyspnea, early and subtle, depressive and anxiety symptoms were significantly worse for those who experienced threshold crossings or had threshold crossings between 4 and 23 days.

Only depressive symptoms were also significantly worse for participants with threshold crossing of 24 days or more.

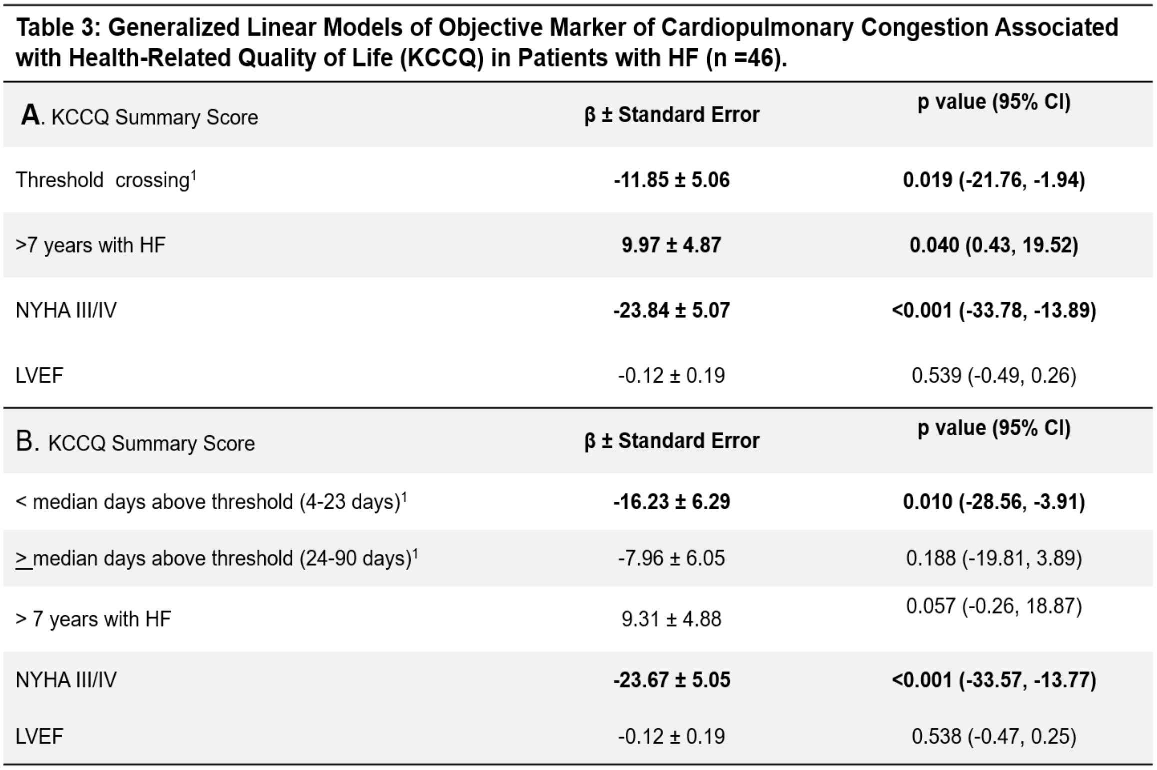

Table 3: Generalized Linear Models of Objective Marker of Cardiopulmonary Congestion Associated with Health-Related Quality of Life (KCCQ) in Patients with HF (n =46).

A. KCCQ Summary Score	**β ± Standard Error**	**p value (95% CI)**
Threshold crossing[1]	**-11.85 ± 5.06**	**0.019 (-21.76, -1.94)**
>7 years with HF	**9.97 ± 4.87**	**0.040 (0.43, 19.52)**
NYHA III/IV	**-23.84 ± 5.07**	**<0.001 (-33.78, -13.89)**
LVEF	-0.12 ± 0.19	0.539 (-0.49, 0.26)
B. KCCQ Summary Score	**β ± Standard Error**	**p value (95% CI)**
< median days above threshold (4-23 days)[1]	**-16.23 ± 6.29**	**0.010 (-28.56, -3.91)**
≥ median days above threshold (24-90 days)[1]	-7.96 ± 6.05	0.188 (-19.81, 3.89)
> 7 years with HF	9.31 ± 4.88	0.057 (-0.26, 18.87)
NYHA III/IV	**-23.67 ± 5.05**	**<0.001 (-33.57, -13.77)**
LVEF	-0.12 ± 0.19	0.538 (-0.47, 0.25)

Table 3 Legend: Threshold crossing/above threshold = exceeding the 60 Ω Optivol Index threshold in the 3 months prior to study enrollment.

Discussion

In this prospective observational study of 49 patients with symptomatic HF and Optivol®-enabled pacemarker/ICDs, we found that the presence and duration of a device-detected cardiopulmonary congestion event in the previous 3 months was associated with higher physical and psychological symptom burden and worse HRQOL. To the knowledge of the authors, this is the first study to show a metric of intrathoracic impedance (Optivol® Index) associated with patient-reported symptoms and HRQOL. The results of this study enhance our understanding of symptoms and HRQOL in HF and suggest monitoring of intrathoracic impedance may be a valuable tool in addressing symptom burden and quality of life in patients with symptomatic HF.

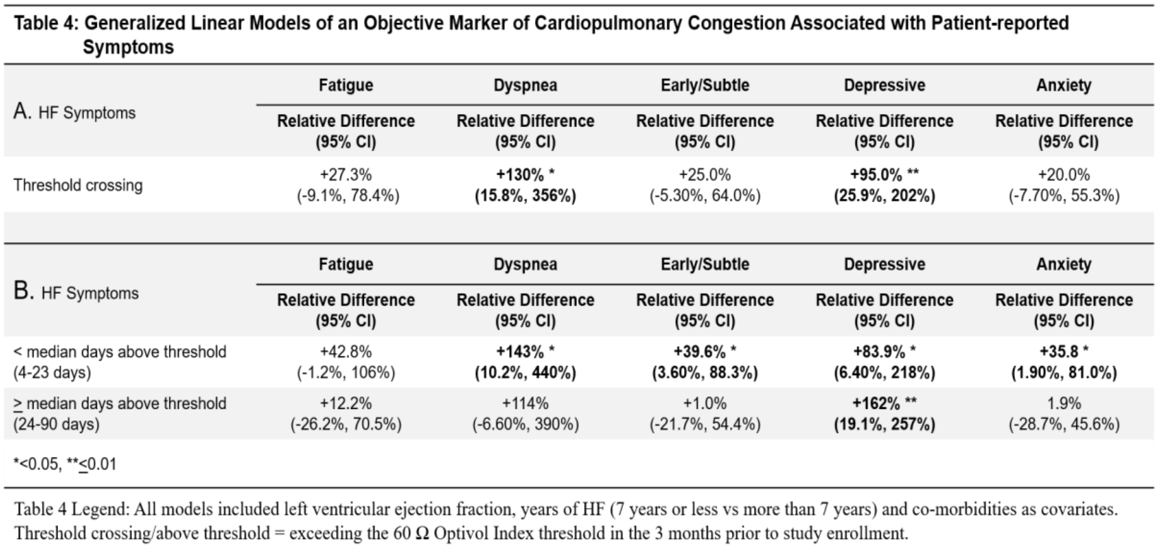

Table 4: Generalized Linear Models of an Objective Marker of Cardiopulmonary Congestion Associated with Patient-reported Symptoms

A. HF Symptoms	Fatigue	Dyspnea	Early/Subtle	Depressive	Anxiety
	Relative Difference (95% CI)	**Relative Difference (95% CI)**	**Relative Difference (95% CI)**	**Relative Difference (95% CI)**	**Relative Difference (95% CI)**
Threshold crossing	+27.3% (-9.1%, 78.4%)	**+130% *** **(15.8%, 356%)**	+25.0% (-5.30%, 64.0%)	**+95.0% **** **(25.9%, 202%)**	+20.0% (-7.70%, 55.3%)

B. HF Symptoms	Fatigue	Dyspnea	Early/Subtle	Depressive	Anxiety
	Relative Difference (95% CI)	**Relative Difference (95% CI)**	**Relative Difference (95% CI)**	**Relative Difference (95% CI)**	**Relative Difference (95% CI)**
< median days above threshold (4-23 days)	+42.8% (-1.2%, 106%)	**+143% *** **(10.2%, 440%)**	**+39.6% *** **(3.60%, 88.3%)**	**+83.9% *** **(6.40%, 218%)**	**+35.8 *** **(1.90%, 81.0%)**
≥ median days above threshold (24-90 days)	+12.2% (-26.2%, 70.5%)	+114% (-6.60%, 390%)	+1.0% (-21.7%, 54.4%)	**+162% **** **(19.1%, 257%)**	1.9% (-28.7%, 45.6%)

*<0.05, **≤0.01

Table 4 Legend: All models included left ventricular ejection fraction, years of HF (7 years or less vs more than 7 years) and co-morbidities as covariates. Threshold crossing/above threshold = exceeding the 60 Ω Optivol Index threshold in the 3 months prior to study enrollment.

Intrathoracic impedance, quantified using the Opitvol Index, has been considered a gold standard in detecting fluid retention events in patients with HF (Riegel et al., 2018). Although lower intrathoracic impedance (higher Optivol® Index) has been associated with less engagement in HF self-care behaviors, higher clinical event risk and mortality, our study is the first to show a significant relationship between intrathoracic impedance and important patient-reported outcomes of physical and psychological HF symptoms and a clinically meaningful difference in HRQOL (Rathman et al., 2011; Tang et al., 2012). Thus, this is an important finding in our understanding of symptom biology in HF. First, physical symptoms such as dyspnea are the primary reasons patients with HF seek care (Negi et al., 2014). Physical and psychological symptoms are also significant drivers of HRQOL. Furthermore, patients often delay seeking treatment for worsening symptoms due to difficulty in the detection or interpretation of symptoms (Jurgens et al., 2009). Our data suggests objective measures of intrathoracic fluid, such as the Optivol® Index, may provide additional information regarding underlying changes in physiology that may portend worsening symptoms and allow for earlier detection and treatment of burdensome symptoms.

Second, our study suggests the intrathoracic impedance may not be a reliable indicator of fatigue in HF. The experience of fatigue in our sample was not significantly related to cardiopulmonary congestion events. One explanation for the lack of association between an objective measure of cardiopulmonary congestion and fatigue may be that intrathoracic impedance is simply not particularly sensitive to fatigue. Although the pathophysiology of fatigue has not been fully elucidated, it is believed to stem from both physiological sources (inflammation, muscle dysfunction and anemia) and from psychological sources such as depression. Cardiopulmonary congestion, on the other hand, results from elevated pressures in the heart and pulmonary systems that often result in dyspnea. Further research is needed to identify objective HF-related measures associated with fatigue in patients with HF.

Third, an unexpected finding from our study was that patients with the most severe marker of cardiopulmonary congestion (longest duration of threshold crossings) did not report the worst physical or psychological symptom burden or worst HRQOL. Although not all comparisons were statistically significant (likely due to small sample sizes and large standard deviations), patients who experienced more severe congestion (24-90 days), reported , on average, milder symptoms, and better HRQOL compared to patients with less severe cardiopulmonary congestion (4-23 days above threshold). For example, our study showed that compared to having no cardiopulmonary congestion events, early and subtle symptoms and HRQOL were significantly worse for patients with more mild indicators of congestion. Early and subtle symptoms and HRQOL were not significantly different between those with no congestion events and the more severe indicators of cardiopulmonary congestion.

This intriguing finding is consistent with two recent studies which found a mismatch between objective metrics of HF pathophysiology and subjectively-reported HF symptoms (C. S. Lee, Hiatt, Denfeld, Mudd, et al., 2015; Riegel et al., 2018). Both studies showed that there are substantial proportions of patients whose perception of HF symptoms are discordant with objectively measured metrics of HF pathophysiology including intrathoracic impedance. The discordant groups include patients who had mild objective markers of HF with more severe symptoms and patients with more severe objective markers but less severe symptoms. Of particular importance was the observation that those, with what Lee et al.(2015) termed “symptom-hemodynamic mismatch”, were at higher risk for adverse clinical events than those with concordant symptoms and hemodynamics (C. S. Lee, Hiatt, Denfeld, Mudd, et al., 2015). Our study may also reflect a similar mismatch between an objective metric of worsening cardiopulmonary congestion and patient-reported symptoms and HRQOL. One reason for the mismatch may be related to response shift bias. Response shift bias may occur as individuals learn to adapt and compensate for declines in physical or psychological function that often occur in the trajectory of HF. As function declines over time, people with HF may continually develop a “new normal” from which they evaluate symptoms that eventually results in a mismatch between the patient’s subjective interpretation of symptoms and the worsening HF pathophysiology. Alternatively, the symptom-hemodynamic mismatch may be the result of interceptive dysfunction that may be a result of worsening HF. Further research is needed to more clearly determine the causes, characteristics and outcomes associated with symptom-hemodynamic mismatch.

Finally, this study suggests the use of validated and reliable instruments to assess patient-reported outcomes may enhance the research of symptom biology in HF. Previous studies, using predominantly single-item symptoms measures, have shown little to no association between metrics of cardiopulmonary function and subjectively-reported HF metrics of symptoms and HRQOL (Guglin et al., 2012; Lewis et al., 2007; Shah et al., 2002). Since this study is one of the first to show moderate to strong effect sizes between an objectives metric of cardiopulmonary congestions and patient-reported outcomes in HF, it may offer insights into the study of HF symptomology that may enhance future research. For example, the use of reliable and validated symptom and HRQOL measures may have enhanced the ability of our study to detect significant associations. The symptom experience is often multifaceted and can be experienced differently by differing patient populations (D. K. Moser et al., 2014). Single-item descriptions of symptoms such as dyspnea and fatigue may capture a narrower range of the symptom experience making it more difficult to detect associations with physiologic markers. The systematic collection of patient-reported data with valid and reliable instruments that assess a wider range of the patient's experience may prove useful in clinical practice and research to identify objective markers of HF that may better predict HF symptoms and HRQOL.

Strengths and Limitations

Our study had several strengths. First, the study examined the association of intrathoracic impedance with both physical and psychological symptoms. The use of physical and psychological symptoms provides a more comprehensive understanding of the patient symptom experience. Second, the use of GLM allowed non-normally distributed variables to be used without transformation. In addition to strengths, there a number of limitations to the study. The sample size was small limiting the ability to detect smaller effects. Additionally, the sample had little variation in self-reported race and the use of certain medications such as beta-blockers and ACE/ARBs. This prevents our study from making any inferences about how these variable may have affected the results. Finally, the sample was comprised predominantly of non-ischemic, married, self-described white participants with more severe functional limitations. These characteristics of the sample hinder the generalizability of the results to the general HF population.

Conclusion

Medtronic Optivol fluid index threshold crossings over 3 months were significantly associated physical and psychological HF symptoms and HRQOL. Optivol threshold crossings can provide additional information regarding symptom burden and HRQOL that may enhance clinical assessment of symptoms and facilitate the earlier treatment to improve patient outcomes.

References for Chapter II (See Cumulative References)

CHAPTER III

Self-care Moderates the Relationship between Symptoms and Health-related Quality of Life in Heart Failure

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Abstract

Background: Physical symptoms and depression in heart failure (HF) are key drivers of health-related quality of life (HRQOL). Heart failure self-care behaviors are believed to influence how symptoms affect HRQOL. **Objective:** Determine if HF self-care behaviors moderate the relationships between physical and depressive symptoms and HRQOL. **Methods:** In a cohort of adults with moderate to advanced HF, multivariate linear regression was used to evaluate the interaction between self-care behaviors (Self-Care of HF Index maintenance and management scales) and physical HF symptoms (HF Somatic Perception Scale) on emotional HRQOL (emotional dimension of Minnesota Living with HF Questionnaire). The interaction between self-care behaviors and depression (9-item Patient Health Questionnaire) was evaluated on physical HRQOL (physical dimension of Minnesota Living with HF Questionnaire). **Results**: The mean age of the sample (n=202) was 57±13 years, 50% were women, and 61% had NYHA class III/IV HF. Controlling for age, Seattle HF Score, functional ability and co-morbidities, self-care maintenance and management moderated the relationship between physical HF symptoms and emotional HRQOL. Only self-care maintenance moderated the relationship between depression and physical HRQOL. **Conclusions:** In HF, HRQOL is dependent upon both the severity of physical and depressive symptoms and the level of engagement in HF self-care behaviors. Future research should consider both self-care behaviors and symptoms when examining patient HRQOL.

KEYWORDS: Heart failure, Symptoms, Self-care, Health-related quality of life

Background

Heart failure (HF) is a prevalent cardiovascular syndrome characterized by distressing symptoms and high mortality (Heo et al., 2007; Mozaffarian et al., 2015; Zambroski et al., 2005). The clinical hallmark of dyspnea is the most frequent physical symptom of HF (Jurgens, 2006) and is the primary reason for HF hospitalization (Kociol et al., 2013). Depression is also common in patients with HF, contributing significantly to increased mortality and poor health-related quality of life (HRQOL) (Rutledge, Reis, Linke, Greenberg, & Mills, 2006). Understanding how physical symptoms and depression influence patient outcomes is a priority for clinicians since these HF symptoms predict mortality and are the primary drivers of HRQOL A modifiable factor that may influence the strength and direction of the relationship between symptoms and HRQOL is HF self-care (Riegel et al., 2015a; Riegel, Lee, & Dickson, 2011). Self-care in HF entails adherence behaviors to prevent and monitor symptoms (i.e. maintenance) and behaviors to recognize and self-treat symptoms (i.e. management)(Riegel et al., 2015a). The Situation-specific Theory of HF Self-care proposes physical and emotional symptoms influence self-care and that moderate-to-high levels of self-care are needed to influence outcomes(Riegel et al., 2015a). Additionally, a number of studies have shown physical and depressive symptoms to be associated with HRQOL in HF (Bekelman et al., 2007; Heo et al., 2013; Zambroski et al., 2005), and HF self-care behaviors have been shown to be positively associated with HRQOL (Jonkman et al., 2016; C. S. Lee et al., 2014). In these studies, however, HF symptoms and self-care were examined as independent predictors of HRQOL. But, symptoms and self-care in HF are likely not independent. For example, fewer episodes of pulmonary congestion, a common reason for dyspnea in HF, are associated better HF self-care (Rathman et al., 2011), and higher levels of self-care have been associated with lower odds of having elevated HF biomarkers suggesting that engagement in self-care may influence HF progression resulting in fewer symptoms and better HRQOL (C. S. Lee, Moser, Lennie, Tkacs, et al., 2011; C. S. Lee, Tkacs, & Riegel, 2009). No studies to date, however, have examined how HRQOL is a function of symptoms, HF self-care, and the interaction between the two. This is a significant gap in our knowledge of HF symptomology and self-care since a primary goal of interventions focused on HF self-care is to mitigate the frequency and/or severity of HF symptoms leading to improved HRQOL. A more complete understanding of how HF self-care behaviors (i.e. maintenance and management) and physical HF symptoms and depression interact to influence HRQOL will provide much needed information to develop tailored interventions to reduced symptom burden and improve patient quality of life. The goal of this study was to determine if HF self-care behaviors alter the strength and/or direction of the relationship between symptoms and HRQOL.

Method

Procedure

A secondary analysis was completed on data collected between 2010 and 2013 during a prospective cross-sectional study examining gender differences in symptoms in adults with moderate to advanced HF. The study was conducted at an advanced HF clinic associated with an academic medical center in Pacific Northwest, United States (C. S. Lee et al., 2013). By design, data were collected on 101 men and 101 women with NYHA class II-IV HF. Additional inclusion criteria included age 21 years or older, willingness to provide informed consent, ability to read at least 5th grade English and

Figure 1. Moderation Testing Analysis Plan

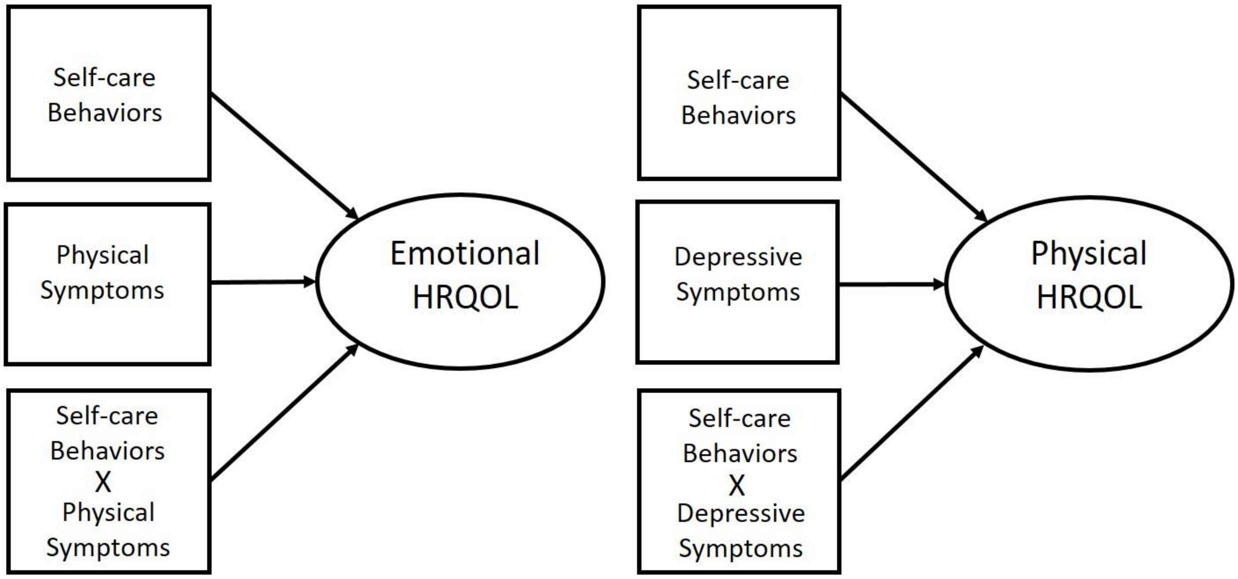

Figure 1 Legend: The analytic approach involves using hierarchical regression to examine whether the interaction of symptoms (physical and depressive) and self-care behaviors significantly influence HRQOL (emotional and physical) above and beyond the independent contributions of symptoms and self-care. Emotional HRQOL was regressed on physical symptoms, each self-care behavior (maintenance and management) and an interaction term combining physical symptoms and a self-care behavior. The same approach was used examine the influence of depression and self-care behaviors on physical HRQOL. The reason a metric of emotional HRQOL was analyzed in relation to physical symptoms and physical HRQOL in relation to emotional symptoms was to avoid inherent measurement overlap.
Abbreviations: HRQOL – health-related quality of life

receiving optimized HF treatment by a cardiologist. Exclusion criteria included a diagnosis of a major cognitive disorder (e.g. Alzheimer’s disease), having received a heart transplant or ventricular-assist device or being unable to complete study requirements. Written and informed consent was obtained from all participants and the study was approved by our institutional review board.

Measurement

A questionnaire was used to obtain participant's sociodemographic and clinical data including age, gender, marital/partnership status, race/ethnicity, employment, and adequacy of financial resources. Comorbid conditions were evaluated with the Charlson Comorbidity Index(Charlson ME, 1987). Clinical and treatment characteristic were collected through an in-depth review of the electronic health record. The Seattle HF Model Score was calculated using data collected from the patient electronic medical record at the time of enrollment. The calculation for the Seattle HF Score was derived from the model developed by Levy et al (Levy, 2006). The model includes demographic (i.e. age-per decade, gender), clinical factors related to HF (i.e. HF etiology, New York Heart Association functional class, systolic blood pressure, left ventricular ejection fraction, hemoglobin, lymphocyte percent, uric acid, total cholesterol, and sodium) and HF treatment (β-blockers, angiotensin converting enzyme inhibitors, allopurinol, diuretic dose, statin use, and device therapy). A composite of the model factors creates a mortality risk-prediction score from -0.16 to 3.85 in this sample, with higher scores indicating greater mortality risk. Self-reported functional ability was assessed using the Duke Activity Status Index (DASI) (Hlatky et al., 1989).

Physical symptoms: Physical HF symptoms were measured with the 18-item HF Somatic Perception Scale (HFSPS) (Jurgens et al., 2015). The HFSPS asks about the presence of HF symptoms and how much the participant was bothered by those symptoms during the last week and provides six response options ranging from 0 (not at all) to 5 (extremely bothersome). The HFSPS has excellent internal consistency (alpha = 0.90) with higher scores on the HFSPS indicating more physical symptom burden(Jurgens et al., 2015).

Depressive symptoms: Depression was measured using the 9-item Patient Health Questionnaire (PHQ9). The PHQ9 provides 4 response options 0 (not at all) to 3 (nearly every day) based on the Diagnostic and Statistical Manual, 4th Edition (Spitzer et al., 1999). Scores range from 0 – 27 with higher scores indicating more depression. The PHQ9 is sensitive and specific for detecting major depression with excellent internal consistency (alpha = 0.86 - 0.89) (Kroenke et al., 2001). Scores on the PHQ9 indicate mild, moderate, moderately severe and severe depression with values of 5, 10, 15 and 20, respectively (Kroenke et al., 2001).

Self-care Behaviors: Heart failure self-care behaviors were measured with the Self-Care of HF Index (SCHFI v.6) self-care maintenance and self-care management scales; responses are standardized scores (0-100; higher values indicate better self-care) (Riegel, Lee, Dickson, & Carlson, 2009). The 10 items of the self-care maintenance scale use a 4-point scale with sufficient internal consistency (global reliability index = 0.82 and model-based internal consistency coefficient = 0.83) (Barbaranelli, Lee, Vellone, & Riegel, 2014). The SCHFI self-care management scale is comprised of 6 items with 4 to 5 response options (Riegel, Lee, et al., 2009). The SCHFI management score has sufficient internal consistency (global reliability index = 0.77 and model-based internal consistency coefficient = 0.76) (Barbaranelli et al., 2014). The SCHFI scores of 70 or greater are considered adequate self-care (Riegel et al., 2015a).

Health-related Quality of Life: Heart failure-specific HRQOL was measured using the Minnesota Living with HF Questionnaire (MLHFQ), a 21 item scale that quantifies the physical (8 items), emotional (5 items), and social (8 items) impact of HF and treatment on patients' lives. Items are rated on a 6 point scale ranging from 0 (no effect) to 5 (very

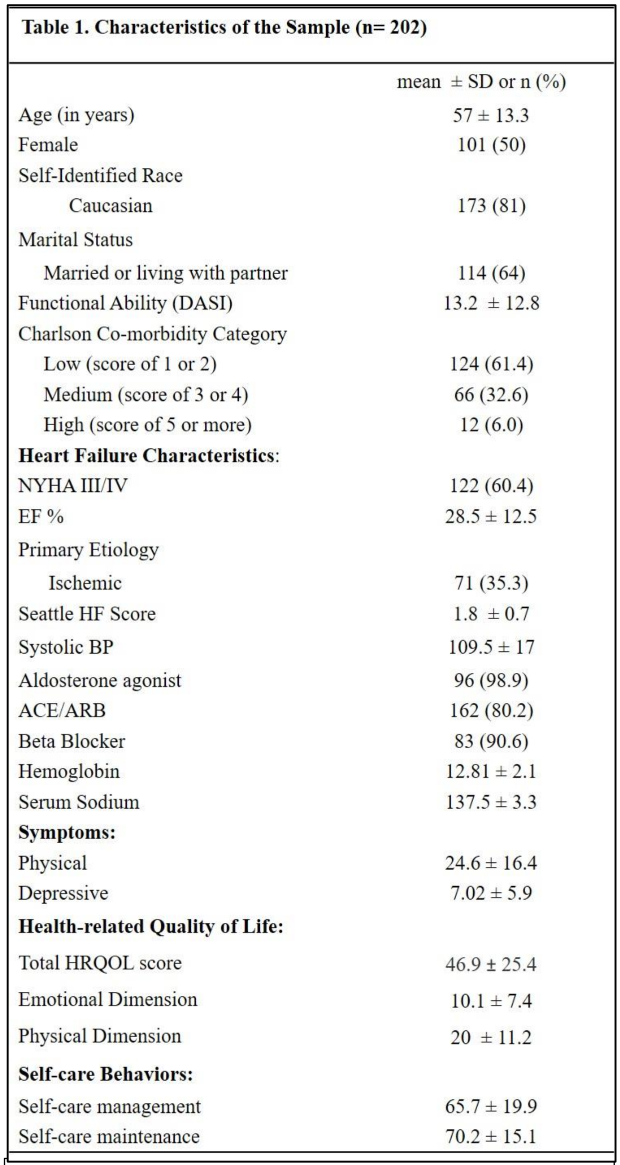

Table 1. Characteristics of the Sample (n= 202)

	mean ± SD or n (%)
Age (in years)	57 ± 13.3
Female	101 (50)
Self-Identified Race	
Caucasian	173 (81)
Marital Status	
Married or living with partner	114 (64)
Functional Ability (DASI)	13.2 ± 12.8
Charlson Co-morbidity Category	
Low (score of 1 or 2)	124 (61.4)
Medium (score of 3 or 4)	66 (32.6)
High (score of 5 or more)	12 (6.0)
Heart Failure Characteristics:	
NYHA III/IV	122 (60.4)
EF %	28.5 ± 12.5
Primary Etiology	
Ischemic	71 (35.3)
Seattle HF Score	1.8 ± 0.7
Systolic BP	109.5 ± 17
Aldosterone agonist	96 (98.9)
ACE/ARB	162 (80.2)
Beta Blocker	83 (90.6)
Hemoglobin	12.81 ± 2.1
Serum Sodium	137.5 ± 3.3
Symptoms:	
Physical	24.6 ± 16.4
Depressive	7.02 ± 5.9
Health-related Quality of Life:	
Total HRQOL score	46.9 ± 25.4
Emotional Dimension	10.1 ± 7.4
Physical Dimension	20 ± 11.2
Self-care Behaviors:	
Self-care management	65.7 ± 19.9
Self-care maintenance	70.2 ± 15.1

Table 1 Legend: Abbreviations: ACE - angiotensin converting enzyme; ARB - angiotensin receptor blocker; BP - blood pressure; DASI - Duke Activity Status Index; EF - ejection fraction; HF - heart failure; HRQOL - health-related quality of life; NYHA - New York Heart Association

much) (Bilbao, Escobar, Garcia-Perez, Navarro, & Quiros, 2016). The MLHFQ has been shown to be a valid and reliable instrument and has been used extensively to assess disease-specific HRQOL in HF research (Bilbao et al., 2016; Grady, 2008; Rector & Cohn, 1992). The score for the MLHFQ physical dimension and the MLHFQ emotional dimension can range from 0 - 40 and 0 - 25 respectively, with a higher score indicating worse HRQOL. A total MLHFQ score > 45 represents poor HF-specific HRQOL and a score < 24 denotes good HRQOL (Behlouli et al., 2009).

Analysis

Means, standard deviations, frequency, and percentages were used to describe the sample using Stata/IC v14.2. Multivariate linear regression was used to model whether HF self-care moderates the relationship between physical symptoms and HRQOL (**Figure 1**). The emotional dimension of the MLHFQ (dependent variable) score was regressed on the physical symptom measure (HFSPS), one self-care behavior (management or maintenance) and an interaction term combining physical symptoms and the specified self-care behavior. Using hierarchical regression, change in R^2 and F-values were examined between models with and without the interaction term of physical symptoms and self-care behaviors. The same method was used to assess the moderation of self-care behaviors on the relationship between depression (PHQ9) and physical HRQOL (physical dimension of the MLHFQ). The purpose of selecting an emotional HRQOL metric in association with physical symptoms, and selecting a physical HRQOL

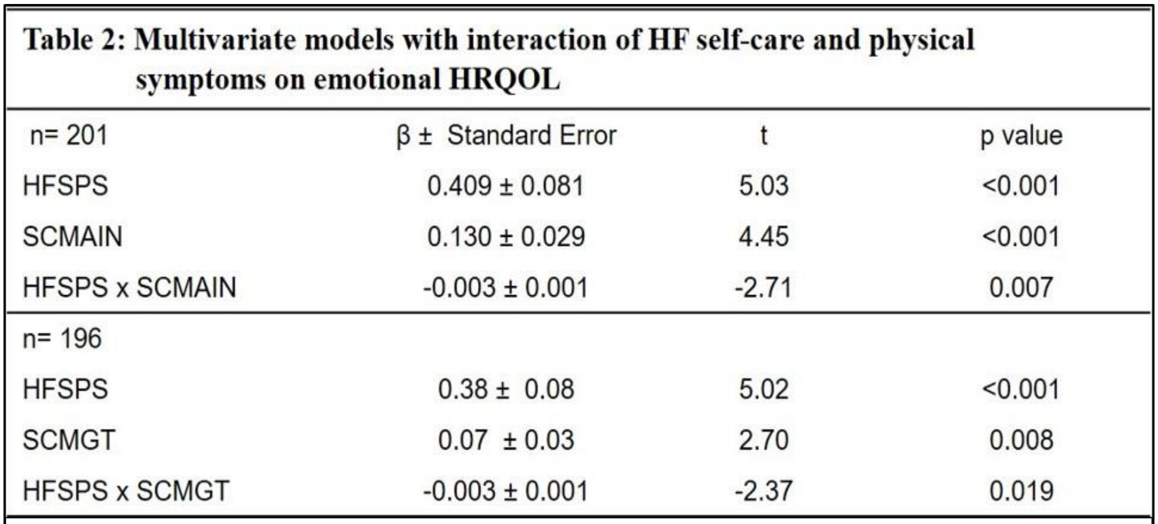

Table 2: Multivariate models with interaction of HF self-care and physical symptoms on emotional HRQOL

n= 201	β ± Standard Error	t	p value
HFSPS	0.409 ± 0.081	5.03	<0.001
SCMAIN	0.130 ± 0.029	4.45	<0.001
HFSPS x SCMAIN	-0.003 ± 0.001	-2.71	0.007
n= 196			
HFSPS	0.38 ± 0.08	5.02	<0.001
SCMGT	0.07 ± 0.03	2.70	0.008
HFSPS x SCMGT	-0.003 ± 0.001	-2.37	0.019

Table 2 Legend: For SCMAIN model: $\Delta R^2 = 0.022$, $\Delta F(1, 194) = 5.98$, $p < 0.001$. For SCMGT model: $\Delta R^2 = 0.015$, $\Delta F(1, 189) = 3.82$, $p < 0.001$. The main effects of physical symptoms and self-care as well as the interaction of self-care (maintenance and management) and physical symptoms were all significant at a p value < 0.05. In addition, a significant change in R^2 was observed with the inclusion of the interaction term indicating self-care behaviors moderate the relationship between physical symptoms and emotional HRQOL. Each model was adjusted for age, Seattle HF Score, functional ability and co-morbidities. Albeit minimal, there was some marginal reduction in sample size due to missingness in model covariates. Abbreviations: HF – heart failure; HFSPS - Heart Failure Somatic Perception Scale; HRQOL - health-related quality of life; SCMAIN- self-care maintenance; SCMGT- self-care management

metric in association with depressive symptoms was to avoid inherent measurement overlap. To account for the effect of other factors associated with HF, each model was adjusted for the Seattle HF Model Score and additional covariates associated with HF-specific HRQOL in previous research, namely age, comorbidities and functional ability. Although age per decade is a factor in the Seattle HF model, the full distribution of patient age per year was used as a covariate in this analysis to more directly control for the potential confounding effects of age. Formal moderation testing was used with an a priori alpha of 0.05. The moderation of self-care on physical symptoms or depression and HRQOL was represented with 1) contour plots generated across the complete observed range of physical and depressive symptoms, self-care behaviors and HRQOL and 2) by plotting the predicted values of HRQOL by physical or depressive symptoms with and without the moderation of self-care behaviors.

Results

The mean age of the sample (n=202) was 57 years old, half were women, a majority (60%) of subjects had Class III-IV HF, and most (65%) had non-ischemic HF (**Table 1**). The average overall HRQOL was low (Behlouli et al., 2009). On average, self-care maintenance was adequate and self-care management inadequate using the common cut-point of 70 (**Table 1**). Better self-care maintenance and management were both independently associated with worse emotional HRQOL in adjusted models (**Table 2**). Worse physical symptoms were independently associated with worse emotional HRQOL ($\beta = 0.409 \pm 0.081$, $p < 0.001$). Self-care maintenance and self-care management moderated the relationship between physical HF symptoms and emotional HRQOL (**Table 2**). As a key example, worse emotional HRQOL was experienced when physical symptoms were mild and when self-care behaviors were high (**Figures 2A** & **2C**). Conversely, better emotional HRQOL was experienced when both physical symptoms and self-care behaviors were high. The relationship between worse physical symptoms and worse emotional HRQOL was not constant across all levels of engagement with self-care (Figure 2B & 2D). That is, the better the self-care the less physical symptoms affect emotional HRQOL. In addition, more severe depression was independently associated

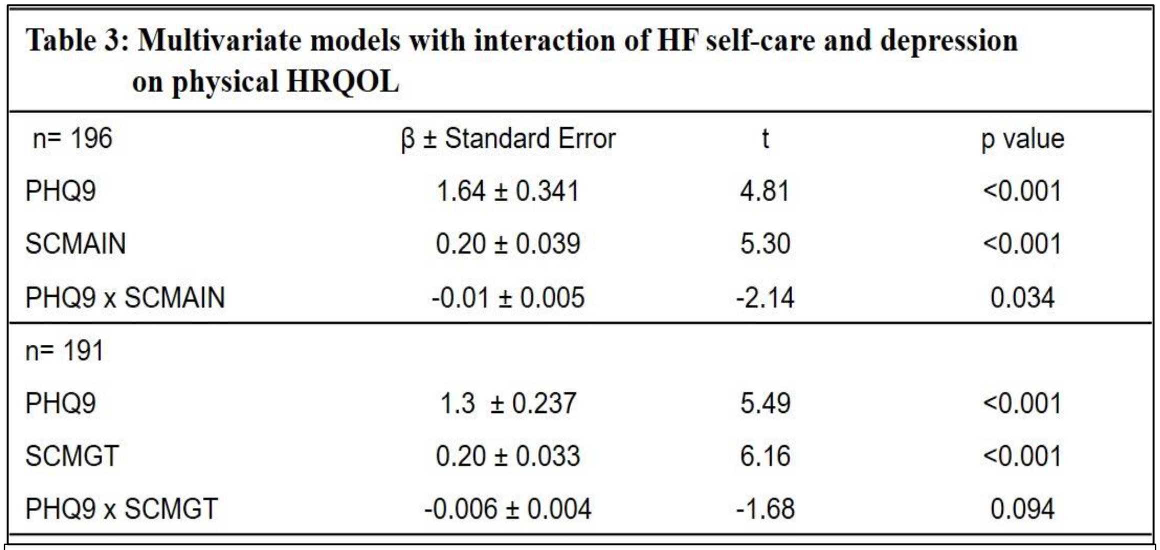

Table 3: Multivariate models with interaction of HF self-care and depression on physical HRQOL

n= 196	β ± Standard Error	t	p value
PHQ9	1.64 ± 0.341	4.81	<0.001
SCMAIN	0.20 ± 0.039	5.30	<0.001
PHQ9 x SCMAIN	-0.01 ± 0.005	-2.14	0.034
n= 191			
PHQ9	1.3 ± 0.237	5.49	<0.001
SCMGT	0.20 ± 0.033	6.16	<0.001
PHQ9 x SCMGT	-0.006 ± 0.004	-1.68	0.094

Table 3 Legend: For SCMAIN model: $\Delta R^2 = 0.009$, $\Delta F(1, 189) = 2.87$, $p = 0.007$; For SCMGT model: $\Delta R^2 = 0.005$, $\Delta F(1, 184) = 1.21$, $p = 0.11$. The main effects of depression and self-care and the interaction of self-care maintenance but not self-care management and depression were significant at a p-value < 0.05. Additionally, a significant change in R^2 was observed with the inclusion of the interaction term (PHQ9 x SCMAIN) indicating self-care maintenance moderates the relationship between depressive symptoms and physical HRQOL. Each model was adjusted for age, Seattle HF Score, functional ability and co-morbidities. Albeit minimal, there was some marginal reduction in sample size due to missingness in model covariates. Abbreviations: HF – heart failure; HRQOL - health-related quality of life; PHQ9 - 9-item Patient Health Questionnaire; SCMAIN - self-care maintenance; SCMGT - self-care management

with worse physical HRQOL (β = 1.64 ± 0.341, $p < 0.001$). Self-care maintenance but not self-care management significantly moderated the relationship between depression and physical HRQOL (Table 3). For example, worse physical HRQOL was associated with poor self-care maintenance and more severe depression (Figure 3A). In contrast, better physical HRQOL was observed when both depression and self-care maintenance were low. As seen with physical symptoms and emotional HRQOL, the relationship between depressive symptoms and physical HRQOL was not constant across all levels of self-care maintenance (Figure 3B). The better the self-care maintenance the less depressive symptoms affect physical HRQOL.

Discussion

In this study of 101 women and 101 men with symptomatic HF, we observed that HRQOL is dependent upon both symptomatology and engagement in HF self-care. The worst HRQOL was reported when physical and depressive symptoms were severe and self-care was poor while, interestingly, the best HRQOL was associated with few symptoms and *low levels of self-care engagement*. Additionally, better emotional HRQOL was reported when both physical symptom and self-care behaviors were high. These findings provide new insights into the complex interaction among self-care behaviors, common HF symptoms and HRQOL.

Heo et al. (2013) and others (Bekelman et al., 2007; Heo et al., 2007; Zambroski et al., 2005) have shown that more severe physical HF symptoms and depression are associated with worse HRQOL. The relationship between self-care behaviors and HRQOL is not clear. In a review of self-care interventions aimed at improving HRQOL in adults with HF, Grady (2008) reported a possible positive association between self-care and

Figure 2. Self-care as a Moderator of Physical Symptoms and Emotional HRQOL

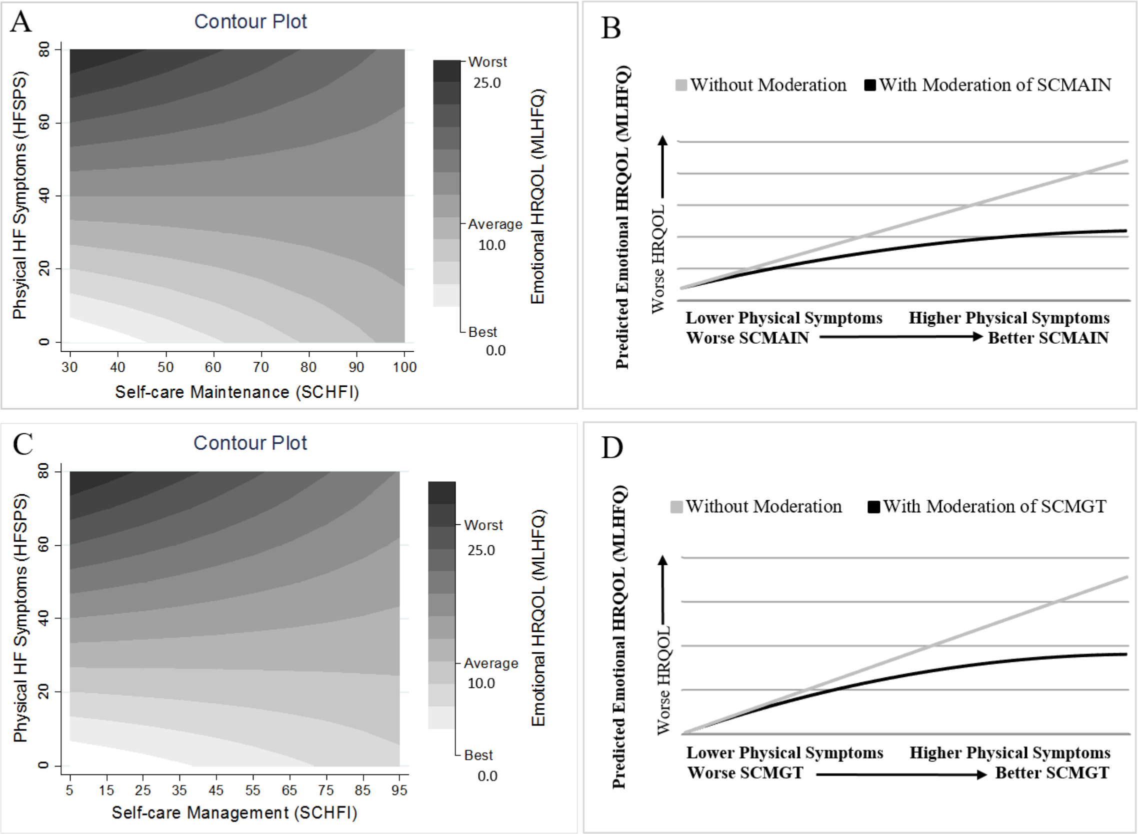

Figure 2 Legend:

Plots A & C: The contour plots show that emotional HRQOL was dependent upon both the level of physical symptoms and self-care (maintenance and management) at all levels. For example, the best emotional HRQOL (white color) was reported when both symptoms and self-care are low, and the worst emotional HRQOL (black color) was reported when symptom were high but self-care was low**. Plots B & D**: Linear regression was used to estimate emotional HRQOL with and without the moderation of self-care (maintenance and management) on the relationship between physical symptoms and emotional HRQOL. The better the self-care, the less physical symptoms affect emotional HRQOL.

Note: Plots B & D represent a simplified moderation for economy of presentation whereas Plots A & C represent the full complexity of moderation.

Abbreviations: HFSPS - Heart Failure Somatic Perceptions Scale; HRQOL - health-related Quality of Life; MLHFQ - Minnesota Living with Heart Failure Questionnaire; SCMAIN - Self-care maintenance; SCMGT - Self-care management

HRQOL. However, small sample sizes and heterogeneity in the study designs and measurement of HRQOL prevented unequivocal conclusions from the review. Additionally, Jonkman et al. (2016), in a meta-analysis of 20 HF self-management

Figure 3. Self-care Maintenance as a Moderator of Depression and Physical HRQOL

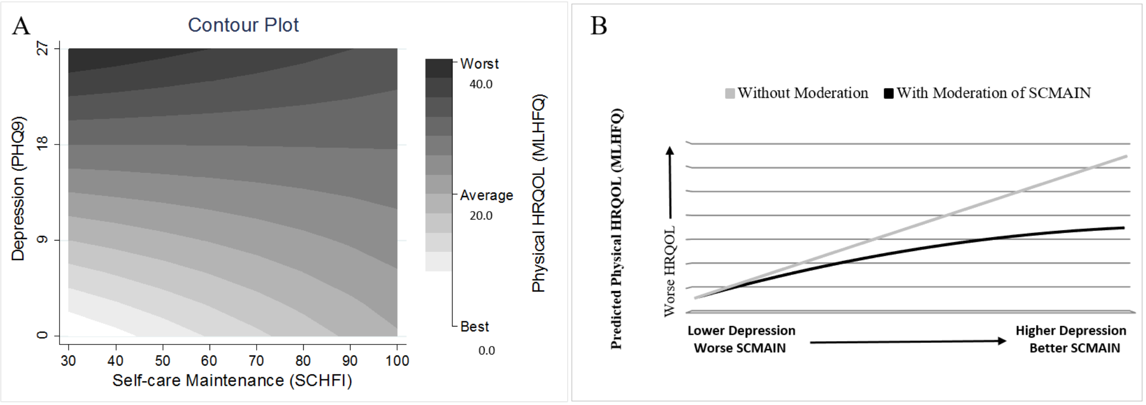

Figure 3 Legend:

Plot A: The contour plot shows physical HRQOL as a function of both depression and self-care maintenance at all levels. The best physical HRQOL was reported when depression was low and self-care maintenance was low, and the worst physical HRQOL was reported when depression was high and self-care was low. Not surprisingly, when depression was high, more engagement in self-care maintenance had little association with better physical HRQOL. This suggests when depression is high, physical HRQOL is poor regardless of the level of self-care. **Plot B**: Linear regression was used to estimate physical HRQOL with and without the moderation of self-care maintenance on the relationship between depression and physical HRQOL. The better the self-care maintenance, the less depression affects physical HRQOL. **Note:** that Plot B represents a simplified moderation for economy of presentation whereas Plot A depicts the full complexity of moderation.

Abbreviations: PHQ9 - 9 item Patient Health Questionnaire; HRQOL - health-related Quality of Life; MLHFQ - Minnesota Living with Heart Failure Questionnaire; SCMAIN - Self-care maintenance

studies, demonstrated self-management interventions had a small but positive effect on HRQOL. The relationship between self-care behaviors and the severity of physical symptoms and depression is also uncertain. Lee et al. (2015) and others (Holzapfel et al., 2009) have shown that worse physical HF symptoms or depression in relatively young HF patients were associated with better self-care suggesting HF symptoms are key drivers of self-care (Kessing, Denollet, Widdershoven, & Kupper, 2016; K. S. Lee, Lennie, Warden, Jacobs-Lawson, & Moser, 2013). Alternatively, Graven et al. (2015) found that among older adults worse physical HF symptoms were associated with lower levels of self-care and with no association between depression and HF self-care. In sum, the relationships between self-care behaviors and symptoms in influencing HRQOL in HF are inconclusive based on prior research. The current study provides new information regarding these complicated relationships that enhances our understanding of how differences in self-care behaviors and symptoms affect HRQOL in patients with HF.

Our findings show that emotional HRQOL is influenced by both the engagement in self-care and the severity of physical symptoms. For example, better emotional HRQOL was observed when self-care maintenance and management were high and physical symptoms were more severe. One explanation for why patients with high levels of symptoms exhibit higher levels of self-care may be that worsening symptoms increase engagement with self-care (Holzapfel et al., 2009; C. S. Lee, Gelow, et al., 2015). Another explanation for the interaction of self-care behaviors and symptoms on HRQOL may be patients with severe physical symptoms are receiving more frequent contact from family members or their healthcare team, who may provide additional teaching or feedback enhancing self-care behaviors and in turn improving emotional HRQOL (C. S. Lee, Moser, Lennie, Tkacs, et al., 2011). Although the focus of this research was on self-care behaviors, others have hypothesized and provided evidence of the role of confidence in self-care. Better self-care confidence has been shown in prior research to be associated with higher levels of self-care behaviors (Riegel, Lee, Albert, et al., 2011) and better HRQOL (Buck et al., 2012; Joekes, Van Elderen, & Schreurs, 2007; Macabasco-O'Connell et al., 2011; Riegel et al., 2015a). Hence, a third possible explanation could be the role of confidence.

Contrasting our results of better HRQOL with severe physical symptoms and better self-care, we found worse emotional HRQOL was associated with mild physical symptoms when self-care was high. This result is consistent with data reported by Peters-Klimm et al. (2013) who also found better self-care related to worse HRQOL in a community-dwelling sample with predominantly less severe symptoms (60% NHYA class I-II). The observation of worse emotional HRQOL in participants with better self-care who were experiencing a low level of physical symptom severity may suggest that some aspect of good self-care is influencing worse HRQOL in these patients. Perhaps excellent self-care in the setting of mild physical symptoms may be perceived by some patients as burdensome, influencing worse emotional HRQOL (Riegel et al., 2015a). Continued research, particularly of longitudinal design, is needed to elucidate the temporal relationships and other factors associated with self-care, physical symptom severity and emotional HRQOL.

Advancing the understanding of self-care, depression and physical HRQOL, our results indicate that self-care maintenance but not self-care management significantly influenced the association of depression on physical HRQOL. Our analysis demonstrated the worst physical HRQOL was observed with the highest levels of depression and poor self-care maintenance. This results is consistent with recent research by Graven et al. (2015) that demonstrated worse physical HF symptoms (similar to the physical dimension of the MLHFQ) were associated with more depression and poor adherence behaviors (self-care maintenance). Furthermore, our results demonstrated better self-care maintenance did not affect HRQOL at high levels of depression. Simply put, with severe depression poor quality of life is a given irrespective of the level of self-care maintenance. Additionally, we found that the best physical HRQOL was associated with low levels of depression and the poorest self-care maintenance. This finding supports research showing less depression is associated with better HRQOL (Bekelman et al., 2007; Heo et al., 2013) and substantiates the idea that less severe symptoms are associated with lower levels of self-care. In other words, mild to absent depression may result in better physical HRQOL for patients with HF creating less motivation to engage in frequent self-care maintenance behaviors.

Our research has several strengths. First, the study sampled equal numbers of men and women; the original study was designed to address gender inequalities in sampling prevalent in the majority of HF literature. Second, our study examined both physical and emotional symptoms in HF providing a broader picture of HF symptomology. Third, the analysis was designed to mitigate the measurement overlap between the physical HF symptoms, depression and the MLHFQ. There are also important limitations that should be taken into consideration when interpreting the results. First, the cross-sectional design of the study prevents drawing conclusions about temporal or causal relationships. Future studies with longitudinal and/or experimental designs are needed to better understand how symptoms, self-care and quality of life are associated over time. Second, the sample was obtained from a clinic associated with a large academic medical center where patients tend to be younger, sicker, and more have HF of non-ischemic etiology that may limit the generalizability of our findings to all HF populations.

Conclusion

In our sample, HRQOL was dependent upon both the level of symptom burden and level of engagement in self-care such that the better the self-care the less physical symptoms and depression affect HRQOL. Furthermore, knowing that self-care behaviors influence the relationship between HF symptoms and HRQOL differently depending on the patient's symptom severity may inform strategies to teach adherence and symptom monitoring skills that minimize negative impacts on HRQOL. The results of this study highlight the need to focus further research, patient education and clinical practice on both HF symptoms and HF self-care in order to optimize outcomes for patients.

References for Chapter III (See Cumulative References)

CHAPTER IV

Patterns of Heart Failure Symptoms are Associated with Self-care Behaviors over 6 Months

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represent the official views of the National Institutes of Health or the American Heart Association.

Abstract

Background: Both heart failure (HF) symptoms and self-care are associated with patient outcomes. Although it is thought that symptoms drive self-care, there is limited evidence to support this assumption over time. **Aims:** Determine whether patterns of physical symptoms are significantly associated with HF self-care over time. **Method:** Latent mixture analysis was used to identify sub-groups based on physical symptoms of dyspnea, sleepiness and edema (using the HF Somatic Perception and Epworth Sleepiness Scales). Growth modeling was used to determine if symptom sub-groups were associated with self-care behaviors (using the Self-care in HF Index) over 6 months. Socio-demographic and clinical variables predicting likelihood of sub-group membership were identified using logistic regression. **Results:** The sample (n=146) was on average 57 years old, 70% were men and 59% had class III/IV HF. Two symptom sub-groups were identified (entropy=0.91); a high symptom group (n=24(16%)) with no significant change in symptoms over time (high sustained), and low symptom group (n=122(84%)) with no significant change in symptoms over time (low sustained). The high sustained group was associated significantly with better self-care behaviors at baseline and over 6 months. Women (OR=3.98, p=0.025) and patients with more depressive symptoms (OR=1.13, p=0.013) were more likely to be in the high sustained symptom group. Those treated with a renin-angiotensin-aldosterone system agent were less likely to be in the high symptom group (OR=0.16, p=0.016). **Conclusion:** Patients bothered more by symptoms are consistently more engaged in self-care behaviors over time. Results of this study support symptoms as an important driver of self-care behaviors.

Keywords: heart failure, symptoms, self-care, symptom management, depression

Introduction

Background

Heart failure (HF) is a growing global problem, affecting an estimated 26 million people worldwide and is the leading cause of hospital admission for older adults in the US (Benjamin et al., 2017; Ponikowski et al., 2014). Exacerbation of physical symptoms such as dyspnea is the primary reason patients with HF seek care often leading to burdensome and costly hospitalizations (Kociol et al., 2013). Symptoms are of primary concern for clinicians and patients as symptoms are associated with mortality risk, strongly affect quality of life and are used to evaluate progression of HF and guide HF therapies (Negi et al., 2014; Yancy et al., 2013). Due to the importance of physical symptoms in HF, self-care behaviors to prevent and monitor symptoms (maintenance) and decision-making behaviors addressing symptoms once detected (management) are cornerstones of HF management (Riegel et al., 2017). More engagement in self-care behaviors is associated with fewer hospitalizations, better quality of life and lower mortality (C. S. Lee et al., 2017). Although assessment of physical symptoms and self-care are essential aspects of HF management, little is known about how symptoms and self-care are related to one another particularly over time.

Studies that have examined the relationship between physical symptoms and HF self-care have yielded inconsistent results. For example, HF symptoms have been shown to be both positively and negatively associated to self-care behaviors. Lee et al (2013) and Rockwell & Riegel (2001) demonstrated higher levels of HF symptoms associated with increased HF self-care behaviors while Graven and colleagues (2015) describe less engagement in HF self-care associated with worse HF symptoms. Similarly, patients less engaged with adherence behaviors, such as eating a low salt diet (S. Heo et al., 2014) have been shown to have more severe symptoms compared to those with higher levels of such behaviors. Furthermore, patients often experience physical symptoms and practice self-care behaviors in distinct patterns which have been shown to provide important information regarding mortality and clinical event risk (C. S. Lee et al., 2017; C. S. Lee et al., 2013). For example, Lee et al. (2013) describe three distinct physical and psychological symptom patterns (mild, moderate, and severe) that were associated with 1 year event free survival. The relationship between patterns of physical symptoms and self-care, however, has yet to be explored. Thus, how HF symptoms and HF self-care behaviors influence one another remains unclear.

Due to the importance of both symptoms and self-care in affecting patient outcomes, understanding the relationship between HF symptoms and self-care behaviors is critical in advancing the care of patients with HF and the understanding of how and why patients engage in self-care behaviors. One limiting factor in elucidating the important relationship between symptoms and self-care is the lack of longitudinal studies in this area. The vast majority of studies are cross-sectional, hindering the ability to examine how symptom are related to self-care over time. Without longitudinal studies we cannot begin to untangle the temporal or directional association of symptoms and self-care in HF. The purpose of this longitudinal study is to determine 1) whether patterns of

HF symptoms are significantly associated with corresponding patterns in self-care behaviors over 6 months and 2) determine socio-demographic and clinical predictors of symptom patterns. The results of this study will provide essential information that may enhance our understanding of HF self-care and physical symptoms to guide the development of interventions focused on improving outcomes for patient with HF.

Methods

Design, Setting, Sample

In this analysis, a sample of 146 participants with symptomatic HF (NYHA Class II-IV) were recruited for a longitudinal study from a community-based HF clinic associated with an academic medical center. Details of the original study have been previously described (C. S. Lee, Gelow, et al., 2015). All participants were being optimally managed by a cardiologist specializing in advanced HF. At a clinic appointment, all participants were provided written informed consent presented by a member of the study team not associated with their care. The study was approved by the Institutional Review Board associated with the academic medical center. The investigation conforms to the principles outlined in the Declaration of Helsinki (World Medical, 2013). Socio-demographic information was collected at enrollment. Additionally, at enrollment, three and six months, participants completed a survey of symptoms (physical and emotional) and engagement of self-care behaviors. Surveys were completed in person during their clinic visit, by mail, or by telephone per the participants' preference. Additional clinical data associated with HF was abstracted at each time point (enrollment, 3 and 6 months). Attrition at 6 months was 9.3%.

Measures

HF symptoms

Dyspnea was measured with the 6-item dyspnea subscale of the Heart Failure Somatic Perception Scale (HFSPS dyspnea) (Jurgens et al., 2015). The HFSPS asks about how much the participant was bothered by HF symptoms related to dyspnea during the last week and provides six response options ranging from 0 (not at all) to 5 (extremely bothersome). The HFSPS dyspnea has excellent internal consistency (alpha = 0.89) concordant validity with the KCCQ functional limitations scale (r = 0.53) and independently predicts HF-related clinical events (per point HR = 1.031, p=0.031) (Jurgens et al., 2015).

Patient-perceived edema was measured with the 3-item edema subscale of the HFSPS (HFSPS edema).(Jurgens et al., 2015) The HFSPS edema asks about how much the participant was bothered by feet swelling, tightness of shoes and weight gain. The HFSPS edema provides six response options ranging from 0 (not at all) to 5 (extremely bothersome) and has good internal consistency (alpha = 0.75) (Jurgens et al., 2015).

Wake disturbance was measured with the Epworth Sleepiness Scale (ESS). The ESS asks participants to rate how likely they are to fall asleep in 8 different situations. The rating range from 0 (never) to 3 (high chance) (Johns, 1991). Scores range from 0-24 with higher values indicating more daytime wake disturbance. The ESS correlates with the Multiple Sleep Latency Test and has been shown to be responsive to treatment effects of continuous positive airway pressure on sleep propensity (Chen et al., 2002; Johns, 1991).

HF self-care behaviors

Heart failure self-care was measured using the Self-care of HF Index (SCHFI v.6) self-care maintenance and self-care management scales with higher values indicating better self-care (standardized scores of 0-100) (Riegel, Lee, et al., 2009). The 10 item self-care maintenance scale uses 4 response options (never, sometime, frequently, always) and has adequate internal consistency (Barbaranelli et al., 2014). The SCHFI self-care management scale has 6 items using a 4 or 5 point scale with adequate internal consistency (Barbaranelli et al., 2014). Self-care of HF Index scores less than 70 are considered inadequate self-care (Riegel et al., 2015a).

Predictors of symptom patterns

Symptoms of depression were measured using the 9- item Patient Health Questionnaire (PHQ9). The PHQ9 asks patients to assess nine depressive symptom with responses ranging from 0 (not at all) to 3 (nearly every day). A higher rating indicates more severe depressive symptoms with scores of 5, 10, 15 and 20 indicative of mild, moderate, moderately severe and severe depression respectively (Kroenke et al., 2001). The PHQ9 has been previously shown to be sensitive and specific for depression in HF with good reliability (Hammash et al., 2013).

Anxiety was measured using the 6-item anxiety sub-scale of the brief symptom inventory (BSI-anxiety). The BSI asks patients to assess their feelings over the previous 7 days and offers 5 response options ranging from 0 (not at all) to 4 (extremely). The sub-scale score is determined by adding the responses and dividing by the total number of items answered. Higher scores on the BSI-anxiety indicate more anxiety (Derogatis &

Melisaratos, 1983). The BSI-anxiety has been shown to be valid and reliable in patients with HF (Khalil, Hall, Moser, Lennie, & Frazier, 2011).

Table 1. Characteristics of the Sample (n= 146)

		---------------- Symptom Group -----------------		
	Sample (n = 146)	Sustained High (n= 24)	Sustained Low (n = 122)	p value
Age (in years)	57 ± 13.5	55.9 ± 3.3	57.7 ± 1.1	0.601
Female	44 (30.1)	11 (45.8)	33 (27.0)	0.067
Self-Identified Race				
Caucasian	126 (86.3)	18 (75.0)	108 (88.5)	0.043
Education				
High School or less	45 (30.8)	8 (33.3)	37 (30.3)	0.473
Marital Status				
Married or living with partner	94 (64.4)	16 (66.7)	78 (63.9)	0.798
Charlson Co-morbidity category				0.378
low (score of 1 or 2)	93 (63.7)	13 (54.2)	80 (65.6)	
medium (score of 3 or 4)	50 (34.2)	11 (45.8)	39 (32.0)	
high (score of 5 or more)	3 (2.1)	0	3 (2.4)	
BMI	32.0 ± 0.6	33.4 ± 1.9	31.7 ± 0.6	0.389
Heart Failure Characteristics:				
NYHA III/IV	86 (58.9)	18 (75.0)	68 (55.7)	0.080
EF %	28.4± 11.6	31.0 ± 2.5	28.0 ± 1.1	0.350
Primary Etiology				
Ischemic	52 (35.6)	5 (20.8)	47 (38.5)	0.109
Systolic BP	109.3 ± 13.9	112.1 ± 3.5	108.8 ±1.2	0.384
Aldosterone Antagonist	66 (45.2)	11 (45.8)	55 (45.1)	0.946
ACE/ARB	126 (86.3)	16 (66.7)	110 (90.2)	0.002
Beta Blocker	134 (91.8)	21(87.5)	113 (92.6)	0.417
Hemoglobin	13.3 ± 2.0	12.8 ± 0.4	13.5 ± 0.2	0.134
Serum Sodium	138.6 ± 3.2	138.1 ± 0.7	138.6 ± 0.3	0.520
Years with HF	6.4 ± ±5.3	5.3 ± 1.0	6.6 ± 0.5	0.253
Baseline HF Symptoms:				
Dyspnea	7.3 ± 7.5	15.0 ± 1.5	5.8 ± 0.6	<0.001
Wake Disturbance	7.9 ± 4.7	11.4 ± 1.2	7.2 ± 0.4	<0.001
Edema	3.0 ± 3.8	10.1 ± 0.6	1.6 ± 0.2	<0.001
Baseline Self-care Behaviors:				
Self-care maintenance	70.4 ± 16.1	75.8 ± 2.6	69.3 ± 1.5	0.036
Self-care management	63.9 ± 21.5	75 ± 3.8	61.7 ± 1.9	0.003
Baseline Depression:	7.0 ± 5.9	10.2 ± 1.3	6.4 ± 0.5	0.009
Baseline Anxiety:	0.5 ± 0.6	0.7 ± 0.1	0.5 ± 0.1	0.287

Table 1 legend: Abbreviations: BMI–body mass index; NYHA–New York heart association classification; EF–ejection fraction; BP–blood pressure; ACE–angiotensin converting enzyme inhibitor; ARB-angiotensin receptor blocker; HF–heart failure.

Data Analysis

Proportions, means and standard deviations were used to describe the sample as a whole. The Student's t test with unequal variances, Mann-Whitney U test, Chi-square or Fisher's exact test were used to describe differences between groups. Hedge's g was also calculated as the effect size to quantify the magnitude of difference in symptoms. The overall approach to examine the association of physical symptom patterns with self-care over time was first to *identify* naturally-occurring sub-groups based on a cluster of physical symptoms (dyspnea, wake disturbance and edema). The physical symptoms were chosen because they approximate hallmark HF symptoms and represent both left- and right-sided HF. The next step was to *associate* the physical symptom sub-groups with baseline values (intercepts) and/or changes in self-care over time (slopes). The final step was to *predict* symptom group membership using sociodemographic and clinical variables.

Our original analytic strategy was to focus on change in symptoms over time. Since there was no significant change in symptoms over time, however, we reverted to latent class mixture analysis (LCMA) (Mplus v7.4, Los Angeles, CA) to identify naturally-occurring groups. The sub-groups were identified based on baseline symptom data because there was no significant variation in symptom slopes indicating the baseline symptoms were representative of the patient experience over 6 months. Alternative models (e.g. 2 classes vs 3 classes) were compared using posterior probabilities (>90%), model convergence (entropy near 1.0), the size of the observed classes (> 5%) and the Lo-Mendell-Rubin Likelihood Ratio Test (LMRT)($p<0.05$) (Ram & Grimm, 2009). Latent growth modeling was then used to associate naturally-occurring symptom groups with intercepts (baseline values) and slopes (change over time) of self-care behaviors over time. Metrics of fit between estimated and observed data for the latent growth models were evaluated with the chi-square test of model fit (>0.05), comparative fit indices and Tucker-Lewis indices ≥ 0.95 (Hu & Bentler, 1998), root mean square errors of approximation <0.10 (MacCallum, Browne, & Sugawara, 1996), and standardized root mean square residuals <0.08 (Hu & Bentler, 1998). Results from LGM are provided in estimates similar to regression coefficients, standard error and p-values for the intercepts (i) and slopes (s).

Finally, clinical and socio-demographic variables predicting the likelihood of belonging to a physical symptom group were evaluated using multivariate backwards stepwise logistic regression with a p value of 0.2 for variable inclusion in the final model (Stata v14, College Station, TX). Logistic regression analyses are reported as odd ratios (OR) with p-values and 95% confidence intervals. P-values less than 0.05 are considered significant in this analysis. Socio-demographic (e.g. age, gender, race, marital status, education) and HF-related covariates (e.g. HF etiology, left ventricular diastolic diameter, ejection fraction, duration of HF, prescription of HF medications) as well as variables previously shown to influence symptoms and self-care (e.g. comorbidities, BMI, depression and anxiety) were included in the stepwise logistic regression analyses.

Results

The sample (n = 146) was 57 years old on average, 30% of participants were women and a majority self-identified Caucasian (86%) **(Table 1)**. A majority of participants had non-ischemic cardiomyopathy (64%) and most experienced NYHA Class III/IV (59%) symptoms at enrollment. Dyspnea, wake disturbance, and patient-perceptions of edema did not change significantly over the course of 6 months as measures at three month intervals **(Table 2)**. Overall, self-care maintenance behaviors were adequate (>70) at baseline and remained stable for the 6 month study period (*i* =70.3±1.4, p<0.001; *s* =0.9±0.6, p=0.112). Self-care management, on the other hand, was inadequate at baseline (<70) and did not improve significantly over the course of the study (*i* =61.2±1.9, p<0.001; *s* =0.02±0.9, p =0.987).

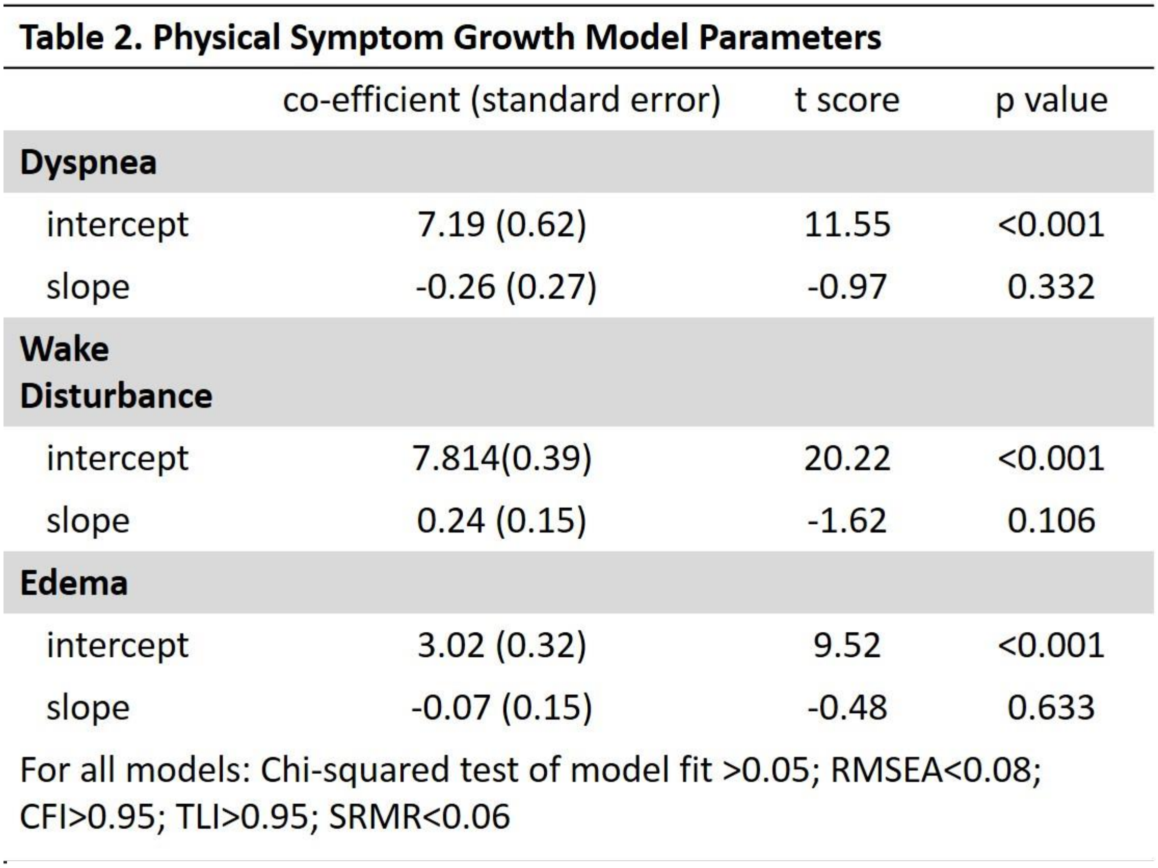

Table 2. Physical Symptom Growth Model Parameters

	co-efficient (standard error)	t score	p value
Dyspnea			
intercept	7.19 (0.62)	11.55	<0.001
slope	-0.26 (0.27)	-0.97	0.332
Wake Disturbance			
intercept	7.814(0.39)	20.22	<0.001
slope	0.24 (0.15)	-1.62	0.106
Edema			
intercept	3.02 (0.32)	9.52	<0.001
slope	-0.07 (0.15)	-0.48	0.633

For all models: Chi-squared test of model fit >0.05; RMSEA<0.08; CFI>0.95; TLI>0.95; SRMR<0.06

Table 2 legend: There was no significant change (slopes) in the physical symptoms over 6 months. Abbreviations: RMSEA – root mean square error of approximation; CFI/TLI- comparative fit indices/Tucker-Lewis indices, SRMR – standardized root mean-square residuals

Based on the LCMA, two distinct physical symptom groups were identified at baseline (LMRT: p = 0.008, posterior probabilities range: 0.92-0.99, entropy: 0.91).

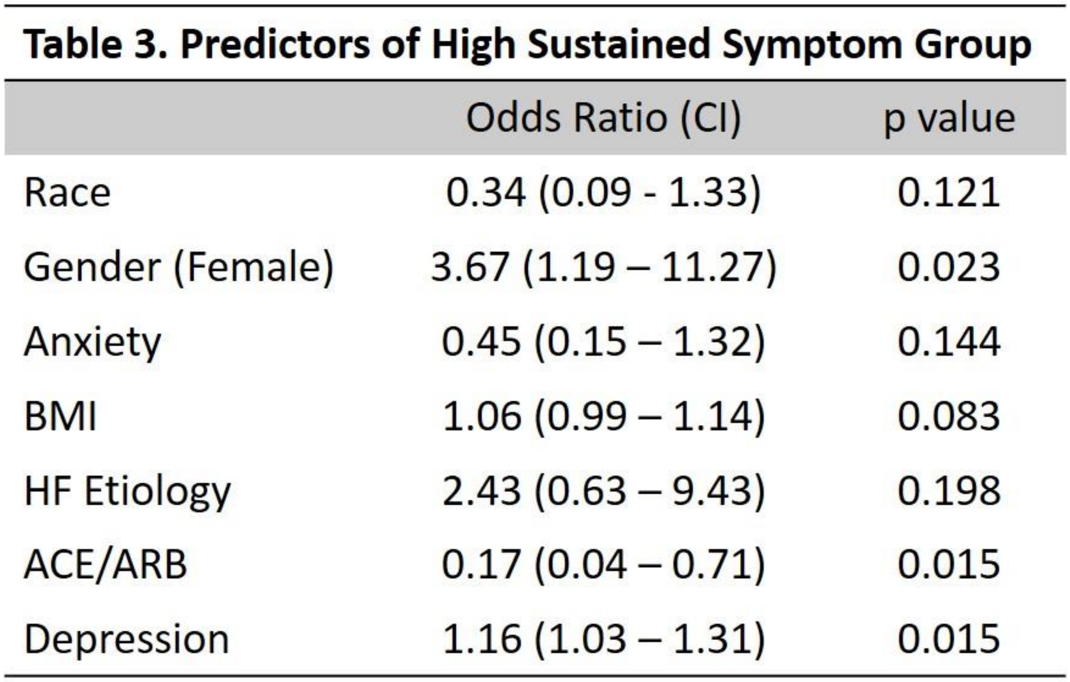

Table 3. Predictors of High Sustained Symptom Group

	Odds Ratio (CI)	p value
Race	0.34 (0.09 - 1.33)	0.121
Gender (Female)	3.67 (1.19 – 11.27)	0.023
Anxiety	0.45 (0.15 – 1.32)	0.144
BMI	1.06 (0.99 – 1.14)	0.083
HF Etiology	2.43 (0.63 – 9.43)	0.198
ACE/ARB	0.17 (0.04 – 0.71)	0.015
Depression	1.16 (1.03 – 1.31)	0.015

Table 3 legend: Factors entered into stepwise model included age, gender, married or living with partner vs living alone, Caucasian vs non-Caucasian, high school education or less vs more than high school, Charlson Co-morbidity Index, BMI, HF etiology, months since HF diagnosis, taking an ACE or an ARB, left ventricular ejection fraction, left ventricular internal diastolic diameter, depression score (PHQ9) and anxiety scores (BSI Anxiety Sub-scale). Variable retained if $p<0.2$. LR Chi-squared=24.43, $p=0.001$, Pseudo $R^2=0.214$. Abbreviations: BMI – body mass index; HF – heart failure; ACE – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; PHQ9 – patient health questionnaire 9; BSI – brief symptom inventory.

Considering the differentiating characteristics **(Table 1)** and no significant rate of change in the symptoms over time, the two groups were labeled high sustained symptoms (HSS) and low sustained symptoms (LSS). The HSS group comprised 16% of the sample (n=24) and had markedly worse dyspnea (hedges g=-1.36), wake disturbance (hedges g=-0.95) and edema (hedges g=-3.95) compared with the LSS group.

Differing patterns of self-care were identified as a function of the physical symptom group membership (HSS vs LSS). For patients belonging to the HSS group, self-care maintenance and management were significantly higher at baseline with sustained high levels of self-care over the 6 months **(Figure 1)**. In contrast, patients belonging to the LSS group showed persistent lower levels of self-care over the 6 months.

There were unadjusted differences in the symptom groups with baseline depression (t = -2.78, p=0.009) and ACE inhibitor/ARB treatment (χ^2=9.37, p=0.002). In multivariate logistic regression, however, the likelihood of being in the HSS group included being female, higher levels of depression and having an ACE inhibitor or ARB prescribed **(Table 3)**. There were no significant differences in depression between women and men within the LSS group (p=0.168) or the HSS group (p=0.648).

Discussion

In this longitudinal analysis of physical HF symptoms and self-care behaviors over 6 month, we aimed to show how patterns of HF symptoms and self-care are associated over time as well as determine predictors of those patterns. Our study of 146 patients with symptomatic HF demonstrated that patient with more severe symptoms are significantly more engaged in self-care behaviors and that sustained high or low levels of symptom burden are associated with concordant and sustained levels of HF self-care behaviors over 6 months. Importantly, we also show clinically relevant differences in symptom groups are associated with gender, depression and an important element in the treatment of HF, prescription of an ACE inhibitor or ARB.

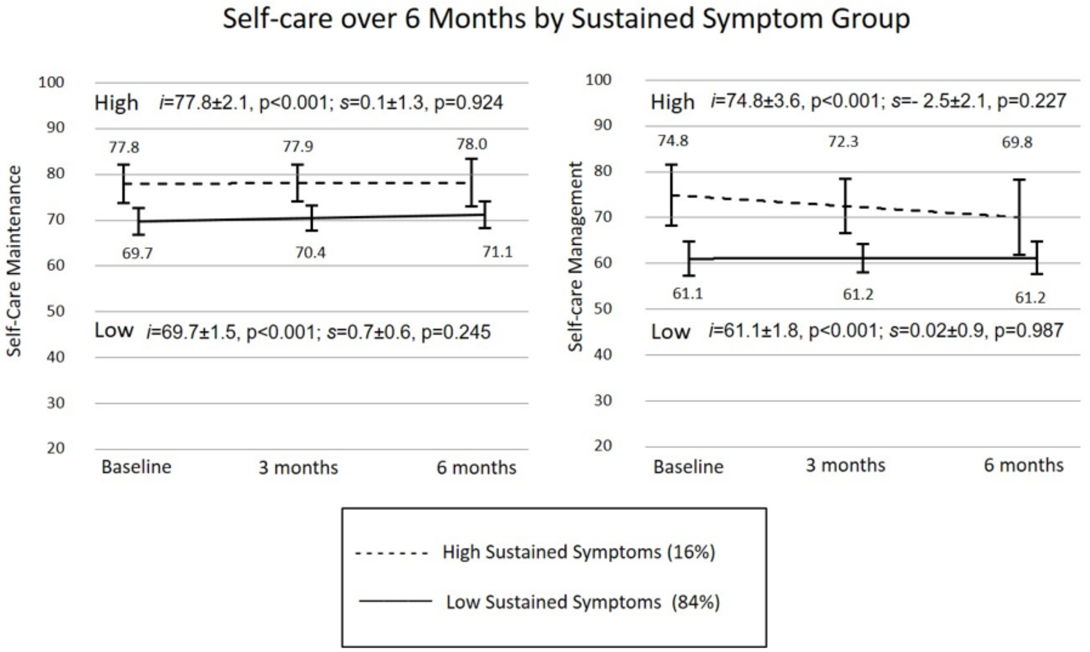

Figure Legend 1: Compared by sustained symptom group (High vs Low), self-care maintenance and management differed significantly at baseline (intercept) with no significant difference between groups in the rate of change (slope) over time (Self-care maintenance by symptom group: *intercept* t=2.1, p=0.035, *slope* t=-0.3, p=0.754; Self-care management by symptom group: *intercept* t=3.0, p=0.003, *slope* t=-0.9, p=0.376). The high sustained symptom group was associated with higher self-care (maintenance and management) at baseline with persistently higher levels of self-care over 6 months. The low sustained symptom group was associated with lower self-care at baseline and consistently lower self-care over 6 months. Metrics of fit for latent growth models: Self-care maintenance: χ^2 test of model fit =0.107; RMSEA=0.092; CFI=0.989; TLI=0.967; SRMR<0.019; Self-care management: χ^2 test of model fit=0.539; RMSEA<0.001; CFI=1.000; TLI=1.019; SRMR<0.016.

The results of this study support symptom severity as an important driver of engagement in HF self-care behaviors. Members of the HSS group were significantly more engaged in both self-care maintenance and self-care management behaviors at baseline and over time while members of the LSS group were less engaged in self-care. Recent research has shown better self-care associated with higher levels of symptom burden. It has previously been suggested that patients more bothered by symptoms may be more motivated to engage in self-care to manage current symptoms or prevent symptoms from worsening further (C. S. Lee, Gelow, et al., 2015; Rockwell & Riegel, 2001).

These longitudinal data provide additional information to better understand the relationship between HF self-care and symptoms. A clearer picture of how symptom and self-care are related in HF may provide new insights into how self-care influences patient outcomes such as quality of life. For example, if symptoms are motivating patients to engage more in self-care, individuals with severe symptoms but little engagement in self-care behaviors may be at increased risk for poor outcomes (J. Auld, Mudd, Gelow, Hiatt, & Lee, 2017). Additionally, our results suggest patients with low symptom burden and thus potentially low engagement in self-care may benefit from further attention to achieve levels of self-care that may delay HF progression, effectively address symptoms and enhance quality of life. Further longitudinal or randomized controlled studies are needed to identify how symptoms and self-care change in relation to one another and how those relationships are associated with outcomes.

We also found women were more likely to be in the HSS group. Gender differences in physical HF symptoms have been noted in previous studies. Lee et al. (2015) demonstrated that gender moderated the association of physical symptoms with left ventricular diameter such that women with smaller ventricles experience worse symptom burden compared to men with smaller ventricles. Gori et al. (2014) found women to be more symptomatic assessed with NYHA Class compared to men. One explanation for more women being in the HSS group may be related to physiological differences in the ventricular size and function in women and men with HF (C. S. Lee, Hiatt, Denfeld, Chien, et al., 2015). For instance, it has been shown that women with HF have smaller and stiffer ventricles with higher filling pressures than men, possibly contributing to more physical symptoms in women with HF (Gori et al., 2014; C. S. Lee, Hiatt, Denfeld, Chien, et al., 2015). Additionally, our observation that women were significantly more likely to be in the HSS group may explain, in part, reports from other studies describing women with HF having lower health-related quality of life compared to men (Comin-Colet et al., 2016; Riedinger et al., 2001). Thus, our study highlights the importance of gender in HF and suggests clinicians and researchers consider gender in developing treatment plans and research projects addressing HF symptoms.

Furthermore, we also found that the HSS group which also included more women was associated with higher levels of HF self-care. Few studies have shown significant gender differences in HF self-care behaviors. Cocchieri et al. (2015) and Ausili et al. (2016) demonstrated gender was a significant predictor of self-care behaviors with women engaging more in self-care than men. It must be noted, however, these studies were based on the same data set with exclusively Italian participants. Lee and colleagues (2009), on the other hand, found no clinically meaningful differences in how men and women with HF practiced self-care in a large heterogeneous multinational sample (C. S. Lee, Riegel, et al., 2009). This is consistent with others (Heo, Moser, Lennie, Riegel, & Chung, 2008; Shuldham, Theaker, Jaarsma, & Cowie, 2007) who also found no gender differences in the level of self-care in patients with HF. While in general, there is little data to support gender-based interventions targeting HF self-care, considering the cultural context of gender and self-care may be beneficial in developing successful interventions (Jaarsma et al., 2013).

Consistent with the literature regarding depression and symptom severity (Bekelman et al., 2007; Seongkum Heo et al., 2014), we show higher levels of depressive symptoms associated with an increased likelihood of being a member of the HSS group. Depression and HF are thought to be reciprocal, each condition exacerbating the other (Ghosh, Ball, Prasad, & Gupta, 2016). Both conditions share a number of pathological process such as elevated inflammatory markers and a reduction of cerebral volume that may influence the perception of symptoms (Kempton, Salvador, Munafò, & et al., 2011; Woo, Kumar, Macey, Fonarow, & Harper, 2009). Depression has also been associated with an increase in reporting of HF symptoms (Bekelman et al., 2007). Additionally, depression is a known barrier to self-care behaviors contributing to poor medication adherence and decreased physical activity (Ghosh et al., 2016; Riegel et al., 2017), potentially exacerbating physical HF symptoms. Our data supports the need to screen patients with HF for depression and address depressive symptoms to mitigate the severity of physical symptom burden and depression in HF.

Finally, we demonstrate that patients prescribed an ACE inhibitor or ARB have a significantly reduced likelihood of being in the HSS group. Our results are similar to other studies that have shown taking an ACE inhibitor/ARB is associated with lower symptom burden (Group*, 1987; K. S. Lee et al., 2010). Thus, the results of our study support ACE inhibitors and ARBs as important medications in the treatment of heart failure that not only improve mortality but also play an important role in reducing symptom severity. Furthermore, our study suggests that for patient who are not able to take ACE inhibitors or ARBs due to contraindications such as kidney dysfunction, low blood pressure or intolerance, alternative strategies to address symptom burden is likely to be needed. Future work should focus on reasons patient are not on guideline-directed therapies and the influence that has on patient-reported outcomes.

Strengths and Limitations

A strength of our analysis was identifying naturally-occurring symptom sub-groups with LCMA. Mixture analysis allows the examination of heterogeneity within the sample that can be masked when only evaluating sample means. Another strength was the use of latent growth modeling to examine differences in self-care at baseline values and over 6 months as a function of symptom burden. A longitudinal analysis of self-care and symptom burden can provide new insights that are not possible with cross-sectional studies. One limitation in this study is the relatively few time points. The use of three time points prevents the identification of non-linear change. Also, the selected time points may have contributed to the inability to detect change in symptoms and self-care over time. That is, changes may have occurred at time points that were not examined. Another important limitation was the use of secondary data. Variables that were not collected in the original analysis were not able to be included in this analysis. A third limitation is the small size of the HSS group may have hindered the ability of this study to detect smaller effects. Additional studies that intentionally sample patients with high and low symptom burden would facilitate a more complete understanding of differing levels of symptoms. Finally, the younger age, more prevalent non-ischemic etiology and predominantly male gender in the sample may hinder generalizability.

Conclusions

Sustained high levels of physical symptoms over 6 months were associated with persistently high levels of self-care while low symptom burden was associated with sustained lower levels of engagement in self-care. Female gender and more depressive symptoms predicted membership in the high symptoms group while being prescribed ACE inhibitors or ARBs was associated with a decreased likelihood of being in the high symptom group. Results of this study support physical symptoms as an important driver of self-care behaviors and identifies important sociodemographic and clinical factors associated with physical symptom burden that inform the care and study of patients with HF.

Implications for Practice

- In HF, high levels of self-care may indicate a high level of symptom burden.
- Low levels of symptom burden could indicate low levels of self-care that may need to be addressed to optimize long-term outcomes.
- Physical symptoms, particularly in women, may be improved by addressing depressive symptoms.
- Patients unable to take ACE inhibitors/ARBs will likely need alternative strategies to reduce symptoms.

Declaration of conflicting interests

The Authors declare that there is no conflict of interest.

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References for Chapter IV (See Cumulative References)

Chapter V

Discussion and Implications

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Chapter 5: Discussion

The purpose of this dissertation was to gain new knowledge regarding the biologic underpinnings of HF symptoms and the associations of HF symptoms with self-care behaviors. In addition, this dissertation aimed to enhance our understanding of how an objective marker of worsening HF and self-care behaviors influence HRQOL. Multiple data sources, including secondary and original data with cross-sectional and longitudinal designs, were used to address the three aims of this dissertation; 1) Quantify associations between device-detected congestion with both patient reported HF symptoms and health-related quality of life over time, 2) determine whether self-care behaviors moderate the relationship between patient-reported HF symptoms and HRQOL and 3) identify naturally-occurring patterns of change in heart failure symptoms over 6 months and examine how patterns in symptom change are associated with self-care behaviors. The three studies addressing these aims provided novel insights to both HF symptoms and self-care behaviors that can be used to develop more tailored intervention to enhance self-care, reduce symptom burden and improve the quality of life for patients with HF.

Summary of Findings

In brief, we found that an objective marker of cardiopulmonary congestion was associated with both higher levels of symptom burden and worse HRQOL. Additionally, we showed that worse symptoms were associated with better self-care behaviors over 6 months and that self-care behaviors moderated the relationship between symptoms and HRQOL. Additional major findings are reported in **Table 1**. This final section of the dissertation will discuss themes identified from the results across studies, place the results of the three studies in the context of the current literature, describe strengths and limitations of the overall approach and discuss theoretical, practice and research implications.

Table 1. Summary of Major Findings by Dissertation Aim

Aim	Major Findings
Aim 1. *Quantify associations between device-detected congestion with both patient reported HF symptoms and health-related quality of life over time*	• The presence and duration of threshold crossings were significantly associated with more dyspnea, early and subtle symptoms, depression and anxiety. • Fatigue was not associated with device-detected pulmonary congestion • The presence and duration of threshold crossing were associated significantly with worse HRQOL.
Aim 2. *Determine whether self-care behaviors moderate the relationship between patient-reported HF symptoms and HRQOL*	• Self-care maintenance and management moderated the relationship between physical symptoms and HRQOL. • Only self-care maintenance moderated the relationship between depressive symptoms and HRQOL
Aim 3. *Identify naturally-occurring patterns of change in heart failure symptoms over 6 months and examine how patterns in symptom change are associated with self-care behaviors.*	• There was significant variation in the patients' experience of symptoms at baseline but symptoms trajectories did not change significantly over 6 months. • High and low sustained symptom patterns were identified. • Self-care behaviors varied significantly by symptom pattern over 6 months. High sustained symptoms were associated with consistently high self-care while low sustained symptoms were associated with consistently low levels of self-care. • Significant predictors of the high sustained symptom group were being a woman, higher levels of depression and not being prescribed ACE/ARBs.

Subjective and Objective Metrics of Worsening HF

Currently, there are few meaningful objective metrics used in the assessment of HF that can provide helpful information about a patients' subjective symptoms or HRQOL. As described in Aim 1, a central goal of this dissertation was to further our understanding of symptom biology in HF so that clinicians and patients can better predict, prevent and respond to symptoms to improve patient outcomes. In support of this goal, we found that intrathoracic impedance represented by threshold crossings of the Medtronic Optivol Index (an objective metric of device-detected pulmonary congestion and worsening HF) was significantly associated with a number of self-reported physical and psychological hallmark HF symptoms including dyspnea, early and subtle symptoms, depression and anxiety. Specifically, we found that experiencing a threshold crossing in the previous 90 days was significantly associated with more severe physical and psychological symptoms. Interestingly, fatigue was not significantly associated with threshold crossings. In addition, we showed that patients who experience threshold crossings also have worse HRQOL, corroborating the association of threshold crossings with symptoms. Although there are previous studies that have shown objective measures of cardiopulmonary function associated with symptoms, our study has a number of novel contributions to HF symptom science.

First, we demonstrated that the Optivol Index and corresponding threshold crossings are associated with physical and psychological symptoms. Others have found threshold crossings data associated with important outcomes of hospitalizations, self-care and mortality (Rathman et al., 2011; Small et al., 2009; Tang et al., 2012). Our study extends our understanding in that Optivol Index threshold crossings may provide important information regarding the symptom burden of patients with HF providing a key link between the association of threshold crossings and clinical outcomes. Increasing symptoms are associated with healthcare utilization, self-care and mortality (J. P. Auld et al., 2018; Ekman, Kjork, & Andersson, 2007; C. S. Lee, Hiatt, Denfeld, Mudd, et al., 2015). A richer understanding of patient symptomology is important since many patients struggle to recognize and respond to symptoms in a timely manner leading to poor outcomes (Jurgens et al., 2009). Intrathoracic impedance generally and the Optivol Index specifically may be an additional tool clinicians can use to gain insight into the patient symptom experience. Earlier identification of symptoms may allow earlier and less aggressive treatment to improve outcomes.

Second, we observed that the duration of threshold crossings were able to predict a wide range of specific symptoms including depression and anxiety. These results enhance the utility of intrathoracic impedance technology to address a variety of patient symptom profiles. Lung fluid accumulation that accounts for decreases in intrathoracic impedance is a complex process involving a variety of pathophysiological pathways including elevated ventricular pressures, fluid redistribution, inflammation and endothelial dysfunction (Cotter, Metra, Milo-Cotter, Dittrich, & Gheorghiade, 2008; Pappas & Filippatos, 2011). The diversity of processes involved in measuring changes in intrathoracic impedance may be one reason the Optivol threshold crossings were associated with multiple symptoms. For example, inflammation has been shown to be associated with fluid accumulation in lungs and with worse depression (Pappas & Filippatos, 2011; Xiong et al., 2015). It must be noted that fatigue was the only symptom in our study that was not associated with threshold crossings. The reason for the lack of association may be that the pathophysiological processes of lung fluid accumulation (measured by the Optivol Index) are less associated with the processes that cause self-reported fatigue. Alternatively, the measure of fatigue used in this study, the FACIT-F, was originally developed in a population of patients with cancer and therefore may not be particularly sensitive to fatigue experienced by patients with HF. In addition, it has been previously reported that fatigue can be difficult for patients to recognize (Carlson, Riegel, & Moser, 2001; L. Evangelista et al., 2008). Given the FACIT-F is a single dimensional measure, our results may indicate that using a multi-dimensional fatigue instrument may be needed to detect fatigue in HF (Hagell et al., 2006).

Finally, to the knowledge of the authors, we were the first to explore the Optivol Index as a predictor of early and subtle symptoms. Early and subtle symptoms were first described by Jurgens and colleagues (Jurgens et al., 2006) as a group of self-reported symptoms that can occur earlier in the sequela of cardiopulmonary congestion and/or be less obvious such as clothes fitting more tightly, a cough, stomach pain and decreased appetite. Early and subtle symptoms have been shown to predict 1-year survival, yet few studies have examined this cluster of symptoms further (Jurgens et al., 2015). Given early and subtle symptoms may occur earlier in the cardiopulmonary congestion process, integrating intrathoracic impedance and assessment of early and subtle symptoms may allow even earlier detection of worsening HF physiology. So few have looked at these early symptoms, yet they may be key to early detection and prevention of symptom exacerbations. Teaching patients how to detect and respond to early and subtle symptoms may provide the opportunity to intervene earlier and prevent worsening symptoms.

Heterogeneity in HF Symptoms and Self-care

The experience of symptoms and self-care behaviors in HF are heterogeneous. The patient experience of HF can vary widely between individuals with similar etiologies and objective markers of HF (C. S. Lee, Hiatt, Denfeld, Mudd, et al., 2015). Symptoms and self-care can vary over time as the trajectory of HF changes. Accordingly, using latent class mixture analysis (LCMA), we observed important differences in sub-groups of patients with symptomatic HF that may shed important insights on the relationship between symptoms and self-care experiences of HF.

First, we identified two groups with significantly different levels of physical symptom burden, one with high symptom burden over time and one with low symptoms. The high symptom patient profile was significantly associated with higher levels of depression, being female and the prescription of angiotensin blocking agents. The association of depression and symptom burden has been well documented in the literature (Bekelman et al., 2007; Ghosh et al., 2016). As mentioned previously, depression and some physical symptoms share pathophysiologic pathways that may, at least in part, account for this relationship. In addition, depression was associated with less engagement in behaviors that may reduce symptoms (medication adherence and physical activity) and depression has been shown to be associated with reporting more physical symptoms (Bekelman et al., 2007).

Our data showing women experienced higher levels of symptom burden than men was similar to results from other recent studies. Denfield and colleagues (2015) demonstrated women had, on average, significantly higher levels of physical symptom burden measured with the Heart Failure Somatic Perception Scale controlling for sociodemographic variables and objective measures of heart function. Similar findings were reported by Gori and colleagues (2014) who found women with HF with preserved ejection fraction experienced more severe physical symptoms than men assessed with NYHA classification. Furthermore, Lee and colleagues (2009) demonstrated gender differences in symptom perception were related to the size of the left ventricle and pulmonary capillary wedge pressures, a sign of cardiopulmonary congestion. Women with smaller ventricles experienced higher symptom burden and higher pulmonary capillary wedge pressures than men with similar sized ventricles while men experienced higher symptoms and higher pulmonary capillary wedge pressures when ventricles were larger. In addition, women experience higher depression across the lifespan and therefore may be more willing to report higher levels of symptom burden (Leach, Christensen, Mackinnon, Windsor, & Butterworth, 2008) .

Finally, we demonstrated that symptom burden was significantly lower for patients with a prescription of ACE/ARBs. Having ACE/ARBs prescribed was associated with an 83% reduction in the likelihood of a patient belonging to the high symptom profile. Patients who were not prescribed ACE/ARB were simply much more likely to experience higher symptom burden. These data are consistent with a number of studies that have shown patients taking ACE/ARB experience less symptom burden than patients who are not (Group*, 1987; K. S. Lee et al., 2010). The results of our study indicate ACE/ARB treatment is an essential component to symptom management in HF and for patients unable to take ACE/ARB due to kidney dysfunction or intolerance, adjunct therapies to reduce symptoms may be needed. This result highlights the need for further research into the reason patients and clinicians deviate from practice guidelines.

Identifying predictors of patients more likely to experience severe symptoms provides critical information for clinicians and researchers to more effectively identify patients at risk for burdensome symptoms and develop targeted interventions to improve patient outcomes.

Symptoms and HF Self-care Behaviors

Symptoms and HF self-care behaviors are integral to the management of HF. Yet, little is known about how symptoms and self-care interact or are associated with one another, particularly over time. Aims 2 and 3 of this dissertation sought to address these gaps. Across manuscripts, we found that more engagement in self-care behaviors (both maintenance and management) was associated with more physical symptom burden. In our longitudinal study of patterns of symptom and self-care over 6 months, participants with sustained high levels of symptom burden over 6 months were significantly more engaged in self-care behaviors over time. Similarly, those with sustained low symptom burden engaged in significantly lower levels of self-care behaviors over time. Thus, our research suggests the level of symptom burden may drive engagement in HF self-care.

This is an important contribution to our understanding of the relationship between self-care behaviors and symptoms. In the literature, the association between HF self-care and symptoms has been inconsistent with more engagement in self-care associated with both improved and worse symptoms (Graven, Grant, & Gordon, 2015; C. S. Lee et al., 2013; Rockwell & Riegel, 2001). This body of literature was predominantly based on cross-sectional study designs. We showed, in multiple studies with both cross-sectional and longitudinal designs, that engagement in self-care behaviors mirrors the severity of symptom burden. These results were of particular importance in broadening our understanding of what having high or low engagement in self-care behaviors may indicate. In general, the goal of self-care interventions is to increase self-care and improve outcomes such as lowering symptom burden. Our data may suggest a more nuanced view of self-care and symptoms. For example, in patients who are highly motivated to engage in self-care due to severe symptom burden, this may be an indicator that these patients were actively and appropriately engaged in their care but that medical management of HF was less effective in reducing symptom burden. On the other hand, when symptom burden was low, high levels of self-care management behaviors were likely unnecessary. Rather, engaging more in adherence and symptom monitoring behaviors (maintenance) may be the goal in order to further suppress neurohormonal activation and further symptom exacerbation. Thus, less engagement in some aspects of self-care may have been appropriate when symptoms are mild, an indicator that patients were actively self-managing symptoms. Of serious concern may be the patient who was having high levels of symptom burden but was not able to engage adequately in self-care behaviors to effectively manage the symptoms. These patients may be at increased risk of poor quality of life, hospitalization and worse survival. It may also be useful to recognize that patients who were highly engaged in self-care behaviors in spite of having few symptoms, may be negatively affected through overly stringent fluid or dietary restrictions (J. Auld et al., 2017; Peters-Klimm et al., 2013). Therefore, an understanding of both a patient’s symptom burden and self-care may be necessary to fully address their needs and develop individualized interventions.

Further supporting this notion that both symptoms and self-care are integral to patient outcomes in HF, we found that self-care behaviors moderated the relationship between physical symptoms and HRQOL. That is, HRQOL was dependent upon the interaction of the severity of symptoms and the engagement in self-care. When physical symptoms were more severe, more engagement in both self-care maintenance and management was associated with better HRQOL compared to lower levels of self-care engagement with severe symptoms. These results stress the need to collect self-care and symptom data over time to optimize outcomes for patients and accurately describe associations with outcomes in research. Interestingly, only self-care maintenance moderated the relationship between depression and HRQOL. More engagement in adherence and symptom monitoring behaviors buffered the impact of depression on HRQOL. This may suggest that routine adherence and symptom monitoring behaviors (self-care maintenance) were less affected by depression than self-care management. Perhaps, patients with depression could more consistently continue routine behaviors that comprise self-care maintenance while decision-making behaviors were more impaired. Knowing that patients with depression are at increased risk of low engagement in self-care, additional support and resources to engage effectively in self-care is likely needed for patients with depression (Holzapfel et al., 2009).

Influence of time

Heart failure is a progressive syndrome that worsens over time and is more common in older adults. How patients experience HF over time at different stages of the illness and at different stages in their lives is an essential consideration in the clinical practice and research of HF. In spite of the importance of time in HF, very few studies have examined symptom burden or self-care over time. Across our longitudinal and cross-sectional studies, we found intriguing insights into how time may influence symptoms and self-care. First, we observed that there was no significant variation in physical symptom trajectories over 6 months. The lack of change in symptoms within patients over time was observed in spite of significant variability between patients. In other word, patients were initially quite different from one another in their level of symptom severity (some high, some low) but that level of severity did not change significantly over 6 months. This was a surprising result since we know that there is variation in HF symptoms (supported by significant between-patient variability), especially as symptom exacerbations occur and are treated. In addition, symptoms tend to worsen as HF progresses over time. One reason that we may not have detected change in symptoms over time was our observational study design with convenience sampling. Many of the participants were in different phases of their HF trajectory and in different phases of life. There was no consistent event or common "starting point" for the illness trajectory (e.g. HF diagnosis, hospital admission) from which differences in trajectory could be evaluated. Another important consideration that may have impacted the ability to detect change over time was the number of data collection time points. In our longitudinal study, we performed 3 data collection waves over 6 months which may have been insufficient to detect changes in symptoms or self-care behaviors. Study designs that take a meaningful "start point" across patients into consideration, such as experimental studies or observational studies that begin with hospital admission, discharge or time of HF diagnosis, may better allow comparison of different patient trajectories or changes over time and improve the process of selecting the appropriate time points that are likely to detect changes. Given that changes in symptoms or clinical events can occur rapidly in HF, more nuanced longitudinal studies are needed.

Another interesting aspect of time in our study was the observation that the duration of threshold crossing (in days) was significantly associated with symptoms and HRQOL. Participants who experienced the longest duration of threshold crossings (above the median days) did not experience the worst symptoms or the worst HRQOL. Rather, those who experienced a milder duration of threshold crossings (below the median but more than 0) had the most severe symptom burden (early and subtle) and worst HRQOL. A similar mismatch between objective measures of HF and subjective patient-reported measures has been previously observed by others in patients with HF (C. S. Lee, Hiatt, Denfeld, Mudd, et al., 2015; Riegel et al., 2018).

The reason for these counter-intuitive results has yet to be elucidated. Considering how patients' perceptions of HF symptoms may change over time, however, might provide some intriguing directions for future research. For example, social psychology and education research frequently discuss a phenomenon termed response shift bias (Rosenman, Tennekoon, & Hill, 2011). Response shift bias can occur as one learns and has new experiences. Previous perceptions can be altered by the new experiences and a "new normal" can then become the basis for appraisal. Perhaps, as patients have new experiences or become accustomed to their symptoms over time, they continually form and reform a new normal from where they assess symptoms. Over time, symptoms earlier perceived as bothersome may be perceived as less severe even as the objective HF metrics are worsening. An alternative explanation for the possible mismatch between symptoms and Optivol threshold crossings could be that the biobehavioral perceptual systems in the body, also known as interoception, may be altered in patients with HF (Riegel et al., 2018). That is, the interoception systems may decline as HF worsens making it more difficult for patients to detect, interpret and make decisions about increasing symptoms. Lastly, a patient’s knowledge, experience and skill in managing symptoms may improve over time allowing patients to reduce symptoms and improve HRQOL in spite of worsening cardiac function.

The lack of longitudinal and experimental research in biobehavioral studies of HF symptoms prevents elucidation of the temporal and causal association of symptoms, biological marker, self-care and outcomes. Without understanding how these variables change in relation to one another over time, the development of appropriate interventions to address symptoms and self-care to improve outcomes will be limited. Further longitudinal and experimental research in necessary to more fully understand the complex biobehavioral relationships in HF symptoms research.

Strengths and Limitations

This dissertation had a number of important strengths. First, the body of work includes longitudinal data that provided new insights into how symptoms and self-care behaviors are associated over time. Few studies in this area of research used longitudinal or experimental study designs limiting the ability to examine temporal and causal associations. Second, we used LCA to identify naturally-occurring sub-groups within the sample. This approach allows the examination of heterogeneity within the sample that may otherwise be overlooked. Third, the use of growth mixture modeling facilitated the evaluation of different self-care trajectories over 6 months as a function of patient symptom burden. Finally, we examined individual physical and psychological symptoms to provide information on a range of hallmark HF symptoms which may allow insight into specific symptoms rather than symptoms generally.

There are also a number of important limitations in these dissertation studies. First, the sample and/or group size was relatively small in aim 1 and aim 3. The small sample sizes limited the number of covariates that could be examined in the models and hindered the power of the studies to detect significant effects. Second, aim 1 and aim 2 used cross-sectional study designs. The use of cross-sectional designs precludes the evaluation of temporal or causal associations in our studies. Third, in the longitudinal study, we had only three time points which did not allow the analysis of non-linear change. It is possible that symptoms did change but reverted back to baseline values by our final time point. Fourth, all of the samples were derived from an academic healthcare organization in the Pacific Northwest that were younger, whiter, had more advanced HF and more non-ischemic HF than the general HF population. These regional and site specific characteristics of the sample limit the generalizability of our results. Finally, intrathoracic impedance has only moderate specificity and sensitivity to detect HF symptom exacerbations. It cannot be ruled out that some threshold crossing may have been unrelated to cardiopulmonary congestion.

Implications

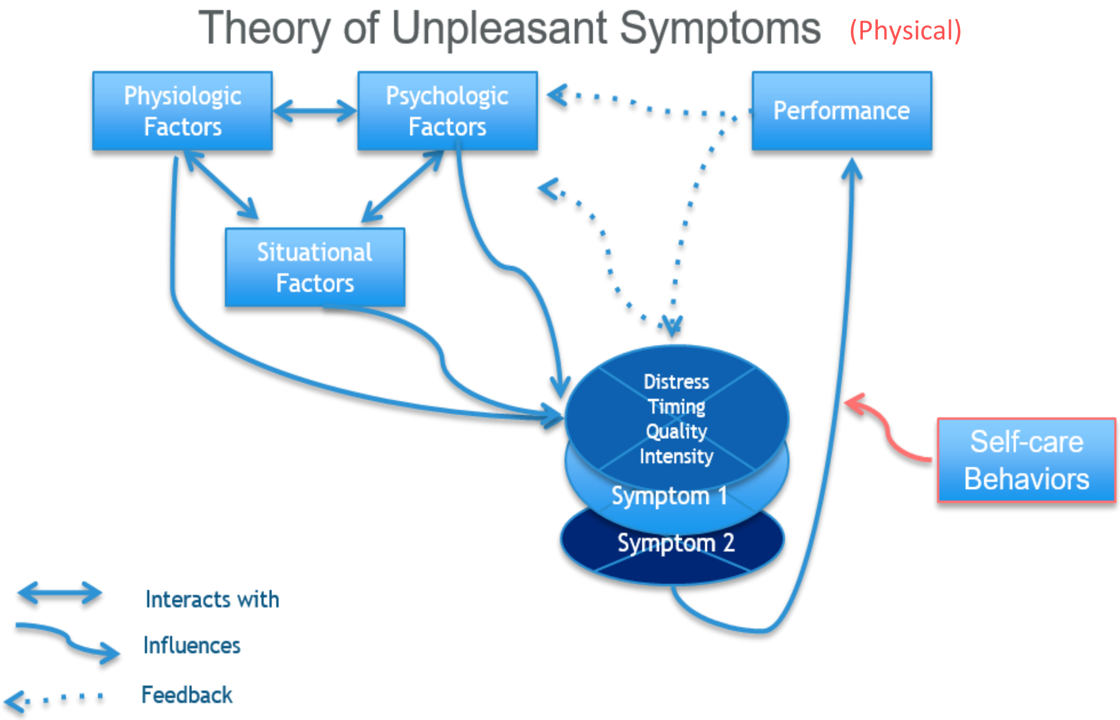
Implications for Theory

The research presented in this dissertation has several important theoretical implications. The theories used to support this work are the Theory of Unpleasant Symptoms (TOUS) and the Situation-specific Theory of HF Self-care. Both theories are previously described in detail in Chapter 1. The rationale for blending these two theories was that each model individually described specific concepts and processes of our research but neither theory provided information on all. In other words, we found the models complimentary; each framework filling gaps in the other to guide our research as a whole. For example the TOUS, describes the relationships between physiology, symptoms and outcomes which guided dissertation aim 1. The TOUS, however, lacks a description of how patient behaviors to prevent or respond to symptoms may influence those important relationships (Lenz et al., 1997). In order to fill those gaps, the Situation-specific Theory of Self-care was used to describe the symptom self-care behaviors and address gaps in the theory about how self-care behaviors are associated with symptoms and HRQOL (Riegel et al., 2015a). In addition, the TOUS was used as the theoretical foundation for the main physical symptom measure used in the dissertation, the Heart Failure Somatic Perception Scale. Similarly, the Situation-specific Theory of HF Self-care was the theoretical basis for the Self-care in HF Index which was used to measure self-care in our studies. Therefore, our research in this body of work supports a number of the relationships described in the two theories and provides new information to further develop each theory.

Theory of unpleasant symptoms. In general, we found our research supported a number of the concepts and relationships described in the TOUS. As detailed in the TOUS, we found a marker of patient physiology (Opitovl Index) associated with multiple hallmark HF symptoms. We also showed that worse symptoms were associated with poorer performance, conceptualized as HRQOL in our studies. In line with the TOUS, we also observed psychological and situational factors associated with symptom severity; depression and ACE/ARB prescription were associated with the likelihood of belonging to a high symptom group.

Although the TOUS has been used to describe the symptoms experience in HF, there are some aspects of the model that may prove problematic for further HF symptom research. First, the presence of symptoms often elicit a self-care response which we showed in our research is associated with both symptoms and performance (HRQOL). The addition of moderators of the symptoms/performance relationship such as self-care behaviors may be useful for the model to guide biobehavioral research. Second, the model conceptualizes symptoms such as depression and anxiety as psychological factors that influence symptoms of HF (**Figure 1**). For researchers and clinicians who may consider depression a symptom of HF, the model may be less intuitive and more difficult to use. Thus, to avoid confusion, we propose that the theory be used in HF primarily for physical symptoms.

Figure 1: Proposed Revisions to the Theory of Unpleasant Symptoms (changes in red)



Situation-specific theory of HF self-care. We found the concepts of the Situation-specific Theory of HF Self-care to be helpful in describing self-care behaviors namely, adherence, and symptom response. We were also able to address two assumptions laid out by the authors of the theory. First, the authors state that high levels of self-care are needed to affect outcomes. We found that our data supported this assumption. We showed that when symptoms were more severe, high levels of self-care were associated with better HRQOL compared to participants with severe symptoms and lower levels of self-care. Our research, however, also challenges the idea that more engagement in self-care is always better. We found that for participants who have low levels of symptom burden, HRQOL was worse with high levels of self-care compared to those with low symptom burden and lower levels of self-care. Others have also found that some self-care behaviors can be burdensome for patients. Second, the authors state that clusters of physical and emotional symptom influence self-care. We found that engagement in self-care over time was different depending upon the level of a physical symptom cluster (dyspnea, wake disturbance, edema) experienced by a group of patients.

In light of our research and critical analysis of the Situation-specific Theory of HF Self-care, we propose several revisions of the self-care framework that may warrant further investigation. Below, we discuss the possible revision to the key concepts of the Situation-Specific Theory of HF Self-care.

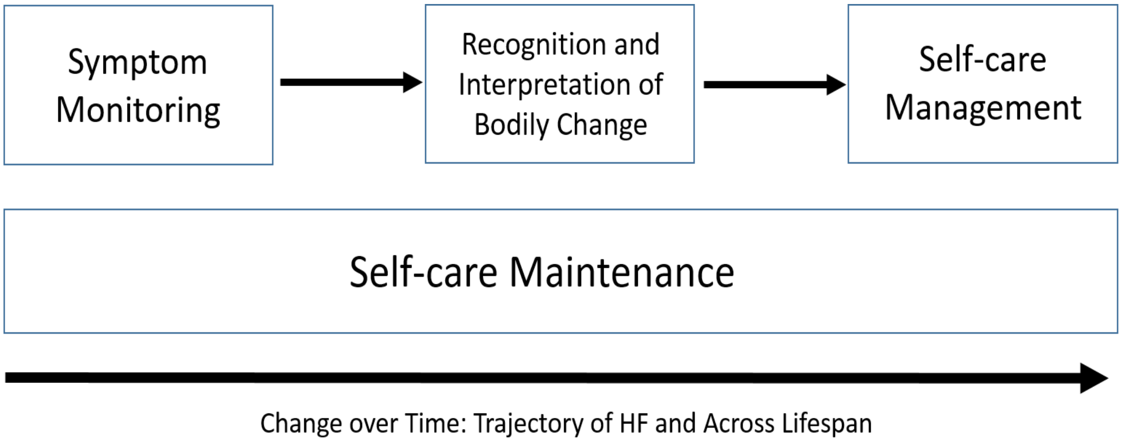
Self-care maintenance. We propose two revisions to the concept of self-care maintenance. First, we suggest limiting self-care maintenance to adherence behaviors. This revision is in line with the updated version of the Theory of HF Self-care published in 2015 which describes the purpose of maintenance behaviors as maintaining physiologic stability. In addition, there is evidence that self-care maintenance behaviors, such as medication adherence and reductions of dietary sodium, can influence neurohormonal activation and inflammation potentially slowing the progression of HF to maintain physiologic stability (C. S. Lee, Tkacs, et al., 2009). Other symptom monitoring behaviors, previously considered self-care maintenance (daily weighing and checking for edema) would become part of a new concept labeled “symptom monitoring” which is described below under symptom perception.

The second revision to self-care maintenance would be changing the sequential relationship of self-care maintenance as the start of the self-care process. Our revision places self-care maintenance in a position of supporting the other concepts in the model rather than start of the self-care process that proceeds linearly from maintenance to symptom perception to management (**Figure 2**). There are two reasons maintenance is placed in this supporting position. One, there is evidence that maintenance behaviors such as medication adherence and adherence to dietary sodium restrictions, can reduce neurohormonal activation. Less neurohormonal activation may mitigate physiologic processes associated with mild cognitive dysfunction and depression which may in turn support engagement in all other aspects of the self-care process. A study by Vellone and colleagues (2013), showed adherence behaviors significantly associated with symptom monitoring, symptom detection, and self-management behaviors further supporting our revised position of self-care maintenance. Two, there is little evidence that adherence behaviors themselves are the beginning of the self-care process or that adherence behaviors (maintenance) precede self-care management behaviors in time. Rather, based on observations from our research and practice, patients typically engage in both adherence (maintenance) and management behaviors simultaneously.

Symptom perception. We propose two revisions to the concept of symptom perception. In the updated description of the Theory of HF Self-care from 2015, the authors describe symptom perception as including both behaviors used to monitor symptoms (e.g. daily weighing and body listening) and the actual perception or sensation of the physiologic change (symptom detection) and interpretation of those sensations. Our 1st revision is to redefine symptom perception as "detection and interpretation of a bodily change" (**Figure 2**). Redefining symptom perception brings the concept in line with theories of symptom appraisal. Symptom appraisal theories define symptoms as the detection and interpretation of a physiologic bodily change (Whitaker, Scott, & Wardle, 2015). The perception or sensations can be generalized (fatigue), specific (shortness of breath), visible/palpable (lumps or swelling), or auditory (wheezes). Furthermore, interpretation of bodily change as a symptom (or sign) of an illness is necessary for engagement in decision-making behaviors to manage the symptoms (or sign). Lastly, in contrast to the concept of symptom perception defined by Riegel et al.(2015a), detection and interpretation of bodily change does not include behaviors to monitor symptoms. Accordingly, our 2nd proposed change is to add an additional concept of "symptom monitoring" to the self-care model to separate the symptom monitoring behaviors from the non-behavioral detection and interpretation of bodily change. In support of our revised model, Vellone and colleagues (2013) demonstrated, using structural equation modeling, a separate concept of symptom monitoring was significantly associated with the concept of symptom detection and interpretation. We have no additional revision for self-care management.

Change over time. Our final revision to the Situation-specific Theory of HF Self-care is to address how the self-care concepts change individually and in relation to one another over time. HF is a progressive syndrome and there is evidence from our studies and others that the patient experience of HF can be different over time. We showed that the having a cardiopulmonary congestion event was associated with having lived longer with a HF diagnosis and others have shown that having more experience with HF is associated with better self-care (Cameron, Worrall-Carter, Page, & Stewart, 2010). To fully understand the self-care process in HF and to provide guidance for successful interventions, the relationships between self-care concepts must be studied over the HF trajectory of illness and over the lifespan of patients with HF.

Figure 2. Proposed Revisions to the Situation-specific Theory of HF Self-care



In summary, recommendations for revisions to the TOUS and the Situation Specific theory of HF Self-care were proposed. For the TOUS, integrating symptom response behaviors as moderator of the relationship between symptoms and performance may enhance the use of this model in research and clinical practice. In addition, the

TOUS may be more descriptive of physical symptoms in HF. For the Situation specific Theory of HF self-care, we suggested re-defining symptom perception as detection and interpretation of bodily change an offer an alternative structure for how the self-care concepts are associated. Furthermore, we recommended further longitudinal studies examine how these concepts are related over time.

Implications for Practice and Continued Research

Practice implications. Across all of our studies, we identified several important implications for clinical practice. First, the key clinical outcome of HRQOL was dependent upon both self-care and symptoms. We have shown that both engagement of self-care behaviors and symptoms may provide new insights into the patient experience of HF to optimize outcomes. For example, patients with high levels of symptom burden and low engagement in self-care may need additional interventions focused on self-care compared to patients with high symptom burden who are more engaged in self-care. In addition, the clinician may need to identify and address barriers to self-care such as depression or mild cognitive dysfunction. The systematic collection of self-care and symptom data may enhance the clinician's understanding to provide a more tailored treatment approach.

Second, intrathoracic impedance or the Optivol Index over the previous 90 days was shown to be significantly associated with multiple hallmark HF symptoms. Since patients with HF are typically seen every 3 months, the review of intrathoracic impedance data between clinic visits, when available, may provide additional information regarding patient symptom burden. Evaluation of intrathoracic impedance data, in addition to evaluation of early and subtle symptoms, may be particularly helpful for patients who struggle to detect symptoms. Declines in impedance or increases in the Optivol index may elicit further question from clinicians regarding symptom burden and self-care practices that may improve identification and treatment of burdensome symptoms.

Third, our studies indicate clinicians pay particular attention to a number of predictors for higher levels of symptom burden. Our data suggests the need for clinicians to address depression in addition to physical symptoms of congestion in order to optimize outcomes. Being a woman was another important predictor of significantly higher physical symptoms. Recognizing that women may be of particular risk for more severe symptom burden may enhance early detection and treatment. Finally, our research suggests patients unable to take ACE/ARBs may need addition remedies to relieve symptoms.

Fourth, our research may indicate that healthcare organizations need to develop systems to integrate biological and behavioral data into the process that can inform clinical decision-making and further research. Biological data are routinely collected when patients with HF utilized healthcare services. Behavioral data are often not collected or evaluated systematically. We have shown in this dissertation that both biological and behavioral information can be important in better understanding the patient experience in HF. Developing systems that facilitate the collection of biobehavioral data and the ability for clinicians to review information and respond to patient needs in a timely manner may be an important factor to improve patient outcomes.

Implications for continued research. The results of this dissertation have addressed a number of gaps in the relationships between patient physiology, symptoms, self-care behaviors and HRQOL. Accordingly, we have identified several areas to focus continued research in order to move the biobehavioral science of HF symptoms forward. First, our understanding of symptom biology and the relationship of self-care with symptoms is limited by cross-sectional study designs. There is a strong need for rigorous longitudinal research that has a definitive “start” point for all participants with adequate time points to detect change and assess linear and non-linear patterns over time. In order to develop successful interventions to improve patient outcomes, longitudinal and experimental studies are needed to fully understand how symptom biology, patient-reported symptoms and self-care behaviors change over time and in relationship to one another.

Another area for continued research is the exploration of objective markers of HF that are associated with symptoms and HRQOL. Our data suggest intrathoracic impedance may be one objective metric of worsening HF associated with symptoms, yet intrathoracic impedance has limitations. First, intrathoracic impedance is used only in patients with intrathoracic impedance-enabled devices. Although, many patients with HF have these devices, they make up only a relatively small portion of all HF patients. This technology is simply not available for most patients with HF. Second, intrathoracic impedance has been shown to have only moderate sensitivity and specificity to detect HF-related events (Vollmann et al., 2007; Yu et al., 2005). The rate of unexplained threshold crossings preclude this marker from being a direct measure of worsening congestion in HF. Thus, intrathoracic impedance data may be appropriate to gather additional information about lung fluid accumulation and symptom status but there is little evidence clinical decisions should be based solely on intrathoracic impedance data.

In order to facilitate earlier detection of symptoms and declines in quality of life, further research is necessary to uncover new associations between objective markers of HF and subjectively reported outcomes in HF.

A third topic in need of further investigation is the structure and temporal and directional relationship for the Situation-specific Theory of HF Self-care. The sub-scales used to assess HF self-care are designed as one dimensional instruments. Yet, a recent study has indicated a multidimensional structure for the self-care in HF index sub-scales (Barbaranelli et al., 2014). Since the sub-scales are based on specific theoretical constructs, those constructs may also need to be reassessed. Furthermore, the content of the individual items in the self-care maintenance sub-scale do not align well with the most recent description on the theory on which they are based. The self-care maintenance sub-scale appears to have items that belong to multiple theoretical concept which may limit the validity of the measure. Additionally, little is known about how self-care behaviors change over time or in relations to one another. Continued research is needed to clarify the concepts of the theory of HF self-care, establish valid and reliable measures of those concepts and determine the direction of the relationships over time.

In this dissertation, specific methodologies were used to examine heterogeneity inherent in the study of patient-reported outcomes and patient behaviors in HF. Continued research into how patient experience HF and respond to symptom differently is important to develop tailored interventions to improve patient outcomes. Much of the current biobehavioral research in HF symptom biology rely on the analysis of mean values. As we have showed in our research, evaluation of only the mean can mask clinically significant differences within a sample. For example, we observed a high and low symptoms group with different profiles of self-care over time using LCMA. Examining only the mean in this study may have missed significant differences in how patients experience and manage physical HF symptoms. Using methodologies such as LCMA and growth mixture modeling can reveal underlying heterogeneity in a sample that may have important clinical implications.

Lastly, further research into the mismatch between the patient experience of HF symptoms and objective measures of HF may reveal new insights that underlie the relationship between objective and subjective metrics of HF. Research in this area should include the study of response shift bias and interoception. These two topics of study have yet to be examined in the context of HF and separately or together may provide an important link between self-care behaviors, symptoms and biology.

Conclusion

In this dissertation, we use a series of cross-sectional and longitudinal studies to examine the biology and behaviors associated with HF symptoms and HRQOL. The overarching theme from this body of work is the importance of examining both biological and behavioral data when seeking to address patient symptom burden and HRQOL. We found both biological and behavioral data can provided significant and clinically meaningful information regarding patient symptoms status and HRQOL. The integration of biological and behavioral data may allow the identification and earlier treatment of patients with HF who need intervention to address symptoms and improve their quality of life.

References

Abraham, W. T., Compton, S., Haas, G., Foreman, B., Canby, R. C., Fishel, R., . . . Hettrick, D. a. (2011). Intrathoracic Impedance vs Daily Weight Monitoring for Predicting Worsening Heart Failure Events: Results of the Fluid Accumulation Status Trial (FAST). *Congestive Heart Failure, 17*(2), 51-55. doi:10.1111/j.1751-7133.2011.00220.x

Adams, K. F., Jr., Fonarow, G. C., Emerman, C. L., LeJemtel, T. H., Costanzo, M. R., Abraham, W. T., . . . Investigators. (2005). Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J, 149*(2), 209-216. doi:10.1016/j.ahj.2004.08.005

Auld, J., Mudd, J. O., Gelow, J. M., Hiatt, S. O., & Lee, C. S. (2017). Self-care Moderates the Relationship between Symptoms and Health-related Quality of Life in Heart Failure. *Journal of Cardiovascular Nursing (In Press)*.

Auld, J. P., Mudd, J. O., Gelow, J. M., Lyons, K. S., Hiatt, S. O., & Lee, C. S. (2018). Patterns of heart failure symptoms are associated with self-care behaviors over 6 months. *European journal of cardiovascular nursing*, 1474515118759074. doi:10.1177/1474515118759074

Ausili, D., Rebora, P., Di Mauro, S., Riegel, B., Valsecchi, M. G., Paturzo, M., . . . Vellone, E. (2016). Clinical and socio-demographic determinants of self-care behaviours in patients with heart failure and diabetes mellitus: A multicentre cross-sectional study. *Int J Nurs Stud, 63*, 18-27. doi:10.1016/j.ijnurstu.2016.08.006

Barbaranelli, C., Lee, C. S., Vellone, E., & Riegel, B. (2014). Dimensionality and Reliability of the Self-Care of Heart Failure Index Scales: Further Evidence From Confirmatory Factor Analysis. *Research in nursing & health, 37*(6), 524-537. doi:10.1002/nur.21623

Bayliss, J., Norell, M., Canepa-Anson, R., Sutton, G., & Poole-Wilson, P. (1987). Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. *Br Heart J, 57*, 17-22.

Behlouli, H., Feldman, D. E., Ducharme, A., Frenette, M., Giannetti, N., Grondin, F., . . . Pilote, L. (2009). *Identifying relative cut-off scores with neural networks for interpretation of the Minnesota Living with Heart Failure questionnaire.* Paper presented at the 2009 Annual International Conference of the IEEE Engineering in Medicine and Biology Society.

Bekelman, D. B., Havranek, E. P., Becker, D. M., Kutner, J. S., Peterson, P. N., Wittstein, I. S., . . . Dy, S. M. (2007). Symptoms, Depression, and Quality of Life in Patients With Heart Failure. *Journal of cardiac failure, 13*(8), 643-648. doi:10.1016/j.cardfail.2007.05.005

Benjamin, E. J., Blaha, M. J., Chiuve, S. E., Cushman, M., Das, S. R., Deo, R., . . . Stroke Statistics, S. (2017). Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation, 135*(10), e146-e603. doi:10.1161/CIR.0000000000000485

Bhardwaj, A., Rehman, S. U., Mohammed, A. A., Gaggin, H. K., Barajas, L., Barajas, J., . . . Januzzi, J. L. (2012). Quality of life and chronic heart failure therapy guided by natriuretic peptides: results from the ProBNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study. *Am Heart J, 164*(5), 793-799 e791. doi:10.1016/j.ahj.2012.08.015

Bilbao, A., Escobar, A., Garcia-Perez, L., Navarro, G., & Quiros, R. (2016). The Minnesota living with heart failure questionnaire: comparison of different factor structures. *Health Qual Life Outcomes, 14*, 23. doi:10.1186/s12955-016-0425-7

Buck, H. G., Lee, C. S., Moser, D. K., Albert, N. M., Lennie, T., Bentley, B., . . . Riegel, B. (2012). Relationship between self-care and health-related quality of life in older adults with moderate to advanced heart failure. *J Cardiovasc Nurs, 27*(1), 8-15. doi:10.1097/JCN.0b013e3182106299

Cameron, J., Worrall-Carter, L., Page, K., & Stewart, S. (2010). Self-care behaviours and heart failure: does experience with symptoms really make a difference? *European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology, 9*(2), 92-100. doi:10.1016/j.ejcnurse.2009.10.004

Carlson, B., Riegel, B., & Moser, D. K. (2001). Self-care abilities of patients with heart failure. *Heart and Lung, 30*, 351-359. doi:10.1067/mh1.2001.118611

Cella, D., Lai, J.-s., Chang, C.-H., Peterman, A., & Slavin, M. (2002). Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer, 94*(2), 528-538. doi:10.1002/cncr.10245

Cella, D., Y., S., Sorensen, M., Chartash, E., Sengupta, N., & Grober, J. (2005). Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. *J Rheumatol, 32*, 811-819.

Ceunen, E., Vlaeyen, J. W., & Van Diest, I. (2016). On the Origin of Interoception. *Front Psychol, 7*, 743. doi:10.3389/fpsyg.2016.00743

Charlson ME, P. P. A. K. L. M. C. R. (1987). A New Method of Classifying Prognostic in Longitudinal Studies : Development and Validation. *J Chronic Dis., 40*(5), 373-383. doi:10.1016/0021-9681(87)90171-8

Chen, N., Johns, M. W., Li, H., Chu, C., Liang, S., Shu, Y., . . . Wang, P. (2002). Validation of a Chinese Version of the Epworth Sleepiness Scale. *Quality of Life Research, 11*, 817-821.

Cocchieri, A., Riegel, B., D'Agostino, F., Rocco, G., Fida, R., Alvaro, R., & Vellone, E. (2015). Describing self-care in Italian adults with heart failure and identifying determinants of poor self-care. *Eur J Cardiovasc Nurs, 14*(2), 126-136. doi:10.1177/1474515113518443

Comin-Colet, J., Anguita, M., Formiga, F., Almenar, L., Crespo-Leiro, M. G., Manzano, L., . . . researchers, V.-I. m. s. (2016). Health-related Quality of Life of Patients With Chronic Systolic Heart Failure in Spain: Results of the VIDA-IC Study. *Rev Esp Cardiol (Engl Ed), 69*(3), 256-271. doi:10.1016/j.rec.2015.07.030

Cotter, G., Metra, M., Milo-Cotter, O., Dittrich, H. C., & Gheorghiade, M. (2008). Fluid overload in acute heart failure--re-distribution and other mechanisms beyond fluid accumulation. *Eur J Heart Fail, 10*(2), 165-169. doi:10.1016/j.ejheart.2008.01.007

Craig, A. D. (2003). Interoception: the sense of the physiological condition of the body. *Current Opinion in Neurobiology, 13*(4), 500-505. doi:10.1016/s0959-4388(03)00090-4

Darling, C., Saczynski, J. S., McManus, D. D., Lessard, D., Spencer, F. A., & Goldberg, R. J. (2013). Delayed hospital presentation in acute decompensated heart failure: Clinical and patient reported factors. *Heart & Lung: The Journal of Acute and Critical Care, 42*(4), 281-286. doi:https://doi.org/10.1016/j.hrtlng.2013.01.007

Denfeld, Q. E., Mudd, J. O., Gelow, J. M., Chien, C., Hiatt, S. O., & Lee, C. S. (2015). Physical and Psychological Symptom Biomechanics in Moderate to Advanced Heart Failure. *Journal of Cardiovascular Nursing, 30*(4), 346-350. doi:10.1097/JCN.0000000000000171

Derogatis, L. R., & Melisaratos, N. (1983). The Brief Symptom Inventory-an introductory report-1983.pdf (Vol. 13, pp. 595-605).

Ekman, I., Kjork, E., & Andersson, B. (2007). Self-assessed symptoms in chronic heart failure--important information for clinical management. *Eur J Heart Fail, 9*(4), 424-428. doi:10.1016/j.ejheart.2006.10.020

Evangelista, L., Moser, D. K., Westlake, C., Pike, N., Ter-Galstanyan, A., & Dracup, K. (2008). Correlates of Fatigue if Patients with Heart Failure. *Progress in cardiovascular nursing, 23*(1), 12-17.

Evangelista, L. S., Dracup, K., & Doering, L. V. (2000). Treatment-seeking delays in heart failure patients. *The Journal of heart and lung transplantation : the official* *publication of the International Society for Heart Transplantation, 19*(10), 932-938. doi:10.1016/S1053-2498(00)00186-8

Friedman, M. M. (1997). Older adults' symptoms and their duration before hospitalization for heart failure. *Heart & Lung: The Journal of Acute and Critical Care, 26*(3), 169-176. doi:http://dx.doi.org/10.1016/S0147-9563(97)90053-4

Gheorghiade, M., Abraham, W. T., Albert, N. M., & et al. (2006). Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA, 296*(18), 2217-2226. doi:10.1001/jama.296.18.2217

Gheorghiade, M., Filippatos, G., De Luca, L., & Burnett, J. (2006). Congestion in acute heart failure syndromes: an essential target of evaluation and treatment. *Am J Med, 119*(12 Suppl 1), S3-S10. doi:10.1016/j.amjmed.2006.09.011

Ghosh, R. K., Ball, S., Prasad, V., & Gupta, A. (2016). Depression in heart failure: Intricate relationship, pathophysiology and most updated evidence of interventions from recent clinical studies. *Int J Cardiol, 224*, 170-177. doi:10.1016/j.ijcard.2016.09.063

Gori, M., Lam, C. S., Gupta, D. K., Santos, A. B., Cheng, S., Shah, A. M., . . . Investigators, P. (2014). Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction. *Eur J Heart Fail, 16*(5), 535-542. doi:10.1002/ejhf.67

Grady, K. L. (2008). Self-care and Quality of Life Outcomes in Heart Failure Patients. *Journal of Cardiovascular Nursing, 23*(3), 285-292.

Graven, L. J., Grant, J. S., & Gordon, G. (2015). Symptomatology and Coping Resources Predict Self-Care Behaviors in Middle to Older Age Patients with Heart Failure. *Nurs Res Pract, 2015*, 840240. doi:10.1155/2015/840240

Graven, L. J., Grant, J. S., Vance, D. E., Pryor, E. R., Grubbs, L., & Karioth, S. (2015). Predicting depressive symptoms and self-care in patients with heart failure. *Am J Health Behav, 39*(1), 77-87. doi:10.5993/AJHB.39.1.9

Group*, T. C. T. S. (1987). Effects of Enalapril on Mortality in Severe Congestive Heart Failure. *New England Journal of Medicine, 316*(23), 1429-1435. doi:10.1056/nejm198706043162301

Guglin, M., Patel, T., & Darbinyan, N. (2012). Symptoms in heart failure correlate poorly with objective haemodynamic parameters. *International Journal of Clinical Practice, 66*(12), 1224-1229. doi:10.1111/j.1742-1241.2012.03003.x

Hagell, P., Höglund, A., Reimer, J., Eriksson, B., Knutsson, I., Widner, H., & Cella, D. (2006). Measuring Fatigue in Parkinson's Disease: A Psychometric Study of Two Brief Generic Fatigue Questionnaires. *Journal of Pain and Symptom Management, 32*(5), 420-432. doi:10.1016/j.jpainsymman.2006.05.021

Hammash, M. H., Hall, L. A., Lennie, T. A., Heo, S., Chung, M. L., Lee, K. S., & Moser, D. K. (2013). Psychometrics of the PHQ-9 as a measure of depressive symptoms in patients with heart failure. *Eur J Cardiovasc Nurs, 12*(5), 446-453. doi:10.1177/1474515112468068

Harkness, K., Heckman, G. A., Akhtar-Danesh, N., Demers, C., Gunn, E., & McKelvie, R. S. (2014). Cognitive function and self-care management in older patients with heart failure. *Eur J Cardiovasc Nurs, 13*(3), 277-284. doi:10.1177/1474515113492603

Hasselblad, V., Gattis Stough, W., Shah, M. R., Lokhnygina, Y., O'Connor, C. M., Califf, R. M., & Adams, K. F., Jr. (2007). Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. *Eur J Heart Fail, 9*(10), 1064-1069. doi:10.1016/j.ejheart.2007.07.011

Heidenreich, P. A., Albert, N. M., Allen, L. A., Bluemke, D. A., Butler, J., Fonarow, G. C., . . . Trogdon, J. G. (2013). Forecasting the Impact of Heart Failure in the United States: A Policy Statement From the American Heart Association. *Circulation: Heart Failure, 6*(3), 606-619. doi:10.1161/HHF.0b013e318291329a

Heo, S., Moser, D. K., Lennie, T. A., Fischer, M., Smith, E., & Walsh, M. N. (2014). Modifiable correlates of physical symptoms and health-related quality of life in patients with heart failure: a cross-sectional study. *Int J Nurs Stud, 51*(11), 1482-1490. doi:10.1016/j.ijnurstu.2014.03.005

Heo, S., Moser, D. K., Lennie, T. A., Riegel, B., & Chung, M. L. (2008). Gender differences in and factors related to self-care behaviors: a cross-sectional, correlational study of patients with heart failure. *Int J Nurs Stud, 45*(12), 1807-1815. doi:10.1016/j.ijnurstu.2008.05.008

Heo, S., Moser, D. K., Lennie, T. A., Zambroski, C. H., & Chung, M. L. (2007). A comparison of health-related quality of life between older adults with heart failure and healthy older adults. *Heart & lung : the journal of critical care, 36*(1), 16-24. doi:10.1016/j.hrtlng.2006.06.003

Heo, S., Moser, D. K., Pressler, S. J., Dunbar, S. B., Dekker, R. L., & Lennie, T. A. (2014). Depressive Symptoms and the Relationship of Inflammation to Physical Signs and Symptoms in Heart Failure Patients. *American Journal of Critical Care*, *23*(5), 404-413. doi:10.4037/ajcc2014614

Heo, S., Moser, D. K., Pressler, S. J., Dunbar, S. B., Kim, J., Ounpraseuth, S., & Lennie, T. A. (2013). Dose-dependent relationship of physical and depressive symptoms with health-related quality of life in patients with heart failure. *Eur J Cardiovasc Nurs, 12*(5), 454-460. doi:10.1177/1474515112470996

Hjollund, N. H., Andersen, J. H., & Bech, P. (2007). Assessment of fatigue in chronic disease: a bibliographic study of fatigue measurement scales. *Health and quality of life outcomes*, *5*, 12-12. doi:10.1186/1477-7525-5-12

Hlatky, M. A., Boineau, R. E., Higginbotham, M. B., Lee, K. L., Mark, D. B., Califf, R. M., . . . Pryor, D. B. (1989). A brief self-administered questionnaire to determine functional capacity (The Duke Activity Status Index). *The American journal of cardiology, 64*(10), 651-654. doi:http://dx.doi.org/10.1016/0002-9149(89)90496-7

Holzapfel, N., Lowe, B., Wild, B., Schellberg, D., Zugck, C., Remppis, A., . . . Muller-Tasch, T. (2009). Self-care and depression in patients with chronic heart failure. *Heart Lung, 38*(5), 392-397. doi:10.1016/j.hrtlng.2008.11.001

Hu, L., & Bentler, P. (1998). Fit Indices in Covariance Structure Modeling: Sensitivity to Underparameterized Model Misspecification. *Psychological Methods, 3*(4), 424-453.

Jaarsma, T., Stromberg, A., Ben Gal, T., Cameron, J., Driscoll, A., Duengen, H. D., . . . Riegel, B. (2013). Comparison of self-care behaviors of heart failure patients in 15 countries worldwide. *Patient Educ Couns*, *92*(1), 114-120. doi:10.1016/j.pec.2013.02.017

Jencks, S. F., Williams, M. V., & Coleman, E. A. (2009). Rehospitalizations among patients in the Medicare fee-for-service program. *The New England journal of medicine*, *360*(14), 1418-1428. doi:10.1056/NEJMsa0803563

Joekes, K., Van Elderen, T., & Schreurs, K. (2007). Self-efficacy and overprotection are related to quality of life, psychological well-being and self-management in cardiac patients. *J Health Psychol, 12*(1), 4-16. doi:10.1177/1359105306069096

Johns, M. W. (1991). A New Method for Measuring Daytime Sleepiness: The Epworth Sleepiness Scale. *Sleep, 14*(6), 540-545. doi:10.1093/sleep/14.6.540

Jonkman, N. H., Westland, H., Groenwold, R. H. H., Ågren, S., Atienza, F., Blue, L., . . . Hoes, A. W. (2016). Do Self-Management Interventions Work in Patients With Heart Failure? *An Individual Patient Data Meta-Analysis, 133*(12), 1189-1198. doi:10.1161/circulationaha.115.018006

Jurgens, C. Y. (2006). Somatic Awareness, Uncertainty, and Delay in Care-Seeking in Acute Heart Failure. *Research in nursing & health, 29*, 74-86. doi:10.1002/nur

Jurgens, C. Y., Fain, J. A., & Riegel, B. (2006). Psychometric testing of the heart failure somatic awareness scale. *The Journal of cardiovascular nursing, 21*(2), 95-102.

Jurgens, C. Y., Hoke, L., Byrnes, J., & Riegel, B. (2009). Why do elders delay responding to heart failure symptoms? *Nursing Research, 58*(4), 274-282. doi:10.1097/NNR.0b013e3181ac1581

Jurgens, C. Y., Lee, C. S., & Riegel, B. (2015). Psychometric Analysis of the Heart Failure Somatic Perception Scale as a Measure of Patient Symptom Perception. *J Cardiovasc Nurs*. doi:10.1097/JCN.0000000000000320

Kempton, M. J., Salvador, Z., Munafò, M. R., & et al. (2011). Structural neuroimaging studies in major depressive disorder: Meta-analysis and comparison with bipolar disorder. *Archives of General Psychiatry, 68*(7), 675-690. doi:10.1001/archgenpsychiatry.2011.60

Kessing, D., Denollet, J., Widdershoven, J., & Kupper, N. (2016). Psychological Determinants of Heart Failure Self-Care: Systematic Review and Meta-Analysis. *Psychosom Med, 78*(4), 412-431. doi:10.1097/PSY.0000000000000270

Khalil, A. A., Hall, L. A., Moser, D. K., Lennie, T. A., & Frazier, S. K. (2011). The psychometric properties of the Brief Symptom Inventory depression and anxiety subscales in patients with heart failure and with or without renal dysfunction. *Arch Psychiatr Nurs, 25*(6), 419-429. doi:10.1016/j.apnu.2010.12.005

Kociol, R. D., McNulty, S. E., Hernandez, A. F., Lee, K. L., Redfield, M. M., Tracy, R. P., . . . Investigators. (2013). Markers of decongestion, dyspnea relief, and clinical outcomes among patients hospitalized with acute heart failure. *Circ Heart Fail, 6*(2), 240-245. doi:10.1161/CIRCHEARTFAILURE.112.969246

Kroenke, K., Spitzer, R. L., & Willaims, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med, 16*(9), 606-613.

Leach, L. S., Christensen, H., Mackinnon, A. J., Windsor, T. D., & Butterworth, P. (2008). Gender differences in depression and anxiety across the adult lifespan: the role of psychosocial mediators. *Soc Psychiatry Psychiatr Epidemiol, 43*(12), 983-998. doi:10.1007/s00127-008-0388-z

Lee, C. S., & Auld, J. (2015). Heart Failure: A Primer. *Crit Care Nurs Clin North Am, 27*(4), 413-425. doi:10.1016/j.cnc.2015.07.009

Lee, C. S., Bidwell, J. T., Paturzo, M., Alvaro, R., Cocchieri, A., Jaarsma, T., . . . Vellone, E. (2017). Patterns of self-care and clinical events in a cohort of adults with heart failure: 1 year follow-up. *Heart Lung*. doi:10.1016/j.hrtlng.2017.09.004

Lee, C. S., Gelow, J. M., Denfeld, Q. E., Mudd, J. O., Burgess, D., Green, J. K., . . . Jurgens, C. Y. (2013). Physical and Psychological Symptom Profiling and Event-Free Survival in Adults With Moderate to Advanced Heart Failure. *The Journal of cardiovascular nursing, 00*(0), 1-9. doi:10.1097/JCN.0b013e318285968a

Lee, C. S., Gelow, J. M., Mudd, J. O., Green, J. K., Hiatt, S. O., Chien, C., & Riegel, B. (2013). Profiles of self-care management versus consulting behaviors in adults with heart failure. *European journal of cardiovascular nursing*. doi:10.1177/1474515113519188

Lee, C. S., Gelow, J. M., Mudd, J. O., Green, J. K., Hiatt, S. O., Chien, C., & Riegel, B. (2015). Profiles of self-care management versus consulting behaviors in adults with heart failure. *Eur J Cardiovasc Nurs, 14*(1), 63-72. doi:10.1177/1474515113519188

Lee, C. S., Hiatt, S. O., Denfeld, Q. E., Chien, C. V., Mudd, J. O., & Gelow, J. M. (2015). Gender-Specific Physical Symptom Biology in Heart Failure. *J Cardiovasc Nurs, 30*(6), 517-521. doi:10.1097/JCN.0000000000000191

Lee, C. S., Hiatt, S. O., Denfeld, Q. E., Mudd, J. O., Chien, C., & Gelow, J. M. (2015). Symptom-Hemodynamic Mismatch and Heart Failure Event Risk. *The Journal of cardiovascular nursing, 30*(5), 394-402. doi:10.1097/JCN.0000000000000175

Lee, C. S., Moser, D. K., Lennie, T., & Riegel, B. (2011). Event-free survival in adults with heart failure who engage in self-care management. *Heart & lung : the journal of critical care, 40*(1), 12-20. doi:10.1016/j.hrtlng.2009.12.003

Lee, C. S., Moser, D. K., Lennie, T. A., Tkacs, N. C., Margulies, K. B., & Riegel, B. (2011). Biomarkers of myocardial stress and systemic inflammation in patients who engage in heart failure self-care management. *J Cardiovasc Nurs, 26*(4), 321-328. doi:10.1097/JCN.0b013e31820344be

Lee, C. S., Mudd, J. O., Hiatt, S. O., Gelow, J. M., Chien, C., & Riegel, B. (2014). Trajectories of heart failure self-care management and changes in quality of life. *Eur J Cardiovasc Nurs*. doi:10.1177/1474515114541730

Lee, C. S., Riegel, B., Driscoll, A., Suwanno, J., Moser, D. K., Lennie, T. A., . . . Worrall-Carter, L. (2009). Gender differences in heart failure self-care: a multinational cross-sectional study. *International Journal of Nursing Studies, 46*(11), 1485-1495. doi:10.1016/j.ijnurstu.2009.04.004

Lee, C. S., Tkacs, N. C., & Riegel, B. (2009). The Influence of Heart Failure Self-care on Health Outcomes Hypothetical Cardioprotective Mechanisms. *J Cardiovasc Nurs, 24*(3), 179-187.

Lee, K. S., Lennie, T. A., Warden, S., Jacobs-Lawson, J. M., & Moser, D. K. (2013). A comprehensive symptom diary intervention to improve outcomes in patients with HF: a pilot study. *J Card Fail, 19*(9), 647-654. doi:10.1016/j.cardfail.2013.07.001

Lee, K. S., Song, E. K., Lennie, T. A., Frazier, S. K., Chung, M. L., Heo, S., . . . Moser, D. K. (2010). Symptom Clusters in Men and Women With Heart Failure and Their Impact on Cardiac Event-Free Survival. *Journal of Cardiovascular Nursing, 25*(4), 263-272. doi:10.1097/JCN.0b013e3181cfbb88

Lenz, E. R., Pugh, L., Milligan, R. A., Gift, A., & Suppe, F. (1997). The middle-range theory of Unpleasant Symptoms: An update. *Adv Nurs Sci, 19*(3), 14-27.

Levy, W. C. (2006). The Seattle Heart Failure Model: Prediction of Survival in Heart Failure. *Circulation, 113*(11), 1424-1433. doi:10.1161/CIRCULATIONAHA.105.584102

Lewis, E. F., Lamas, G. a., O'Meara, E., Granger, C. B., Dunlap, M. E., McKelvie, R. S., . . . Pfeffer, M. a. (2007). Characterization of health-related quality of life in heart failure patients with preserved versus low ejection fraction in CHARM. *European Journal of Heart Failure, 9*(1), 83-91. doi:10.1016/j.ejheart.2006.10.012

Macabasco-O'Connell, A., DeWalt, D. A., Broucksou, K. A., Hawk, V., Baker, D. W., Schillinger, D., . . . Pignone, M. (2011). Relationship between literacy, knowledge, self-care behaviors, and heart failure-related quality of life among patients with heart failure. *J Gen Intern Med, 26*(9), 979-986. doi:10.1007/s11606-011-1668-y

MacCallum, R., Browne, M., & Sugawara, H. (1996). Power Analysis and Determination of Sample Size for Covariance Structure Modeling. *Psychological Methods, 1*(2), 130-149.

Mentz, R. J., & O'Connor, C. M. (2015). Pathophysiology and clinical evaluation of acute heart failure. *Nature Reviews Cardiology*, 1-9. doi:10.1038/nrcardio.2015.134

Moser, D. K., Dickson, V., Jaarsma, T., Lee, C., Stromberg, A., & Riegel, B. (2012). Role of self-care in the patient with heart failure. *Current Cardiology Reports, 14*(3), 265-275. doi:10.1007/s11886-012-0267-9

Moser, D. K., Lee, K. S., Wu, J. R., Mudd-Martin, G., Jaarsma, T., Huang, T. Y., . . . Riegel, B. (2014). Identification of symptom clusters among patients with heart failure: an international observational study. *Int J Nurs Stud, 51*(10), 1366-1372. doi:10.1016/j.ijnurstu.2014.02.004

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., . . . Turner, M. B. (2016). Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation, 133*(4), e38-360. doi:10.1161/CIR.0000000000000350

Mozaffarian, D., Benjamin, E. J., Go, a. S., Arnett, D. K., Blaha, M. J., Cushman, M., . . . Turner, M. B. (2015). Executive Summary: Heart Disease and Stroke Statistics--2015 Update: A Report From the American Heart Association. *Circulation, 131*(4), 434-441. doi:10.1161/CIR.0000000000000157

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *Journal of the American Geriatrics Society, 53*, 695-699.

Negi, S., Sawano, M., Kohsaka, S., Inohara, T., Shiraishi, Y., Kohno, T., . . . Fukuda, K. (2014). Prognostic Implication of Physical Signs of Congestion in Acute Heart Failure Patients and Its Association with Steady-State Biomarker Levels. *PLoS One, 9*(5), e96325-e96325. doi:10.1371/journal.pone.0096325

Nohria, A., Tsang, S. W., Fang, J. C., Lewis, E. F., Jarcho, J. a., Mudge, G. H., & Stevenson, L. W. (2003). Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *Journal of the American College of Cardiology, 41*(10), 1797-1804. doi:10.1016/S0735-1097(03)00309-7

Pappas, L., & Filippatos, G. (2011). Pulmonary Congestion in Acute Heart Failure: From Hemodynamics to Lung Injury and Barrier Dysfunction. *Revista Española de Cardiología (English Edition), 64*(9), 735-738. doi:10.1016/j.rec.2011.05.010

Parrinello, G., Greene, S. J., Torres, D., Alderman, M., Bonventre, J. V., Di Pasquale, P., . . . Gheorghiade, M. (2015). Water and Sodium in Heart Failure: A Spotlight on Congestion. *Heart failure reviews, 20*(1), 13-24. doi:10.1007/s10741-014-9438-7

Peters-Klimm, F., Freund, T., Kunz, C. U., Laux, G., Frankenstein, L., Muller-Tasch, T., & Szecsenyi, J. (2013). Determinants of heart failure self-care behaviour in community-based patients: a cross-sectional study. *Eur J Cardiovasc Nurs, 12*(2), 167-176. doi:10.1177/1474515112439964

Pilkonis, P. A., Choi, S. W., Reise, S. P., Stover, A. M., Riley, W. T., Cella, D., & Group, P. C. (2011). Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS(R)): depression, anxiety, and anger. *Assessment, 18*(3), 263-283. doi:10.1177/1073191111411667

Ponikowski, P., Anker, S. D., AlHabib, K. F., Cowie, M. R., Force, T. L., Hu, S., . . . Filippatos, G. (2014). Heart failure: preventing disease and death worldwide. *ESC Heart Fail, 1*(1), 4-25. doi:10.1002/ehf2.12005

Ram, N., & Grimm, K. J. (2009). Growth Mixture Modeling: A Method for Identifying Differences in Longitudinal Change Among Unobserved Groups. *Int J Behav Dev, 33*(6), 565-576. doi:10.1177/0165025409343765

Rathman, L. D., Lee, C. S., Sarkar, S., & Small, R. S. (2011). A critical link between heart failure self-care and intrathoracic impedance. *The Journal of cardiovascular nursing, 26*(4), E20-E26. doi:10.1097/JCN.0b013e3181ee28c8

Rector, T. S., Anand, I. S., & Cohn, J. N. (2006). Relationships between clinical assessments and patients' perceptions of the effects of heart failure on their quality of life. *Journal of cardiac failure, 12*(2), 87-92. doi:10.1016/j.cardfail.2005.10.002

Rector, T. S., & Cohn, J. N. (1992). Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: Reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. *American heart journal, 124*.

Riedinger, M. S., Dracup, K. A., Brecht, M.-L., Padilla, G., Sarna, L., & Ganz, P. A. (2001). Quality of life in patients with heart failure: Do gender differences exist? *Heart & Lung: The Journal of Acute and Critical Care, 30*(2), 105-116. doi:10.1067/mhl.2001.114140

Riegel, B., Dickson, V. V., & Faulkner, K. M. (2015a). The Situation-Specific Theory of Heart Failure Self-Care. *The Journal of cardiovascular nursing, 31*(3), 226-235. doi:10.1097/JCN.0000000000000244

Riegel, B., Dickson, V. V., & Faulkner, K. M. (2015b). The Situation-Specific Theory of Heart Failure Self-Care: Revised and Updated. *J Cardiovasc Nurs*. doi:10.1097/JCN.0000000000000244

Riegel, B., Dickson, V. V., Lee, C. S., Daus, M., Hill, J., Irani, E., . . . Bove, A. (2018). A mixed methods study of symptom perception in patients with chronic heart failure. *Heart Lung*. doi:10.1016/j.hrtlng.2017.11.002

Riegel, B., Jaarsma, T., & Stromberg, A. (2012). A middle-range theory of self-care of chronic illness. *ANS Adv Nurs Sci, 35*(3), 194-204. doi:10.1097/ANS.0b013e318261b1ba

Riegel, B., Lee, C. S., Albert, N. M., Lennie, T., Chung, M. L., Song, E. K., . . . Moser, D. K. (2011). From Novice to Expert: Confidence and Activity Status Determine Heart Failure Self-care Performance. *Nursing Research, 60*(2), 132-138. doi:10.1097/NNR.0b013e31820978ec

Riegel, B., Lee, C. S., & Dickson, V. V. (2011). Self care in patients with chronic heart failure. *Nature reviews. Cardiology, 8*(11), 644-654. doi:10.1038/nrcardio.2011.95

Riegel, B., Lee, C. S., Dickson, V. V., & Carlson, B. (2009). An update on the self-care of heart failure index. *The Journal of cardiovascular nursing, 24*(6), 485-497. doi:10.1097/JCN.0b013e3181b4baa0

Riegel, B., Moser, D. K., Anker, S. D., Appel, L. J., Dunbar, S. B., Grady, K. L., . . . Whellan, D. J. (2009). State of the science: promoting self-care in persons with heart failure: a scientific statement from the American Heart Association. *Circulation, 120*(12), 1141-1163. doi:10.1161/CIRCULATIONAHA.109.192628

Riegel, B., Moser, D. K., Buck, H. G., Dickson, V. V., Dunbar, S. B., Lee, C. S., . . . Outcomes, R. (2017). Self-Care for the Prevention and Management of Cardiovascular Disease and Stroke: A Scientific Statement for Healthcare Professionals From the American Heart Association. *J Am Heart Assoc*, *6*(9). doi:10.1161/JAHA.117.006997

Riegel, B., & Weaver, T. E. (2009). Poor sleep and impaired self-care: towards a comprehensive model linking sleep, cognition, and heart failure outcomes. *Eur J Cardiovasc Nurs, 8*(5), 337-344. doi:10.1016/j.ejcnurse.2009.06.003

Rockwell, J. M., & Riegel, B. (2001). Predictors of self-care in persons with heart failure. *Heart & Lung, 30*, 18-25.

Rosenman, R., Tennekoon, V., & Hill, L. G. (2011). Measuring bias in self-reported data. *Int J Behav Healthc Res, 2*(4), 320-332. doi:10.1504/IJBHR.2011.043414

Rutledge, T., Reis, V. a., Linke, S. E., Greenberg, B. H., & Mills, P. J. (2006). Depression in Heart Failure. A Meta-Analytic Review of Prevalence, Intervention Effects, and Associations With Clinical Outcomes. *Journal of the American College of Cardiology, 48*(8), 1527-1537. doi:10.1016/j.jacc.2006.06.055

Schwarz, K. A., & Elman, C. S. (2003). Identification of factors predictive of hospital readmissions for patients with heart failure. *Heart Lung, 32*(2), 88-99. doi:10.1067/mhl.2003.15

Shah, M. R., Hasselblad, V., Stinnett, S. S., Kramer, J. M., Grossman, S., Gheorghiade, M., . . . O'Connor, C. M. (2002). Dissociation between hemodynamic changes and symptom improvement in patients with advanced congestive heart failure. *European journal of heart failure : journal of the Working Group on Heart*

Failure of the European Society of Cardiology, 4(3), 297-304. doi:http://dx.doi.org/10.1016/S1388-9842%2801%2900202-1

Sharma, V., Rathman, L. D., Small, R. S., Whellan, D. J., Koehler, J., Warman, E., & Abraham, W. T. (2015). Stratifying patients at the risk of heart failure hospitalization using existing device diagnostic thresholds. *Heart & Lung: The Journal of Acute and Critical Care, 44*(2), 129-136. doi:10.1016/j.hrtlng.2014.07.007

Shimiaie, J., Sherez, J., Aviram, G., Megidish, R., Viskin, S., Halkin, A., . . . Topilsky, Y. (2015). Determinants of Effort Intolerance in Patients With Heart Failure: Combined Echocardiography and Cardiopulmonary Stress Protocol. *JACC Heart Fail, 3*(10), 803-814. doi:10.1016/j.jchf.2015.05.010

Shuldham, C., Theaker, C., Jaarsma, T., & Cowie, M. R. (2007). Evaluation of the European Heart Failure Self-care Behaviour Scale in a United Kingdom population. *J Adv Nurs, 60*(1), 87-95. doi:10.1111/j.1365-2648.2007.04371.x

Small, R. S., Whellan, D. J., Boyle, A., Sarkar, S., Koehler, J., Warman, E. N., & Abraham, W. T. (2014). Implantable device diagnostics on day of discharge identify heart failure patients at increased risk for early readmission for heart failure. *Eur J Heart Fail, 16*(4), 419-425. doi:10.1002/ejhf.48

Small, R. S., Wickemeyer, W., Germany, R., Hoppe, B., Andrulli, J., Brady, P. A., . . . Tang, W. H. (2009). Changes in intrathoracic impedance are associated with subsequent risk of hospitalizations for acute decompensated heart failure: clinical utility of implanted device monitoring without a patient alert. *J Card Fail, 15*(6), 475-481. doi:10.1016/j.cardfail.2009.01.012

Spertus, J. A., & Jones, P. G. (2015). Development and Validation of a Short Version of the Kansas City Cardiomyopathy Questionnaire. *Circulation: Cardiovascular Quality and Outcomes, 8*(5), 469-476. doi:10.1161/CIRCOUTCOMES.115.001958

Spitzer, R. L., Kroenke, K., & Williams, J. D. W. (1999). Validation and Utility of a Self-report Version of PRIME-MD: The PHQ Primary Care Study. *JAMA, 282*(18), 1737-1744.

Stewart, S., MacIntyre, K., Hole, D. J., Capewell, S., & McMurry, J. J. V. (2001). More ‘malignant’ than cancer? Five-year survival following a first admission for heart failure. *The European Journal of Heart Failure, 3*, 315-322.

Tang, W. H., Warman, E. N., Johnson, J. W., Small, R. S., & Heywood, J. T. (2012). Threshold crossing of device-based intrathoracic impedance trends identifies relatively increased mortality risk. *Eur Heart J, 33*(17), 2189-2196. doi:10.1093/eurheartj/ehs121

Vellone, E., Riegel, B., D'Agostino, F., Fida, R., Rocco, G., Cocchieri, A., & Alvaro, R. (2013). Structural equation model testing the situation-specific theory of heart failure self-care. *Journal of Advanced Nursing, 69*(11), 2481-2492. doi:10.1111/jan.12126

Vollmann, D., N??gele, H., Schauerte, P., Wiegand, U., Butter, C., Zanotto, G., . . . Lamp, B. (2007). Clinical utility of intrathoracic impedance monitoring to alert patients with an implanted device of deteriorating chronic heart failure. *European Heart Journal, 28*(15), 1835-1840. doi:10.1093/eurheartj/ehl506

Wang, L. (2007). Fundamentals of intrathoracic impedance monitoring in heart failure. *Am J Cardiol, 99*(10A), 3G-10G. doi:10.1016/j.amjcard.2007.02.009

Whitaker, K. L., Scott, S. E., & Wardle, J. (2015). Applying symptom appraisal models to understand sociodemographic differences in responses to possible cancer symptoms: a research agenda. *Br J Cancer, 112 Suppl 1*, S27-34. doi:10.1038/bjc.2015.39

Woo, M. A., Kumar, R., Macey, P. M., Fonarow, G. C., & Harper, R. M. (2009). Brain injury in autonomic, emotional, and cognitive regulatory areas in patients with heart failure. *J Card Fail, 15*(3), 214-223. doi:10.1016/j.cardfail.2008.10.020

World Medical, A. (2013). World medical association declaration of helsinki: Ethical principles for medical research involving human subjects. *JAMA, 310*(20), 2191-2194. doi:10.1001/jama.2013.281053

Xiong, G. L., Prybol, K., Boyle, S. H., Hall, R., Streilein, R. D., Steffens, D. C., . . . Investigators, S.-C. (2015). Inflammation Markers and Major Depressive Disorder in Patients With Chronic Heart Failure: Results From the Sertraline Against Depression and Heart Disease in Chronic Heart Failure Study. *Psychosom Med, 77*(7), 808-815. doi:10.1097/PSY.0000000000000216

Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E., Drazner, M. H., . . . Wilkoff, B. L. (2013). 2013 ACCF/AHA guideline for the management of heart failure: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. *Circulation, 128*(16), 240-327. doi:10.1161/CIR.0b013e31829e8776

Yellen, S. B., Cella, D. F., Webster, K., Blendowski, C., & Kaplan, E. (1997). Measuring Fatigue and Other Anemia-Related Symptoms with the Functional Assessment of Cancer Therapy (FACT) Measurement System. *Journal of Pain and Symptom Management, 13*(2), 63-74.

Ypenburg, C., Bax, J. J., van der Wall, E. E., Schalij, M. J., & van Erven, L. (2007). Intrathoracic impedance monitoring to predict decompensated heart failure. *The American journal of cardiology, 99*(4), 554-557. doi:10.1016/j.amjcard.2006.08.066

Yu, C. M., Wang, L., Chau, E., Chan, R. H., Kong, S. L., Tang, M. O., . . . Lau, C. P. (2005). Intrathoracic impedance monitoring in patients with heart failure: correlation with fluid status and feasibility of early warning preceding hospitalization. *Circulation, 112*(6), 841-848. doi:10.1161/CIRCULATIONAHA.104.492207

Zambroski, C. H., Moser, D. K., Bhat, G., & Ziegler, C. (2005). Impact of symptom prevalence and symptom burden on quality of life in patients with heart failure. *European journal of cardiovascular nursing, 4*(3), 198-206. doi:10.1016/j.ejcnurse.2005.03.010