Physical Activity in Association with Prognostic Determinants Across Heart Failure Continuum

by

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Abstract

Heart Failure (HF) is a complex syndrome that greatly contributes to declining physical function in older adults and causes a substantial economic burden for health care systems. Older adults at risk of developing HF typically have other comorbidities. In addition, patients with HF often experience periods of exacerbations as the disease progresses. Despite recent improvements in medical treatments, the prognosis of older adults diagnosed with HF is poor and their quality of life deteriorates quickly. Near half of the patients with HF have preserved ejection fraction (HFPEF) with an increasing prevalence compared to those with HF and reduced ejection fraction (HFREF). Although the underlying mechanisms to develop the two phenotypes are different, the reduced aerobic capacity is one of the important clinical features in both. While historically exercise training has been prescribed to improve exercise intolerance in patients with HF, there is no consensus regarding the characteristics of an effective training program. Moreover, the low rate of referrals to some exercise-based rehabilitation programs and poor compliance may not bode well for a long-term behavior change. Some investigators suggest daily physical activity (PA) as a more practical substitute in older adults with HF.

The role of PA in promoting cardiovascular health and improving symptoms, function and health-related quality of life in patients at risk of with HF (At-risk) has been understudied. In addition, for many HF patients daily PA may be closely linked to clinical prognosis. With the advancements of technology reliable devices capable of monitoring PA in a broader range of intensities are available now. However, the objectively measured PA in the two phenotypes of HF and those at risk of HF compared to healthy controls are unknown. Therefore, the purpose of the first study was to assess daily PA across the HF continuum. The findings showed that patients

with HFPEF had the lowest volume of PA across the four groups. Also, patients with HFREF spent a higher amount of time in bouts of moderate-vigorous PA than patients with HFPEF. In addition, our results suggested the steps/day as the most robust measure in evaluating PA in this population.

The second and third studies in this thesis aimed not only to investigate the association between daily PA (i.e., steps/day) and prognostic determinants in patients with HF but also to assess if these associations are different across the HF continuum. Evaluating the associations between the markers of PA, aortic distensibility (AD), and myocardial stress biomarkers could also help in the development of pathways leading to earlier diagnosis, more precise classifications, and a better prognosis for patients with HF.

The results of the second study showed that the association between steps/day and AD may not be similar across the continuum of HF. The findings showed there was a direct relationship, such that a higher range of steps/day was associated with a higher AD, but only in our small HFREF group. The findings of the third study also indicated the association between steps/day and BNP or NT-proBNP were not comparable across groups, from healthy controls, to those At-risk and with HFPEF. In fact, the association between steps/day and biomarkers were more prominent in the At-risk group compared to HFPEF group.

In summary, the findings of three studies in this thesis suggest that the majority of patients at risk or with HF have a sedentary lifestyle. In addition, the daily PA performed by the majority of patients with HF might not reach the minimum volume required to improve AD or reduce biomarkers. The information provided by the objective assessment of PA could be used as an important tool to establish realistic rehabilitation goals and design individualized programs.

Although the ultimate goal in this population should be to meet the current recommendations, for a majority of patients it appears to be achievable only through a tailored increase in the volume of PA. In addition, the association between a single marker of PA such as steps/day and important prognostic determinant of HF underscores the importance of regular assessment of this behavior. Despite the different mechanisms by which PA benefits individuals across HF continuum, it is critical to recognize risk factors associated with a sedentary lifestyle and proper strategies to tackle this issue.

Preface

The introduction in Chapter 1 and the literature review in chapter 2, as well as the general discussion and conclusion in chapter 6 of this thesis, are the original work by Milad Yavari.

Chapter 3, 4 and 5 are sub-studies of the **H**eart Failure **E**tiology and **A**nalysis **R**esearch **T**eam (HEART) research project which has received research ethics approval from the University of Alberta Health Research Ethics Board, Project Name "AHFMR Interdisciplinary Team Grant on Understanding and Treating Diastolic Heart Failure: Novel Mechanisms, Diagnostics and Potential Therapeutics ", No. Pro00007105, March 28, 2012.

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Dedication

To my parents whose sacrifice made it possible for me to follow my dreams. Thank you for your support and encouragement from miles away.

To my amazing wife, Nasim, for her endless love and inspiration. You have always been a tremendous support for me.

To my little boy, Taha, whose laughs always fill my heart with joy and love.

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Table of Contents

List of Tables

Chapter 1 Introduction

1.1. Introduction and Purpose

Despite improvements in medical interventions and longevity of cardiac patients, heart failure (HF) remains a significant burden to our health care system (1, 2). Within the Canadian population, HF affects ~1.5 to 2.0% of all Canadians, with 50,000 new patients diagnosed each year (3, 4).

The American Heart Association (AHA) defined HF as "*a complex clinical syndrome resulting from any structural or functional impairment of ventricular filling or ejection of blood"* (5-page 246). The previously known form of HF has been characterized by reduced ejection fraction (HFREF) and different degrees of left ventricular (LV) enlargement (5). However, up to 50% of patients diagnosed with HF have a preserved ejection fraction (EF) and are categorized as diastolic HF (HFPEF) (6-8).

Until the 1980s, physical activity (PA) restriction was the treatment of choice for patients with HF. However, it was subsequently proven that exercise capacity in patients with LV dysfunction was not related to ventricular filling pressures and EF (9). Since that time, there has been a gradual move towards incorporating PA and exercise training into the therapeutic plan for patients with HF. Several recent studies have demonstrated the beneficial effects of exercise training on patients with HF (10-12). Unfortunately, exercise training may not be feasible for all patients with HF and their adherence to exercise training can be problematic (12-14). Indeed, some investigators suggest that daily PA may be considered as a viable substitute to regimented

exercise training, as it includes occupational, leisure time, household activities and can be accomplished throughout the day (15, 16). For example, one study showed that by increasing daily walking duration, both exercise capacity and the general well-being of patients with HF is improved (15).

Monitoring daily PA may also offer additional useful information about functional status in patients with HF because performance is evaluated in terms of routine activities as opposed to test-specific expectations and abilities. Moreover, assessing free-living PA allows day-to-day fluctuations to be taken into account, which periodical cardiopulmonary exercise stress tests does not. As several studies have shown, PA is a relatively strong predictor of clinical status, prognosis, and survival in patients with HF. Therefore, daily PA may be a valuable therapeutic tool in the management of HF (17, 18).

Most PA guidelines encourage elderly individuals and patients to be active for at least 30 minutes on most days of the week at a moderate to vigorous intensity (i.e., PA ≥ 3 METs) (19-22). Patients who do not meet these time and intensity thresholds historically have been labeled as sedentary (i.e., inactive). However, due to recent advancements in PA measurement devices researchers can now monitor a broader range of intensities of activity that may occur throughout the day (23). Hence sedentary behavior has been redefined as "*any waking behavior characterized by an energy expenditure ≤ 1.5 METs and a sitting or reclining posture*" (24-page 540). Also, the lower end of PA continuum that is recognized as light intensity PA (i.e., 1.6-3 METs) has recently gained attention. There is evidence supporting the beneficial effects of light intensity PA in elderly individuals and those with heart diseases (25-27).

Sedentary behavior has been extensively studied in healthy populations; however, there are scarce data in patients with HF, especially patients with HFPEF. In healthy populations, several studies have demonstrated excess television viewing to be negatively associated with metabolic risk factors (28). Based on a recent meta-analysis, higher levels of sedentary behavior appear to be associated with a 112% increase in the risk ratio for diabetes, 147% increase in the risk ratio for cardiovascular (CV) events, 90% increase in the risk for CV mortality and a 49% increase in the risk of all-cause mortality (29). One unique aspect of this thesis is the objective measurement of sedentary behavior in patients with both types of HF and the comparison with healthy individuals (Control) and those at risk of developing HF (At-risk).

In a recent study, Dontje et al. reported considerable variability in daily PA for patients with HF (30) and only 50% were performing equally or above the range of step/day (~ 5,000 steps/day) recommended for older adults with disabilities, such as HF (31). In addition, for many HF patients daily PA may be closely linked to clinical prognosis (16-18). Aortic dispensability (AD) and cardiac natriuretic peptides are well-documented determinants of prognosis in patients with HF (32-35). The association between daily PA and these determinants of prognosis across the whole continuum of HF is unknown.

The initial study in this thesis examines the daily volume and patterns of PA in two phenotypes of HF and contrast it with At-risks and Controls. The second study will evaluate the association between markers of PA and AD across the HF continuum. The final study examines the relationship between a marker of PA and brain natriuretic peptides (BNP) and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels across three groups of patients with HFPEF, those at risk of developing HF and healthy controls.

From the clinical standpoint, this series of studies could provide a clearer picture of the functional status of individuals At-risk of HF versus those patients suffering from HF. In addition, having objectively measured daily PA across the continuum of HF patients might help to adjust exercise training targets and establish realistic rehabilitation goals that may, in turn, result in more motivated patients and improved outcomes. Moreover, investigating the associations between daily PA and AD and cardiac natriuretic peptides could help in the development of pathways leading to earlier diagnosis, more precise classifications, and better prognosis of HF. The results might also provide a better understanding as to the extent of sedentary behavior in patients with HF and the possible contribution of inactivity to the prognosis of patients across the HF continuum.

1.2. Hypotheses

The lack of comprehensive and objectively measured daily PA and sedentary behavior in patients with HF and those At-risk of HF is the rationale for the first study (30, 36). In this study we will use a multi-sensor activity monitor to objectively quantify daily PA across the HF continuum. Although some reports have suggested the low levels of daily PA in patients with HF (16, 37) most of these studies had several limitations including; small sample sizes, self-reported measures of PA or combining patients with HFPEF and HEFREF into a single group (30, 38). For the first study it is hypothesized that there is a difference between the volume of PA and sedentary time across the HF continuum, from healthy control participants to patients at risk of HF and those patients with HFREF or HFPEF. Further, there is an emerging trend of evidence

suggesting patients with HFPEF would benefit more from PA than their HFREF peers (39). Therefore, we hypothesize that the daily PA of patients with HFPEF and HFREF will differ.

A primary symptom of both phenotypes of HF is exercise intolerance (40), and while exercise is a powerful intervention to improve peak VO_2, there is evidence suggesting different mechanisms and pathways by which patients with HFPEF and HFREF respond to exercise (39, 41). However, there is no evidence of how patients with different level of daily PA would benefit in terms of changes in prognostic determinates of HF. Thus, our second study is based on the premise that investigating the relationship between daily PA and markers of arterial stiffness across the continuum of HF may help with our understanding of the mechanisms and pathways associated with HFREF and HFPEF. It is hypothesized that the association between daily PA with AD will differ across the continuum of HF.

Several reports have shown different levels of blood biomarkers between patients with HF and healthy controls (42, 43). In addition, Jehn et. al., (18) showed that, in patients with HF, objectively measured PA is closely linked to prognostic parameters such as NT-pro-BNP level. However, the differences between the association of daily PA and cardiac natriuretic peptides across the HF spectrum is unknown. Thus, the third study hypothesizes that there will be a difference in the association between daily PA and the BNP, NT-pro-BNP across patients with HFPEF, those at-risk of HF and healthy controls.

Chapter 2 Literature Review

2.1. Heart Failure

The lack of a universal definition of HF based on objective and verifiable measures has led to diagnosis of patients largely based on clinical interpretation of subjective criteria (44). Heart Failure has been defined by American Heart Association as “a clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood” (45-page 397). Recently, Canadian Cardiovascular Society has also defined HF as “a complex clinical syndrome in which abnormal heart function results in, or increase subsequent risk of , clinical symptoms and signs of reduced cardiac output and/or pulmonary or systemic congestion at rest or stress (46).Despite medical advancements and improved prognosis of CV diseases, HF remains a major healthcare problem with high morbidity and mortality rate (47, 48). The 5-year mortality of HF is almost 50%, and in the US, 30-day mortality has been reported to be as high as 10-12% (48). Furthermore, the healthcare burden of HF is high, with more than 75% of the costs attributed to hospitalization (48).

Heart failure is not simply a single disease but rather a complex multi-system clinical syndrome with a collection of symptoms resulted from the impairment of several organs and physiologic systems. The main clinical symptoms of HF include limited exercise tolerance, dyspnea, and fluid retention. In the latter stages of the disorder, pulmonary or splanchnic congestion and/or peripheral edema are also common (5). The clinical manifestations of HF are diverse, and the diagnosis is largely based on history and medical examination (5). Usually,

regardless of ejection fraction (EF), abnormalities of systolic and diastolic function are present and often coexist (5) The complex syndrome of HF affects primarily the elderly (about 10% of men and 8% of women) and its prevalence increases with age (48). The prevalence of HF is projected to increase by 46% from 2012 to 2030 (47).

It may seem contradictory that, the prevalence of HF is growing while there are striking improvements in the prognosis of individual cardiac conditions, such as acute coronary syndrome, valvular and congenital heart diseases. There are several possible explanations for this paradox (48). First, for the majority of the individuals with a cardiac condition, mortality is declining but morbidity remains high. Second, the frequency of myocyte death and its various adverse cardiac consequences increases with aging. Lastly, the slow slope in the decline of the age-adjusted mortality rate will lead to an increased prevalence of this condition.

The clinical-hemodynamic profile of patients with HF appears to be changing (48). Patients with HFPEF can account for up to 50% of HF hospital admissions, and their prevalence is rising, but the outcomes in both phenotypes are comparable (49). The American Heart Association has categorized the development of HF in four stages consisting of asymptomatic and symptomatic phases (5, 45). This staging system recognizes that HF has established risk factors and structural prerequisites (45).

- *Stage A: At risk for HF but without structural heart disorder or symptom of HF*
- *Stage B: Structural heart disease but without sign or symptoms of HF*
- *Stage C: Structural heart disease with prior or current symptoms of HF*
- *Stage D: refractory HF required specialized interventions*

Heart Failure is a progressive and complex syndrome, and usually, once the it advanced to later stages it has been shown to be associated with reduced 5-years survival, and it is rare to

regress to an earlier stage (5). While therapeutic interventions aim to modify the risk profile of patients in stage A, the primary goal in stage B is treating the structural heart disease. In the more severe stages (C and D) treatment strategies focus on reducing morbidity and delaying mortality (5).

Many comorbidities or conditions are related to the increased propensity for structural heart disease. However, hypertension, diabetes mellitus, metabolic syndrome, and atherosclerotic disease are the most common risk factors (5). Other modifiable risk factors with indirect effects include a sedentary lifestyle (50), smoking, diet, and alcohol consumption (5). In addition, the latest update of AHA's guideline for the management of HF recommends screening of natriuretic peptides and, if elevated, early intervention may prevent or significantly delay the onset of HF (51).

Patients with a history of signs and symptoms of HF are often referred to as patients with "chronic HF" (52). A stable patient is defined as someone whose signs and symptoms remained unchanged for at least a month. Whenever a patient with chronic stable HF deteriorates, that patient may be described as "decompensated" and the patient is said to have "Acute HF" (52).

The severity of signs and symptoms of patients with HF may be graded by the New York Heart Association's (NYHA) four functional levels (52).

- *Class I: No limitation of PA. Ordinary PA does not cause undue breathlessness, fatigue, or palpitations.*
- *Class II: Slight limitation of PA. Comfortable at rest, but ordinary PA results in symptoms of HF.*
- *Class III: Marked limitation of PA. Comfortable at rest, but less than normal PA results in symptoms of HF.*

- *Class IV: Unable to carry on any PA without discomfort. Symptoms of HF present at rest.*

It should be noted that symptom severity (i.e., NYHA Classifications) is poorly correlated with ventricular function (52). Moreover, symptoms can suddenly change, and acute decompensation attacks and rapid worsening of the symptoms are important determinants of prognosis in patients with HF (52). Due to the nature of the HF syndrome which involves several physiologic systems, even patients with lower NYHA classes and no symptoms could have poor outcomes (53). In fact, in a large trial with patients with HFREF, sudden cardiac death found responsible for the greatest proportion of cardiovascular death in patients with milder HF symptoms (54). In addition, the NYHA functional classes are assigned based on physician's consultation and have poor reproducibility (53). Also, the patient's perception of symptoms is influenced by variety of none-HF factors such as deconditioning, motivation and tolerance of discomfort (55). Other researchers also have suggested that factors beyond LV function such as musculoskeletal, vascular, pulmonary end even metabolic system might play a role in severity of symptoms presented in patients with HF (56). Therefore, it could be possible that dissociation of hemodynamic properties and symptoms be more prominent in patients with HFPEF.

2.1.1. Heart failure with reduced ejection fraction

Individuals with HF and an EF ≤ 40% are classified as patients with reduced EF or HFREF (5). In addition to conventional risk factors of HF, coronary artery disease (CAD) with prior myocardial infarction is the primary cause of HFREF (50). In many patients with HF abnormalities of systolic and diastolic dysfunction coexist, irrespective of EF. In patients with systolic dysfunction, maladaptive changes occurring in surviving myocytes and extracellular matrix after

myocardial injury lead to pathophysiological remodeling of the ventricle with dilatation and impaired contractility (50). Stroke volume (SV) is usually maintained by an increase in end-diastolic volume (EDV) that is due to LV enlargement (50). The more severe the systolic dysfunction, the greater the reduction in EF and generally, the higher the EDV and end-systolic volume (ESV) (50). Reoccurrence of further myocyte death and systemic responses, such as neurohormonal activation induced by systolic dysfunction are responsible for the progressive worsening of ventricular changes (50).

The HFREF phenotype has been studied extensively in terms of pathophysiology and treatment (50). In fact, it is only in patients with HFREF that beneficial therapies have been demonstrated (5). This might be due to a better understanding of HFREF phenotype and more complex and heterogeneous nature of HFPEF.

2.1.2. Heart failure with preserved ejection fraction

In elderly populations HF with preserved EF is becoming more prevalent (57). Patients with HFPEF are usually older obese females (52). They are less likely to have a history of CAD and are more likely to suffer from hypertension and atrial fibrillation (52). One possible explanation is that, increased adiposity promotes inflammation, hypertension and insulin resistance which all contribute to the pathophysiology of HFPEF (58). According to the Law of Laplace, LV wall stress is related to the pressure and chamber radius and is inversely related to wall thickness (59). Unlike HFREF, this eccentric enlargement happens and induces greater wall tension, increased wall thickness, and concentric hypertrophy. This is the typical compensation observed in HFPEF to maintain the forward flow (59). The criteria for diagnosing HFPEF include: a) Clinical signs and

symptoms of HF; b) Evidence of preserved or normal EF (≥ 50%); and c) Evidence of abnormal LV diastolic dysfunction. The latter can be determined by Doppler echocardiography or cardiac catheterization (or with surrogate markers of diastolic LV dysfunction such as LV hypertrophy, left atrial (LA) enlargement, atrial fibrillation (AF), or elevated plasma natriuretic peptides (NP) levels) (5).

In addition, the diagnosis of HFPEF is more difficult than HEREF since it needs the exclusion of other potential non-cardiac causes of symptoms suggestive of HF (5). This poor prognosis is likely because of the complex nature of HF in general, including multisystem involvement (e.g., skeletal muscle, vascular dysfunction, pulmonary hypertension, renal failure, anemia, and atrial fibrillation) (60). Despite the alarming increase of HFPEF's prevalence, the pathophysiological mechanisms and diagnostic or therapeutic strategies have remained unclear (60).

Recently, patients with EF between 41%-49% have been categorized into HF with mid-range EF or, HFMEF (46). These patients might represent many different phenotypes, including patients transitioning to and from HFPEF (46). An emerging term of "recovered EF" has also been introduced in recent years referring to patients who had an EF ≤ 40% and now might be classified as HFMEF or FHPEF. The evidence regarding the management and prognosis of HFMEF and those with recovered EF is still scarce (46).

2.2 Physical Activity Assessment

PA has been defined by Caspersen (61-page 126) as “any bodily movement produced by skeletal muscles that result in energy expenditure” (EE), whereas exercise, is a sub-category of PA that is structured, repetitive and planned to maintain or improve an element of physical fitness (PF). The American Academy of Physical Education defined PF as “the ability to carry out daily tasks within vigour and alertness, without undue fatigue and with ample energy to engage in leisure-time pursuits and to meet unforeseen emergencies” (61-page 128). For this thesis, the focus will be on daily PA or non-exercise related PA for several reasons. First, the AHA recommended a regular holistic assessment of all domains of PA (including occupational, domestic, transportation and leisure time activity) since health-enhancing PA may occur in any of these domains (62). It is important to recognize that the entire spectrum of PA intensities is essential and potentially beneficial (63, 64). Second, the majority of evidence suggests that the volume of activity as defined by the product of intensity multiplied by frequency and duration (62) is closely linked to the comprehensive health-benefits and reduced mortality (65). Third, exercise training especially at higher intensities, that may induce structural changes (66), is not always feasible for patients with chronic conditions (e.g., HF) (52). Furthermore, even among patients who are engaging in exercise interventions compliance might be low and sustaining the behavior may be problematic (12). Finally, sedentary behavior is a distinct behavior separate from that of merely not exercising or being physically inactive (67). Historically, sedentary have been attributed to those individuals with insufficient exercise (23). However, with the recent advancements in technology PA monitoring devices can now objectively assess the EE of the

entire range of activities during daily living. Pate et al., have defined sedentary behaviors as waking activities that do not increase EE noticeably above resting level (e.g., watching television, sitting, laying down) (23). Technically, sedentary behavior includes activities at energy level between 1-1.5 metabolic equivalent units (METs) while one MET is the energy cost of resting quietly or oxygen uptake of 3.5 ml/kg/min. Sedentary behavior ranks together with tobacco, alcohol, and obesity as a leading cause of reducing healthy life expectancy (68). In healthy adult sedentary time has been shown to be associated with increased risk of diabetes, CV disease, and CV or all-cause mortality (29). In addition, a recent longitudinal study that followed more than 6,800 individuals for approximately 11 years reported that every hour increase in sedentary time was associated with a 3% increased risk of HF (69). Also, in patients with HF, sedentary lifestyle has been shown to be strongly linked with all-cause mortality (70).

One of the most important lifestyle factors for the maintenance of health is PA (71). Despite the evidence supporting the importance of PA for health, the patterns and the threshold of PA in older adults associated with health benefits are not clearly defined (71). One of the main purposes of evaluating PA in individuals with chronic conditions (e.g., HF), is to develop an accurate treatment plan to improve their long-term behavior (72). A valid, reliable and practical method to quantify PA is essential in determining the goals of a treatment plan, the effectiveness of an intervention, and prognosis of patients. However, usually there is not a holistic method encompassing all these characteristics, and often an instrument is advantageous in one aspect while it tends to lack in another (73). There are three main methods of PA assessments: criterion methods, objective methods, and subjective methods (74).

2.2.1. Criterion methods

Criterion methods are used to validate other techniques for estimating PA (75). Based on the definition of PA, calorimetry is often considered the gold standard for validating field methods of assessing PA. As direct calorimetry (i.e., measuring EE by measuring heat production or heat loss) is not practical, indirect calorimetry and doubly labeled water (DLW) have become accepted criterion methods for the validation of both laboratory and field studies (74). The principle of DLW is to measure the difference in elimination rate of two ingested stable isotope (^{2}H and ^{18}O) to estimate EE (74). Although the DLW has been shown to accurately measure EE in different populations, it is expensive and therefore only suitable as a gold standard for assessing PA (74).

2.2.2. Subjective Methods

Activity questionnaires primarily assess purposeful movements in terms of exercise or transport and focus predominantly on activities with moderate to heavy intensities (76). Low-intensity occupational or routine activities such as household chores, gardening, walking, or standing are usually only superficially accounted for (62, 77). Although questionnaires have been composed specially for patients with functional limitations (78, 79), it is difficult to compose questions that are general enough to target a large group of people yet, at the same time, capture sufficient detail about ubiquitous, nonspecific activities (80, 81).

The most common subjective method to measure daily PA is a questionnaire. Several studies have used questionnaires to assess PA under controlled and free-living conditions in various patient populations (82, 83). While questionnaires cover a broad spectrum of activities

and are relatively simple to use, they are memory dependent, which can be especially problematic in the elderly (84). Moreover, these subjective tools are highly influenced by social desirability and recall bias (74, 85).

2.2.3. Objective Methods

Over the past decade, motion sensors such as pedometers and accelerometers became more popular for objective measurement of PA. Pedometers are easy to use and low in cost, but there are several limitations associated with their use. For example, they are unreliable at detecting steps during slow and irregular walking (37, 86, 87). In addition, pedometers only record walking-related activities, and they are not able to measure correctly upper body movements, cycling, swimming or other activities such as carrying a load or moving on a graded surface (74). Unlike pedometers, accelerometers provide more detailed information about exercise intensities and time spent in the activity (85). They also reduce human errors in reporting bias and PA recalls (88). The typical tri-axis accelerometer uses a piezoelectric transducer and microprocessors to quantify the magnitude and direction of acceleration (74). Although, accelerometers have solved many shortcomings of pedometers, some limitations of recording complex movements (e.g., upper body, graded surface, cycling) still remain (74). Therefore, by incorporating multiple physiologic sensors to accelerometers pattern recognition monitors have emerged to address these limitations (89). The SenseWear armband mini ™ (SWA; Body Media Inc., Pittsburg, USA) is an excellent example of a pattern recognition device which integrates information from physiologic sensors (heat flux, temperature, galvanic skin response) with a tri-axes accelerometer and user demographics to estimate EE, duration of PA in various intensities and step counts. The SWA measurement has been validated against doubly labeled water

technique and shown to be reliable in the elderly population and during exercise (89-91). In addition, the reports show that the EE estimation of walking by SWA are comparable to other triaxial accelerometers (92-95). In non-weight bearing activities such as cycling which has been a common weakness of triaxial accelerometers, SWA appears to provide a more precise estimate (96). Studies that compared the EE estimates of several activity monitors within free-living condition against indirect calorimetry have concluded SWA is a valid tool for quantifying EE during low-intensity activities (97, 98). Another study by Ryan et al. compared three activity monitors against indirect calorimetry and determined SWA provided the most accurate estimate of EE across a range of PA intensities (99). Other investigation on the validity of SWA in patients with chronic conditions such as COPD reported SWA to be a sensitive device that provides repeatable measurements (100).

2.2.4. Physical Activity Measures

Daily PA is closely associated to exercise capacity and clinical prognosis in patients with HF (101, 102). A recent report suggests the impact of inactivity is similar to smoking in relation to the burden of non-communicable diseases (103). The authors estimated about 9% of premature mortality could be related to inactivity and by changing sedentary lifestyle to active, people could expect about 1.3 to 3.7 years added to their life (103). The objective measurement of daily PA could be used to identify those at risk of a sedentary lifestyle and thus with worse prognosis (104). In fact, a recent guideline of the American Heart Association in 2013 (62) recommended PA assessment as regular as other major risk factors.

PA causes an increase in EE above resting level and the rate of EE is directly associated with the intensity of PA (62). PA is commonly quantified by the amount of energy expended in kilocalories or metabolic equivalent (MET) of the task. One MET is equivalent to the resting EE during quiet rest when someone is in the waking state. Another routine method of quantifying PA is to assess the amount of time spent in different intensities per day. Therefore, the most common markers of accelerometer-based motion sensors like SWA are physical activity energy expenditure (PAEE), sedentary behavior (i.e. <1.5 METs), Light PA (i.e. 1.6- 2.9 MET) and moderate-to-vigorous PA (MVPA, ≥ 3 MET). In addition, daily step count (e.g., steps/day) has been used to estimate the volume of PA.

Despite the former belief of a "minimum intensity threshold" associated with health benefits of PA (64), there has been accumulating evidence suggesting the biggest drop in the risk of all-cause mortality belongs to those sedentary individuals who decide to start an active lifestyle (65, 105). Indeed, some activity is preferred over being sedentary, but more is better (65). Manini et al. showed that the daily PAEE regardless of intensity was associated with a lower risk of mortality in healthy elderly (105). They reported that every 287 kcal/day in free-living PAEE could lower the risk of mortality by 30%.

Perhaps one of the most prevalent measures of PA is simply the amount of time spent in MVPA (62). In 1986, the American College of Sports Medicine recommended moderate intensity PA (i.e., 40-60% peak VO_2) as the minimum requirement to improve physical fitness, (64). It is now clear that PA volume may not fully compensate for intensity across the range (65). For example, regular walking cannot develop the physiologic capacities of which regular fast running

requires, no matter how much regular walking you do. Therefore, although the value of light PA needs to be recognized, MVPA remains important. In the recently published PA guideline a few interesting points have been raised (106). The assumption is that for any given level of MVPA, the time spent in light intensity PA (i.e. 1.6 – 3 MET) and the time spent on sedentary behavior is reciprocal. In other words, the amount of time spent on waking sedentary will displace light PA and vice versa. In those with PA patterns representing a relatively lower volume of MVPA, even replacing sedentary behavior with light PA reduces the risk of premature mortality. Performing regular activities at intensities > 3 METs (i.e., MVPA) is essential to reach the greatest all-cause mortality risk reduction. For an equal risk reduction, increasing the volume of MVPA is considerably more cost-efficient (i.e., less time) than increasing light PA. Finally, for those with PA patterns at the relatively highest volume of MVPA (about 35-38 Met-h/week), the negative effect of time spent in sedentary behavior becomes negligible (106).

The intensity of a given aerobic power can be described in absolute or relative terms. Absolute intensity typically refers to the energy expenditure during the activity regardless of a person's cardiorespiratory fitness or aerobic power (107). The standard unit of absolute intensity is metabolic equivalent (MET) of the task. Relative intensity is the level of effort required to do a task relative to a person's aerobic capacity (107). The two measures of intensity (absolute vs relative) are not linearly related. For instance, an activity which is defined as light in terms of absolute intensity may, in fact, be perceived as moderate or even vigorous PA in elderly populations or those with chronic conditions.

From all types of daily PA, walking is probably the most popular form of leisure time PA (108). That is perhaps why tracking the number of steps/day has been one of the early tools for screening, prescription, and promoting PA and evaluating a patient's progress while participating in a rehabilitation intervention (108). For instance, steps/day has been widely used as the principal marker of daily PA to identify the minimum required volume of PA associated with health benefits or risk of adverse outcomes. Schmidt et al. showed that those individuals who take ≥ 5,000 steps/day had a significantly lower prevalence of cardiometabolic risk factors (109). In addition, in a chronically ill population known with a lower level of PA, steps/day correlates with fitness (110). For healthy older adults (>50 years) it has been recommended that they strive to achieve between 6,000-8,500 steps/day in order to achieve the health benefits associated with PA (111). For elderly adults living with a disability or chronic diseases the expected step count range has been reported to be 3,500-5,500 steps/day (112). It is noteworthy that, the recommended step range for HF population is between 7,100-8,000 steps/day (111). Step counts inherently are not able to differentiate PA intensity whereas speed could be used to determine the intensity during ambulation (113). For example, Tudor-Locke suggested a minimum of 100 steps/min as the absolute minimum value for moderate-intensity walking in healthy adults (114). Recently use of cadence as a marker of PA intensity has been growing and studies showed clinical and practical values of providing both volume and cadence (i.e. intensity) targets (115, 116).

2.3. Heart Failure and Physical Activity

The 2018 PA guideline of US department of Health and Human Services reported strong to moderate evidence that PA provides health benefits to elderly people with frail health (117). The

growing number of older adults with HF relates largely to the high prevalence of traditional CV risk factors in this population (57). Data from several nation-wide or community–based studies show that coronary heart disease, hypertension, obesity, and diabetes are responsible for a substantial percentage of HF incidence (57, 118, 119). While even a slight improvement in the management of these risk factors could result in a significant reduction in the incidence of HF (57), it is well documented that the various risk factors associated with HF could be improved by PA (64, 107, 120, 121). Indeed, in a recent longitudinal study of the Framingham cohort, investigators suggested that there is a causal relationship between a lower volume of PA and a higher risk of the HF incident (120). The underlying mechanisms by which increasing PA could prevent incident HF are multifaceted. The most apparent effect is reducing the risk factor profile of patients who are at risk of developing HF (e.g. lower BMI, lower blood pressure and better glycemic profile). In addition, the positive impact of PA on the heart itself is another possible pathway. Examples of beneficial effects of PA on the heart include better systolic and diastolic function and prevention of age-related cardiac remodeling. Finally, PA induces beneficial changes on the vasculature including improved endothelial function and enhanced angiogenesis (120).

While the beneficial effects of PA on HF have been known for a long time, a common limitation of many studies has been self-reported PA data. The objective evaluation of daily PA in HF population goes back to the early 90s (122) and until now PA has been reported to be a strong determinant of mortality in patients with HF (16, 123). In fact, Loprinzi found that for every 60 min of additional PA at any intensity above the sedentary level, the risk of all-cause mortality in HF population drops by 35% (123). The protective effect of PA on the development of HF

appears to be linear, hence the greatest volume of MVPA is associated with the lowest risk of HF (117).

For patients with chronic conditions such as HF, guidelines recommend the same volume and intensity of PA as is recommended for healthy adults (approximately 150 to 300 minutes a week of MVPA) adding that the emphasis should be on moving more and sitting less (107). While studies have documented the beneficial effects of exercise training for patients with HF adherence to such programs may be problematic (12, 13). As an alternative to exercise training some investigators suggest that simple daily PA may be a practical alternative as it encompasses occupational, leisure time, household activities and can be accomplished throughout the day (15, 16). Corvera-Tindel et al. showed that by increasing daily walking duration, both the exercise capacity and general well-being of patients with HF was improved (15). In addition, patients with HF have severely reduced exercise tolerance. Therefore, activities of daily living may require near-maximal effort for them (40). Encouraging patients with HF to perform daily PA may reduce mortality, hospitalizations, and risk for other comorbidities (19). Moreover, daily PA may decrease disease progression and improve function, independency, and quality of life (10, 12).

Several studies have reported low daily PA with wide variability in HF population (30, 122, 124). The National Health and Nutrition Examination Survey indicated that for healthy adults age $\geq$60 years, sedentary behavior accounts for ~60-65% of waking time (125). A review by Healy et al. reported that patients with various chronic diseases spent between 75-88% of their time sedentary (126). In older adults (>60 years) light activity accounts for approximately 30% of waking time (127). Indeed, participation in light PA throughout the day has been shown to both reduce sedentary time and result in greater engagement in overall daily activity (128).

2.4. Aortic Distensibility

One of the key functions of large arteries, such as the aorta, is to act as an elastic reservoir for blood flow, thereby reducing the afterload imposed on the heart (129, 130). With aging, the elastic reserve of the aorta decreases due to diminished distensibility of the aortic wall and this may consequently cause systolic hypertension in the elderly (131). Arterial stiffness is the primary determinant of age-related systolic and pulse pressure increases, a major predictor of stroke and myocardial infarction, and it has also been associated with HF (132-134). The aorta accounts for most of the global arterial stiffening and is a key player in the atherosclerosis beginning and its subsequent complications (135). In other words, aortic stiffness is a sensitive marker of arterial ageing and in time may lead to arterial dysfunction, atherosclerosis and potentially cardiovascular abnormalities. It is well documented that arterial stiffens is associated with increased CV morbidity and mortality (136). In patients at risk of developing HF (e.g., hypertension or diabetes) aortic distensibility (AD) is lower compared to age-matched individuals (137, 138). In patients with HFREF impaired ventricular-vascular coupling and endothelial function has been associated with abnormal aortic elastic properties and hence reduced aortic distensibility (i.e., increased stiffness) (35, 139) whereas, for patients with HFPEF, central arterial changes may occur as a consequence of hypertension (140). Several studies have confirmed that reduction of AD, beyond normal aging, is associated with exercise intolerance in patients with HF and can be positively modified by PA/exercise interventions (136, 139, 141).

Arterial compliance (C) is the absolute change in area or diameter whereas distensibility is the relative change in area for a given pressure at a fixed vessel length (142). Assuming that the

vessel area or wall thickness is approximately stable, the speed which the pulse wave travels through a certain vessel length could be indicative of vessel stiffness, which is called the Pulse Wave Velocity (PWV) (142). There is an inverse relationship between PWV and vascular compliance and distensibility.

Magnetic resonance imaging (MRI) is a validated technique that can combine the assessment of ventricular and aortic geometry and provide a reliable non-invasive measurement of aortic strain, distensibility and PWV (135, 143). Using MRI has several advantages over other methods such as PWV or Ultrasound (142). It enables researchers to detect more subtle changes in regional stiffness and provides a 3-dimensional visualization of the vessel. In addition, with MRI, velocity data is recorded simultaneously in 2 aortic locations and the distance between them can be measured with high precision (142).

2.5. Aortic Distensibility and Physical Activity

The complex interaction between vascular smooth muscle cells and the extracellular matrix is an important determinant of aortic stiffness (142). Moreover, mechanical stress and repetitive stretching of the elastic vessel wall contributes to structural changes such as increased collagen deposition and calcification which consequently lead to arterial stiffness (142). Deposition of oxidized low-density lipoprotein in the subendothelial space of arterial walls is an important starting point for atherosclerosis because it contributes to foam cell generation, inflammatory processes, and endothelial dysfunction (144). The positive effect of regular PA on slowing atherosclerosis development is widely recognized (145-147). The preventive effect of PA on the aging of the arterial wall has also been demonstrated (129, 148). Performing regular PA

and avoiding sedentary behavior has been reported to be associated with better arterial distensibility (149-151). In a recent longitudinal study, investigators showed that over time, increasing PA is associated with slower progression of aortic stiffness (149). These authors also concluded that spending more time at MVPA and less time being sedentary were each associated with a slower age-related aortic stiffness, independent of traditional vascular risk factors. Other studies have also shown the beneficial effect of light intensity PA on arterial stiffness but only in older adults (152, 153). One of the possible pathways accounting for the positive impact of MVPA on arterial stiffness is cardiorespiratory fitness. Boreham et al. found that the inverse relationship between cardiorespiratory fitness and arterial stiffness was independent of PA (154). The investigators suggested that the beneficial effects of MVPA on arterial stiffness are most likely to accumulate if the PA is designed to improve cardiorespiratory fitness. Other plausible mechanisms through which PA is related to arterial stiffness are improving vascular compliance, arterial remodeling and improved endothelial function (149). Other studies have also speculated that metabolic factors such as blood glucose and adiposity could influence the relation between PA and arterial stiffness (153, 155).

There is some evidence suggesting a minimum threshold of volume and/or intensity of PA required to positively affect arterial stiffness. For example, Aoyagi et al. found a graded relationship between steps/day and central arterial stiffness at a minimum volume of approximately 6,600 steps/day or 16 minutes of MVPA/day (156). The results of a recent systematic review of 20 studies reported that for each additional 1,000 steps/day the PWV was reduced by 0.18 m/s which translates to approximately a 3% decrease in vascular events and mortality (155). In addition, the systematic review showed that the association between PA and

arterial stiffness is curvilinear, with a small PWV reduction associated with sedentary behavior (< 5,000 steps/day) and light PA (5,000 – 7,499 steps/day) but a larger reduction when PA reached the level of 7,499 to 9,999 steps/day (i.e., active).

2.6. Myocardial stress Biomarkers

B-type natriuretic peptide (BNP) was first discovered in the brain, (which explains why it is also coined brain natriuretic peptide), however, the majority of BNP is produced in the heart ventricles (157). The BNP and its inactive N-terminal fragment (NT-proBNP) are synthesized in response to myocyte stretch and/or pressure overloads such as dilated or hypertrophic ventricles, or increased wall tension (34, 157). The net physiologic effects of natriuretic peptides (NPs) are the reduction of pre-load and after-load by inducing the intravascular fluid to move into the interstitial space and reducing smooth muscle tone of the vasculature (157). However, the kidneys clear natriuretic peptides and their secretion increases by hypervolemia and hypertension characteristic of renal failure (34). Previous studies have reported a higher level of NPs in those with either hypertension, diabetes or CAD compared to healthy controls (158-160). Some studies suggest that NPs have a mediating role in metabolic and endocrine systems in those people with lower fittness level (161).

The NPs has been used over a decade to help in the diagnosis of HF (162). Furthermore, as ventricular systolic dysfunction is typically associated with larger chamber radius and greater wall stress, it has been documented that patients with HFREF typically have a higher level of NPs than those with HFPEF (163, 164). Also, individual and inter-individual variations of NPs both in healthy

and stable patients with HF have been noticed by several studies (157, 162, 165). The level of NPs are inversely associated with visceral fat, BMI, waist circumference, and serum insulin level .(166)

2.7. Myocardial Stress Biomarkers and Physical Activity

Both PA and myocardial stress biomarkers have been shown to be predictors of prognosis in patients with HF (18, 34). In addition, a few studies reported a negative association between PA and the level of NPs in healthy elderly and HF populations (167, 168). On the other hand, the findings of studies investigating the effect of exercise training on improvements in biomarker levels are controversial (169). A systematic review of 9 small randomized controlled studies showed a favorable effect of exercise on BNP and NT-proBNP in patients with HF (170). However, in a large prospective study Ahmed et al., found that exercise training did not lead to meaningful changes in the level of NT-proBNP in patients with HF (169). These findings may imply that the relationship between PA and biomarkers reported in observational studies might not be a cause-and-effect relationship (169). Also, there is some recent evidence suggesting abnormal changes of NPs in response to PA in those with metabolic diseases such as diabetes, dyslipidemia, and obesity (160, 171). For instance, Hamasaki et.al. reported even light intensity PA was positively associated with plasma BNP in individuals with glucose intolerance and type 2 diabetic patients (172).

The effects of duration and intensity of PA on changes in NPs are not extensively studied. The plasma level of NT-proBNP has been shown to be a function of the duration of exercise rather than intensity in healthy adults (166). In addition, Benda et. al. recently showed that the exercise induced changes in BNP were similar between 30-min isocaloric endurance exercise and single

bout high intensity interval exercise in both HFREF and healthy controls (42). However, they reported that the changes were larger in HFREF compared to controls. The plasma level of NPs in the elderly and those with metabolic diseases might be more susceptible to cardiac stress (e.g. PA and exercise) depending on the intensity of PA and physical fitness of the individuals (166).

In summary, the volume and pattern of daily PA in patients with HFPEF and HFREF against those at risk of developing HF and healthy elderly adults are not clear. Moreover, assessment of association of PA and other determinants of prognosis and mortality in HF population, such as AD and myocardial stress biomarkers, could provide a better understanding of the different mechanism through which PA may affect patients across the HF continuum. Further, the results of the current series of studies may provide more information toward designing a rehabilitation program with long-term effects.

Chapter 3

Volume and Patterns of Physical Activity across the Health and Heart Failure Continuum

3.1. Introduction

Heart failure (HF) is one of the most prevalent cardiovascular syndromes worldwide and is associated with high morbidity and mortality rates (173). Patients with HF have severely reduced exercise tolerance; therefore, activities of daily living may require near-maximal effort (40). Encouraging patients with HF to perform daily physical activity (PA) may reduce mortality, hospitalizations, and the risk of other comorbidities (19). Moreover, daily PA may decrease disease progression and improve function, independence, and quality of life (10, 12).

For patients with HF, PA guidelines typically recommend at least 30 min of moderate intensity PA on most days of the week or exercise training at a moderate to vigorous intensity (i.e., PA $\geq$3 METs) (174). While studies have documented the beneficial effects of exercise training for patients with HF, adherence to such programs may be problematic (12, 13). As an alternate to exercise training, some investigators suggest that simple daily PA may be a viable substitute as it encompasses occupational, leisure time, household activities and can be accomplished throughout the day (15, 16). For example, Corvera-Tindel et al., showed that by increasing daily walking duration, both the exercise capacity and general well-being of patients with HF was improved (15). For many patients with HF daily PA may also be closely linked to clinical prognosis (16, 102). Several reports suggest that, for patients with HF, daily PA may be as strong a predictor

of survival as is peak oxygen uptake (16, 175). Walsh et al., reported that daily PA, or more specifically inactivity in daily life (i.e., sedentary living), was a better indicator of disease prognosis and mortality than cardiopulmonary exercise testing (16). The authors speculated that daily PA unlike lab-based exercise test, are more likely to reflect day-to-day fluctuation of symptoms and psychological factors.

Nearly half of the growing population of patients with HF have a preserved ejection fraction (HFPEF) (40), the rest present with reduced ejection fraction (HFREF). The quantity and quality of PA in patients with HFPEF and indeed those at risk of developing HF has not been well studied. In addition, mechanisms of exercise intolerance in patients with HFPEF has been shown to be different than patients with HFREF (40). Thus, the purpose of the present study was to explore the volume and patterns of daily PA in patients with HF and preserved (HFPEF) versus reduced (HFREF) ejection fraction (EF) and to contrast these findings with those from healthy participants and patients at risk of developing HF.

3.2. Methods

3.2.1. Study Design

This was a cross-sectional observational study. The sample size was determined based on a power of 0.80, and an α of 0.05 using Cohen's d of 0.867 (f=0.4335) for daily energy expenditure between patients with HF and healthy controls (176). A total sample size of 55 was calculated. However, since this was a sub-study of the larger Alberta HEART research program (177), (a prospective observational cohort study aimed to define new diagnostic criteria for patients with HF with preserved EF), we were able to recruit 157 participants. The study was approved by the

University's health ethics research board and all participants provided their written informed consent.

3.2.2. Study Participants

All participants were enrolled in the Alberta HEART and were assigned into groups according to their baseline clinical criteria (177). The control group (Controls) was healthy age and gender-matched participants with no evidence of hypertension, coronary artery disease (CAD), diabetes mellitus or any organ diseases and had no evidence of inflammatory or autoimmune conditions and were not taking any cardiac medications. The At-risk group consisted of patients with preserved left ventricular (LV) function but had one or more of the following; hypertension (≥3 medications or LV hypertrophy on ECG or LV mass index > gender-matched upper limit normal on an imaging test); DM (>45 years of age); atrial fibrillation; or obesity (body mass index >30); confirmed acute coronary syndrome >2weeks; chronic CAD with chest pain/shortness of breath or COPD but with no signs of HF. The HF groups included patients with signs and symptoms of HF along with preserved LVEF (HFPEF) or reduced LVEF (HFREF). The HFPEF diagnosis was based on the clinical phenotype of symptoms consistent with HF (including dyspnea, fatigue, exertional intolerance) and a LVEF >45% while HFREF has HF symptoms with LVEF <45%. Exclusion criteria included age <18 years; known malignancy with expected survival <1 year; pregnant or recent pregnancy <6 months; recent event (<2 weeks since Acute Coronary Syndrome, HF or other admissions); severe mitral or aortic stenosis or severe pulmonary hypertension (>60mmHg) (177).

3.2.3. Outcome Measures

Daily PA was assessed objectively using the SenseWear™ Mini Armband (SWA; Body Media, Inc. Pittsburgh, PA). The SWA is a three-axis accelerometer that incorporates data from three additional sensors (heat flux, galvanic skin response, and skin temperature) into its estimations of EE. The SWA data were used to quantify measures of daily energy expenditure (DEE), physical activity energy expenditure (PAEE), daily step counts, and time spent in different intensities of PA (i.e., light, moderate to vigorous, MVPA) and sedentary time. The estimates of EE using the SWA have been validated against the doubly labeled water technique and has also been shown to be valid and reliable in elderly populations and during exercise (90, 91). Participants were instructed to wear the SWA for a minimum of four consecutive days, except during bathing or swimming. Upon completion of the 4 days collection period, the SWA device was returned and the data were analyzed using the manufacturer provided software. To ensure an accurate representation of daily PA, valid days were entered into average when wearing time was >80% of the day (30).

Daily energy expenditure was determined by averaging the minute-by-minute kilocalories expended over each day. Sedentary time was defined as EE <1.5 METs and represented as minute per day (178). PA was reported as steps/day, calculated by averaging the total daily steps from each day over the four-day recording period. Time spent at different PA intensities was estimated by subdivided PA into light PA, consisting of activities requiring >1.5-2.9 METs (e.g., activities of daily living; ADL) and MVPA for PA >3 METs. In addition to defining PAEE as >3 METs ($PAEE_{MV}$), we assessed the PAEE >1.5 METs ($PAEE_{All}$); which has been suggested is an appropriate threshold for sedentary behavior (versus activity) for older adults especially those with chronic conditions

such as HF (178). Finally, The $PAEE_{All}$ was calculated as the sum of PAEE associated with light and MVPA.

To achieve the health benefits associated with PA guidelines recommend that MVPA should be accumulated in bouts of >10 minutes (174). Therefore, distinguishing between continuous MVPA accumulated in bouts of >10 min (bout) from sporadic activities could help depict a more explicit picture of activity behavior for our study population. We developed an algorithm that first identifies minutes of MVPA >3 METs and then calculated the number of bouts within each day. Further, bout length (i.e., min) and the EE (Kcal) for bouts were also calculated. To be defined as a bout, two criteria had to be met; 1) it started and ended with a minute of activity >3 METs, and 2) it was >10 min in duration with only up to 2 minutes of activity below 3 METs in that period (179).

3.2.4. Statistical Analysis

Continuous variables are presented through median with interquartile range (unless otherwise stated) and discrete variables are presented through counts with proportions. The median was chosen as our marker of central tendency because it has been shown that there is a wide PA variability in healthy elderly and patients with HF (30, 111). All statistical analyses were carried out using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics were compared across all 4 groups using the Kruskal-Wallis test and Chi-square for continuous and discrete variables, respectively.

Quantile regression models were used to compare the medians of the 12 PA outcomes across all 4 groups after adjustment for age, gender, BMI and sleeping time. These variables were

included in the model as adjustment variables since they were significantly different across groups.

A similar analysis was repeated to compare 4 activity outcomes of waking sedentary time, time spent at light PA, time spent in MVPA and time spent in bouts between HFPEF and HFREF groups. All tests of significance were two-sided. The level of significance was set at 0.05 for all unadjusted tests of baseline characteristics, valid days, sleeping time, hospitalization and emergency department visits. Bonferroni method was used to adjust the significance levels of comparison tests for activity outcomes and ensure a maximum experiment-wise error rate of 0.05. Specifically, the level of significance was corrected at 0.05/12=0.0042 for the 12 unadjusted tests and 12 adjusted tests for the comparison of 12 activity outcomes across all 4 groups. Also, the level of significance was corrected at 0.05/4=0.0125 for the unadjusted tests comparing 4 activity outcomes between HFPEF and HFREF, since there were no significant differences between the two groups regarding age, gender, BMI or sleeping time.

3.3. Results

3.3.1. Physical Activity

One hundred and fifty-one participants (age 72 [64-78] years, 46% female) were recruited. Data from 6 participants were removed from the analysis because of their inability to comply with the minimum required SWA recording time. Participants wore the SWA for 4 [3-4] days and 23.8 [23.4-23.9] hours/day. Age, gender, BMI and sleeping time were significantly different across groups (Table 3.1) and therefore considered as covariates to be controlled in the model. Because LVEF is a factor defining the group of HF, controlling for that would challenge the

observatory nature of this study although it was significantly different across the groups [p<0.0001]. Based on the unadjusted results (Table 3.2), the groups were comparable in the total wearing time of the SWA (p=0.46), DEE (p=0.15), waking sedentary time (p=0.0125), and $PAEE_{All}$ (p=0.0158). Across the four groups, sedentary time accounted for ~66% of waking time for the Controls and up to 78-79% of waking time with the HF groups. The Control group was the most active followed by At-risk and HFREF groups whereas the HFPEF group was the least active. For the unadjusted data significant differences across four groups were observed for steps/day (p<0.0001), time spent at light (p=0.0003) and MVPA (p=0.0003), $PAEE_{MV}$ (p=0.002), and the number, duration, and energy expenditure of bouts (p<0.0001). However, when covariates were controlled for only steps/day remained significantly different across groups (Table 3.2).

Results demonstrate that waking sedentary time and time spent completing light PA and MVPA were comparable across the two HF groups (p=.04, p=0.6, and p=0.0169 respectively; Table 3.2). The one notable difference between the HFREF and HFPEF groups was the time spent in bouts of PA. The HFREF group completed significantly more time/bout (26 [3.7-46.8] min/day vs 2.4 [0-13.5] min/day) (p=0.007).

3.4. Discussion

To the best of our knowledge, this is the first study to compare PA in healthy, at risk for HF, and patients with HFREF and HFPEF. The major new findings are: i) steps/day was the most robust activity outcome to evaluate daily PA in this population; ii) patients with HFPEF completed the lowest volume of daily PA defined as time in light and MVPA; iii) the only significant difference between HFPEF and HFREF was the time spent at bouts of MVPA.

Step count is a common method to assess PA in both healthy and chronic disease populations. The expected range for healthy older adults (>50 years) has been reported to be 6,000-8,500 steps/day (111). Our control participants step count was consistent with this range, but the At-risk group was not (Table 3.2). For elderly adults living with disability or chronic diseases the expected step count range has been reported to be 3,500-5,500 steps/day (112). In the present study, both HF groups reported significantly fewer steps/day (Table 3.2). It is noteworthy that, the recommended step range for HF population is between 7,100-8,000 steps/day (111).

Despite the low step counts, results demonstrated that across the various PA measures only steps/day remained significant after adjusting for covariates. This finding suggests that for older and overweight individuals regardless of gender, simply monitoring steps/day may provide the best estimate of daily PA as opposed to other measures of PA.

Present results suggest that patients with HFPEF completed the lowest volume of PA (i.e., mild and MVPA) across the four groups. Further, both HF groups completed a lower volume of PA than the Control group. Previous studies have reported that both HF groups have marked reduction in exercise capacity (e.g., 3.9 METs and 3.4 METs, respectively) (180). Thus, for these patients the burden of a given task may require a greater percentage of their peak aerobic power, leading to the early onset of fatigue, termination of a given activity, and a reduction in the overall volume of daily activity.

With respect to continuous MVPA, only the patients with HFREF achieve ~30 minutes per day whereas the HFPEF did virtually no continuous MVPA. This finding may be attributed to

differences in medical history. It has been reported that patients with HFREF have a greater prevalence of myocardial infarction and/or previous cardiovascular procedures (181, 182). Indeed, the medical history of our HFREF cohort appears to be consistent with this observation (Table 3.1). Given the medical history of our HFREF cohort is it conceivable that these patients received more advice regarding the importance of exercise for their condition, both as inpatients and outpatients. In a recent study among of 100,000 patients with HF (48% HFREF, 52% HFPEF) who were eligible for cardiac rehabilitation (CR), only 12% with HFREF and 9% with HFPEF were referred to CR at discharge (183). In the same paper, by reviewing approximately 10 years of hospital records a higher trend of CR referrals for HFREF versus HFPEF was noted. In addition, evidence-based treatment strategies for HFREF are far more established which may have helped them to develop the skills necessary to cope better with their condition and sustain a more active lifestyle (184). By contrast, the complex and heterogeneous nature of HFPEF makes it harder to be diagnosed in early stages and hence it is difficult to ascertain if they received the same level of exposure to exercise recommendations as their HFREF peers (185). In other words, it may be that patients with HFPEF received insufficient PA education and do not perceive the need to be more active beyond ADL. This may partially explain why the HFREF group recorded more time in bouts of PA. In terms of motivation, it is not likely that wearing the SWA affected participants, because it does not have a display and does not provide any feedback (186).

One of the unique aspects of this study was the examination of sedentary behavior. It has been suggested that sedentary behavior is in fact distinctly different than the absence of PA (67). The National Health and Nutrition Examination Survey indicated that, for healthy adults age ≥ 60 years, sedentary behavior accounts for ~60-65% of waking time (125). In this study, our patients

with HF spent ~80% of their waking time sedentary (Table 3.2). A review by Healy et al., reported that patients with various chronic diseases spent between 75-88% of their time sedentary (126). The sedentary time observed in our patients with HF may partially be attributed to a reduced exercise capacity typically seen in patients with HF or perhaps apprehension associated with performing PA given their cardiac history and comorbidities (187). This underscores the need to educate all patients with HF (regardless of phenotype) on the importance of reducing sedentary time and performing mild or MVPA throughout the day.

Light PA encompasses predominately activities of daily living. In elderly adults (>60 years) light activity accounts for approximately 30% of waking time (127). Despite the inevitability of having to perform ADL, both of our HF groups appeared to spend considerably less time performing light PA (Table 3.2). It has been shown that for every 60 min increase of light PA, independent of MVPA, there is ~16% reduction in all-cause mortality (188). Therefore, for patients with HF one of the strategies may be to simply encourage them to engage in higher volumes of light PA. Indeed, participation in light PA throughout the day has been shown to both reduces sedentary time and results in greater engagement in overall daily activity (128).

With respect to the At-risk group, our results show that although they do not have HF, their daily PA was both lower than what was observed in the healthy controls and the recommended levels daily PA (189). The inverse dose-response relationship between PA and risk of HF has been well documented (120, 189). Interestingly, a recent meta-analysis by Pandey et al. reported that participants who engaged in PA at twice or 4 times the basic guideline-recommended levels (~500 MET-min/week) had 19% and 35% lower risk of developing HF,

respectively (189). The PA volume of patients at risk of developing HF observed in this study (380 MET-min/week) failed to achieve the basic guideline-recommended level which highlights the importance of addressing this issue in practice. However, despite the well-documented dose-response relationship between intensity and volume of PA and health benefits, recent evidence suggests that extensive benefits are achievable with a much lower dosage than what has been recommended in the guidelines (190).

3.4.1. Limitations

Some studies suggest that more than 4 days of monitoring is required to ascertain daily PA (191). However, Rowe et al., noted that two days of monitoring is sufficient for older populations (i.e., >60 years) (192). In addition, our understanding of the HFPEF phenotype is still insufficient to fully explain underlying mechanisms of exercise intolerance and activity behavior (193). Finally, we were not able to assess clinical outcomes on this study and therefore further longitudinal research with a larger sample size of HF spectrum is needed.

3.5. Conclusion

In the present study step count was the most robust outcome in evaluating daily PA. By monitoring daily PA, we determined that patients with HF appear to be habitually sedentary, and those with HFPEF did virtually no continuous MVPA. While PA guidelines for HF patients typically recommend at least 30 min of moderate intensity PA on most of the week, our findings suggest that a more realistic initial goal for patients with HF would be to focus on reducing sedentary time and encouraging them to increase the volume daily activity though light PA spread throughout the day.

Table 3-1. Description of characteristics.

Demographics	**Control (n=34)**	**At-risk (n=48)**	**HFPEF (n=53)**	**HFREF (n=16)**
Age, Median [Q1-Q3]	71 [64-76]	66.5 [60.5-73.5]	75 [66-81]	72.5 [63-81] *
Gender, Female, n (%)	23 (68)	21 (44)	22 (42)	3 (19) *
BMI, Median [Q1-Q3]	24.9[23.2-27.6]	28 [25.8-31.4]	30.9 [27.4-34.2]	28.6 [26.7-31.4] *
NYHA class I-II, n (%)	NA	NA	40 (75)	12 (75) *
NYHA class III, n (%)	NA	NA	12 (25)	4 (25) *
LVEF, Median [Q1-Q3]	63.9 [62-66.7]	64.9 [61.2-68.1)	61.7 [54.8-66.2]	37.8 [32.4-49.5] *
SWA Valid days, Median [Q1-Q3]	4 [3-4]	4 [4-4]	4 [3-4]	4 [3.5-4]
Comorbidities and Cardiovascular History				
HTN, n (%)	4 (12)	42 (88)	40 (76)	10 (63)
Type II Diabetes, n (%)	0	8 (17)	21 (40)	4 (25)
COPD, n (%)	0	3 (6)	13 (25)	5 (31)
Dyslipidemia, n (%)	7 (21)	25 (52)	34 (64)	10 (63)
Orthopedic disorders, n (%)	1 (3)	8 (17)	11 (21)	2 (13)
Past CV procedures[a], n (%)	0	5 (10)	10(19)	6 (38)
Previous MI, n (%)	0	10 (21)	14 (26)	8 (50)
Sign and Symptoms				

Dyspnea, n (%)	0	7 (15)	28 (53)	6 (38)
Fatigue, n (%)	2 (6)	8 (17)	25 (47)	9 (56)
Leg Edema, n (%)	0	3 (6)	12 (23)	3 (19)

At-risk, patients at risk of developing Heart failure; HFPEF, heart failure with preserved ejection fraction; HFREF, Heart failure with reduced ejection fraction; BMI, Body mass index; NYHA, New York heart association functional classification; LVEF, left ventricle ejection fraction; SWA, SenseWear Armband; HTN, Hypertension; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; MI, Myocardial infarction. Star (*) indicates significant difference across groups, P<0.05.[a] Previous Cardiovascular procedures including; Pacemaker or Implantable Cardioverter Defibrillator, Coronary Artery Bypass Grafting, or Valve surgery

Table 3-2. Daily measures of physical activity across the four groups.

					Comparison across all 4 groups	
Variable Name	**Control**	**At-Risk**	**HFPEF**	**HFREF**	**Un-adjusted**	**Adjusted+**
Number of Participants	**34**	**48**	**53**	**16**	P-Value	P-Value
Time on body, hr/day	23.7 [23.5-23.8]	23.8 [23.5-23.9]	23.8 [23.2-23.9]	23.8 [23.6-23.9)	0.4613	0.5075
Sleeping time, hr/day	7.0 [6.3-7.5]	7.2 (6.6, 7.8)	7.6 [6.4-8.4]	7.9 [7.5-8.8)	0.0141	n/a
STEPS, n/day	6281 [4399-8744]	4770 [1993-7601]	2121 [1098-3038]	2569 [1486-4673]	<.0001*	0.0005*
Waking sedentary, hr/day	11.1 [9.5-12.4]	12.0 [10.6, 14.1]	12.7 [11.4-14.3]	12.6 [10.9-13.2]	0.0125	0.0721
DEE, Kcal/day	2184.7 [1957.9, 2474.5]	2454.9 [2039.5-2861.6]	2267.2 [1704.4-2675.9]	2564.0 [2275.0-2744.1]	0.1523	0.5074
Light PA (1.6-2.9 METs), hr/day	4.5 [3.2-5.7]	3.4 [2.0-4.4]	2.2 [1.7-3.9]	2.5 [2.0-3.9]	0.0003*	0.0744
MVPA (≥ 3 METs), hr/day	1.1 [0.6-1.5]	0.7 [0.3-1.8]	0.2 [0.1-0.5]	0.6 [0.1-1.4]	0.0003*	0.0075
$PAEE_{All}$ (> 1.5 METs), Kcal/day	875.5 [641.6-1238.0]	735.6 [448.2-1288.6]	445.0 [287.2-822.5]	722.7 [401.5-1123.2]	0.0158	0.1318
$PAEE_{MV}$ (≥ 3 METs), Kcal/day	316.5 [163.0-520.5]	241.8 [82.4-548.4]	56.4 [18.4-176.8]	235.4 [39.2-501.3]	0.002*	0.0185
Bout, n/day	1.7 [1.3-3.0]	1.3 [0.4-3.0]	0.2 [0.0-1.0]	1.8 [0.3-2.6]	<.0001*	0.0073
Bout-Length, minute/day	39.0 [19.8-61.7]	23.0 [6.8-63.1]	2.4 [0.0-13.5]	26.0 [3.7-46.8]	<.0001*	0.0084
Bout-Energy, Kcal/day	205.5 [109.5-291.1]	140.3 [35.7-377.3]	15.4 [0.0-78.1]	139.1 [24.1-291.9]	<.0001*	0.0093

*Data are expressed as median [first quartile - third quartile]. At-risk, patients at risk of developing heart failure; HFPEF, Heart failure patients with preserved ejection fraction; HFREF, Heart failure patients with reduced ejection fraction; DEE, total daily energy expenditure; PA, Physical activity; MET, metabolic equivalent (3.5 ml O2·kg−1·min−1); MVPA, moderate to vigorous physical activity; $PAEE_{All}$, physical activity energy expenditure above sedentary level; $PAEE_{MV}$, physical activity energy expenditure above 3 METs; Bout, Episodes of continuous moderate-to-vigorous physical activity last for at least 10 min. Stars **(*)** means significant at Bonferroni-corrected significance level 0.05/12=0.0042 across all groups. **(+)** Covariates included in the model were baseline grouping, age, gender, BMI and sleep time.*

Chapter 4

Association of Daily Physical Activity and Aortic Distensibility across the Heart Failure Continuum

4.1. Introduction

Approximately half of the patients with heart failure (HF) are reported to have preserved ejection fraction (HFPEF) with similar or higher morbidity and mortality rate than those patients with HF and reduced ejection fraction (HFREF) (194). This is partly due to the fact that diastolic dysfunctions could remain asymptomatic for years and that may result in delayed diagnosis of patients with HFPEF. In addition, HFPEF is more complex and all effective treatments of HFREF seems to be ineffective in this phenotype.

Vascular afterload is an important aspect of ventricular function, especially for patients with heart failure (HF) (195). A major determinant of the vascular afterload is arterial stiffness, which typically increases with advancing age and has a pathological role in the etiology of cardiovascular disease (CVD) and HF (136, 195). Increased arterial stiffness is also linked to increased cardiovascular mortality in older populations (196). In a prospective study by Demir et al., arterial stiffness was found to be a strong predictor of mortality in patients with HF. These authors also suggested that monitoring arterial stiffness could be used to assess the efficiency of treatments and potentially reduce HF-related hospitalizations (35).

Patients with HF have limited aerobic power, which in turn has been shown to be associated with increased arterial stiffness, or more specifically, decreased aortic distensibility

(AD) (139, 141). In healthy individuals, exercise and in general, physical activity (PA) has been shown to preserve and improve arterial compliance (151, 197). Tanaka et al. have suggested that PA could favorably affect arterial stiffness independently of aerobic power (197). It is unknown whether such findings could be extended to patients with preserved or reduced ejection fraction (i.e., HFPEF or HFREF respectively). Conversely, what is known is that these patients with HF typically fail to achieve the minimum recommended level of daily PA (30, 198).

The dose-response effect of physical activity (PA) on mortality in healthy adults and patients with heart disease, including patients with HF, has been well documented (199-201). Recent evidence suggests that there are benefits associated with light-intensity physical activity that result in improved health-related quality of life in HF for patients (26, 202). A study by Izawa et al. investigated the association of several determinants of prognosis with survival in a HF population and showed that only step count was a strong and independent predictor of survival in HF outpatients (201).

The relationship between PA and arterial compliance, measured as AD, has not been evaluated across the HF continuum. Therefore, the purpose of this study was to compare the relationship between PA and AD across two phenotypes of patients with HF (i.e., HFPEF and HFREF) and compare these findings with those from patients at risk of developing HF (At-risk) and healthy controls (Controls). We hypothesize that this association will differ across the HF continuum.

4.2. Methods

This was a cross-sectional substudy of the **H**eart Failure **E**tiology and **A**nalysis **R**esearch **T**eam (HEART) research project (177). The HEART project was a prospective observational cohort study aimed to define new diagnostic criteria for patients with HF with preserved EF. The present study was approved by the University of Alberta's health research ethics board, and all participants provided written informed consent. Sample size calculation was performed based on a power of 0.80 and α of 0.05. For the effect size we used was correlation coefficient of r=-0.21 (156). Aoyagi et al. investigated the association of yearlong objectively measured step count with arterial stiffness (i.e. PWV) in elderly individuals. The total required sample size was calculated to be 176 participants.

4.2.1. Study Participants

All participants were enrolled in the HEART project and were categorized into one of four groups based on their baseline clinical criteria (177). The Control group included healthy age and gender-matched participants with no evidence of hypertension, coronary artery disease (CAD), diabetes mellitus, any organ diseases, or evidence of inflammatory or autoimmune conditions. Further, the participants in the Control group were not taking any cardiac medications. The At-risk group consisted of patients with preserved left ventricular (LV) systolic function but who had one or more of the following conditions; hypertension (≥3 medications or LV hypertrophy on ECG or LV mass index > gender-matched upper limit normal on an imaging test); diabetes; atrial fibrillation; or obesity (body mass index >30); confirmed acute coronary syndrome >2 weeks; chronic CAD with chest pain/shortness of breath or chronic obstructive pulmonary disease but

with no signs of HF. The two HF groups included patients with signs and symptoms of HF along with either preserved LVEF (HFPEF) or reduced LVEF (HFREF). The diagnosis of HFPEF was based on the clinical phenotype of symptoms consistent with HF (including dyspnea, fatigue, exertional intolerance) and LVEF >45% while HFREF was classified by HF symptoms with LVEF ≤45%. Exclusion criteria included age <18 years; known malignancy with expected survival <1 year; pregnant or recent pregnancy <6 months; recent event (<2 weeks since Acute Coronary Syndrome, HF or another admission); severe mitral or aortic stenosis or severe pulmonary hypertension (>60 mmHg) (177). For this study, we were able to include 132 participants categorized into the four groups who had both aortic distensibility measurements and PA data.

4.2.2. Outcome Measures

4.2.3.1. Physical Activity.

Daily PA was assessed objectively using the SenseWear™ Mini Armband (SWA; Body Media, Inc. Pittsburgh, PA). In the previous work by our group on the HEART cohort, results indicated that steps/day was the most robust measure to evaluate PA in HF population (198). Therefore, we used steps/day (from the SWA) as the single measure of PA. Step count was collected for a minimum of 4 consecutive days and averaged over the number of days with valid recording to represent daily PA (198). We categorized step counts into three ranges; low (≤ 3,500 steps/day), moderate (3,500-7,100 steps/day) or high (≥ 7,100 steps/day). The normative data in the literature suggested 3,500 – 5,500 step/day as an expected level of PA for older adults with disabilities such as HF (111). Also, 7,100 steps/day has been proposed as the equivalent of the minimum PA recommended by the public health guideline for older adults with

chronic illnesses (e.g., HF population) (111). The time spent in the cadence of >100 steps/min was calculated as a measure of moderate intensity walking (114).

4.2.3.2. Aortic Distensibility.

Cardiac MRI assessment was performed using a 1.5-T magnetic resonance scanner. Images were acquired in supine using 12-element phased array coil. Aortic distensibility (AD) was measured using the fractional change in cross-sectional area of the ascending aorta over the cardiac cycle, (Amax-Amin) / Amin, normalized by the pulse pressure, ΔP, the difference in systolic and diastolic blood pressure (AD = (Amax-Amin) /(Amin×ΔP)) (142). Amax and Amin are the maximal and minimal cross-sectional area of the aorta over the cardiac cycle, respectively.

4.2.3. Statistical Analysis

The normality of the data was analyzed using the Kolmogorov–Smirnov test. Continuous variables are presented as median with interquartile range (IQR) for skewed variables and mean with standard deviation (SD) when the distribution of the variables was normal. Also, discrete variables are presented as the frequency with proportions unless otherwise noted. To examine the differences in the dependent and descriptive variables across all groups analysis of variance (ANOVA), Kruskal-Wallis and Chi-square were used for continuous and normally distributed, continuous with skewed distribution and discrete variables, respectively. Both AD and step count were log-transformed because of skewed distribution and linear regression analysis was performed to assess the relationship between AD (dependent measure) and step count (independent measure) after adjusting for potential confounding variables including age, gender, BMI, and pulse pressure (PP). Residual analyses were conducted to examine the normality

(residuals) and linearity assumptions of linear regression. A sensitivity analysis of excluding outliers which was determined based on standardized residuals and covariance ratio (203), was performed to evaluate the impact of outliers on the robustness of regression models. Since the results were not different, we are reporting the results of all participants in the cohort. For all of the analyses, a 2-tailed *P* value of <0.05 was required for significance test. All statistical analyses were performed with SPSS 24.0 (SPSS, Inc. Chicago, IL, USA).

4.3. Results

4.3.1. Participants Demographics across Groups

Demographics, comorbidities and clinical characteristics of the participants are shown in Table 4.1. All 132 participants (age, 69.3 ± 11.1 years, 51.5% female) were included in the analyses. Age, BMI, gender, and LVEF were significantly different across groups ($p < 0.05$), with HFPEF group being the oldest and with the highest BMI. The majority of HFPEF or HFREF patients were classified into NYHA class I or II (76% and 83%, respectively).

4.3.2. Physical Activity across Groups

The comparison of the mean across groups showed that the number of steps/day was not comparable. Post-hoc analysis revealed that patients with HFPEF took significantly fewer steps/day than either the At-risk and Control groups ($p < 0.05$; Table 4.1). However, there was no significant difference between the daily step counts of the HFPEF and HFREF groups (2,852 ± 2,771 vs. 3,831 ± 2,592, steps/day, respectively).

In the present study, there was a significant difference across the four groups regarding the average time per day spent walking in >100 steps/min ($p< 0.05$). The HFPEF group spent significantly less time walking at a pace >100 steps/min than both Control and At-risk groups (Table 4.1). While the HFREF group completed 0.9 [0-14.3] min at >100 steps/min, this time was not significantly different from the HFPEF group ($p >0.05$).

4.3.3. Aortic Distensibility across Groups

Comparison of the AD's median across the four groups demonstrated a significant difference between the Control and At-risk groups ($p< 0.05$; Table 4.1). However, when we controlled for age, there were no significant differences between any of the groups. When we tested for differences in AD across the three ranges of step counts (i.e., low, moderate, high), there were no significant differences in AD in the 132 participants ($p=0.083$), HFPEF group ($p= 0.172$) or the non-HF participants (i.e., Controls and At-risk combined; $p=0.476$). However, those patients with HFREF who achieved a high step count range, had a significantly higher AD (median 3.7 [3.7-5.2] 10^{-3} $mmHg^{-1}$) than those categorized into the low step count range (1.3 [0.9-2.5] 10^{-3} $mmHg^{-1}$, $p<0.05$).

4.3.4. The relation between Physical Activity and Aortic Distensibility

Simple linear regression analyses and stepwise model selection revealed that BMI was not significantly associated with AD ($p>0.01$), and therefore it was excluded from further analysis. A multiple linear regression analysis, which included all participants, did not yield any significant interaction between groups and steps/day. However, the results of the interaction analysis suggested that for every 1,000 steps taken, the correspondent change of AD was

disproportionately larger in the HFREF group compared to HFPEF and At-risk groups. Furthermore, the small sample in the HFREF group (12 participants) could partially be responsible for an underpowered analysis of interaction analysis. Therefore, we performed a group-based analysis adjusting for age, gender, and PP, which indicated a significant association between step count and AD in the HFREF groups ($p < 0.05$). In addition, in a cluster analysis of AD across step categories, those with HFREF who achieved ≥ 7,100 steps/day had a significantly higher AD than patients with HFREF who averaged ≤ 3,500 steps/day.

4.4. Discussion

The primary purpose of this study was to determine if there was a relationship between PA and AD across the HF continuum. The major new finding is that the association between daily step count and AD may not be similar across the continuum of HF. The results showed there was a direct relationship, such that a higher range of steps/day was associated with a higher AD, but only in our small HFREF group. The demographic and clinical characteristics of our HF patients were almost consistent with the literature. The HFREF group had a reduced LVEF (39 ± 9%) and close to 60% of the participants in this group had a history of myocardial infarction.

In a previous study, our group showed that the daily step count was the most robust measure of PA in patients with HF (198). When we examined the step count across the continuum of HF groups we noted that patients with HFPEF took significantly fewer steps/day than either At-risk and Control groups. However, there was no difference in the daily step counts between the HFPEF and HFREF groups. The step counts observed in At-risk and HF groups were lower than what has been reported (30, 111). Previous studies report an average between 3,500

to 5,000 steps/day for patients with HF, while healthy older adults have been shown to take 6,000 to 8,500 steps/day (30, 112). The daily step count across groups would categorized participants from our two HF groups as sedentary, while our two non-HF groups would be placed in the low active category (111, 204).

When aortic distensibility (AD) was examined we noted that our Control group had a AD that was lower than what has been reported previously. In a review of 6 studies, the average AD for healthy older adults (age ~63 years) was found to be 1.7 10^{-3} $mmHg^{-1}$ (205). Hundley et al. noted that the AD in healthy older adults (age ~72 years) was 2.2 ± 0.4 10^{-3} $mmHg^{-1}$ (141). We can only speculate that subtle differences in SBP and PP may have been a contributing factor to the difference in the AD observed in our Control group. For patients with HFREF, AD is often observed to be diminished, compared to age-matched healthy control participants. This lower AD that is often seen in patients with HFREF could be attributed to abnormal aortic elastic properties as a consequence of impaired ventricular-vascular coupling and endothelial function (35, 139). However, the AD of our HFREF participants was higher than what has been reported previously (139, 205). In addition, our HFREF group had higher ejection fraction than what is normally observed in previous reports (35, 139). For our patients with HFPEF, we noted that their AD was also higher than what has been reported (141, 205). Desai et al. have suggested that AD is often adversely impacted by chronic hypertension, which is typically seen in patients with HFPEF (140). We can only speculate that discrepancies observed in the AD of our HF groups compared to previous reports might be due to lower SPB and PP (26, 139, 141).

A number of studies have examined the relationship between arterial stiffness and PA (206, 207). For instance, Tanaka et al. noted an association between higher levels of habitual PA and reduced arterial stiffness (197). Laurent et al. made a similar observation when they compared sedentary and aerobically trained individuals (208). Both Laursen et al., and Aoyagi et al., have reported that higher levels of daily PA (e.g., daily PA energy expenditure or steps/day) were associated with lower arterial stiffness in elderly adults (156, 209). Finally, the findings of Tanaka et al., suggest that PA could diminish arterial stiffness independent of aerobic capacity (197). When we examined the relationship between PA and AD across the HF continuum, a significant association in the HFREF groups was found. Also, when we analyzed AD across the categories of steps (i.e., low, medium and high), we noted that those with HFREF and a high daily step count (i.e., ≥ 7,100 steps/day) had higher AD than those HFREF with low step count. However, given the small sample size of our HFREF group, these results should be interpreted cautiously. This observation may imply that a higher volume of PA is needed to achieve higher levels of AD. The overall low step count observed in our HF participants may imply this volume of daily activity may simply not be feasible for the majority of patients with HF (129).

Tanaka et al., (197) suggested that regular moderate to vigorous-intensity PA (MVPA) may be required to favorably affect arterial compliance. They speculated that exercise could "stretch" collagen fibers and modify their cross-link through increase of pulse pressure and mechanical distension, thereby increasing arterial compliance. Authors also suggested that modulation of the sympathetic-adrenergic tone of smooth muscle cells in the arterial wall could play a role in positive effects of MVPA on arterial compliance (197). To gain a greater understanding as to whether or not the step count observed in the present study constitutes MVPA we examine the

intensity of the activity. Tudor-Locke suggested a stepping rate of 100 steps/min as the absolute minimum value for moderate-intensity walking in healthy adults (114). In 2005–2006, the U.S. National Health and Nutrition Examination Survey noted that older adults (i.e., > 60 years old) spend the majority of their waking time below this threshold, with an average cadence of 60 steps/min (113). Indeed, it has been reported that patients with HF spend the vast majority of their waking time in activities below what is defined as moderate intensity (i.e., 100 steps/min) (30, 198). Present findings are consistent with these previous reports, as both our HFPEF and HFPEF groups completed less that one min/day MVPA per day (i.e., >100 steps/min). Further, all four of our groups failed to achieve a duration of 10 minutes or more at a rate of 100 steps/min (see Table 1). This implies that the majority of our study participants were indeed sedentary and their daily PA would be classified in the light category (i.e., activities of daily living) as opposed to the MVPA which may be needed to enhance AD.

In summary, while the current clinical management of HF might not routinely include assessment of AD, PA is among the few interventions proven to have a positive impact on exercise intolerance in HF (210). Therefore, assessment of daily PA level could provide a surrogate meaure for assessment of AD, especially in patients with HFREF. While the evidence suggests a direct relation between central arteries stiffness and exercise intolerance in patients with HF, the positive association between central arteries distensibility and peak VO_2 in patients with HFREF is noticeably greater than those with HFPEF (136, 139). The findings of the present study align with previous reports suggest that there are differences in underlying mechanisms between the two phenotypes of HF in responding to PA (41, 211). Although the generalizability of the current

study is limited, current results suggest that the volume of PA may play a significant role in determining the extent of arterial changes induced by PA.

4.4.1. Limitations

The cross-sectional design of this study and its relatively small cohort may limit the generalizability of the findings. Also, to calculate pulse pressure a non-invasive brachial cuff blood pressure measurement was incorporated instead of invasive assessment. Plus, at the time of the cardiac MRI, blood pressure calculation may have varied as a result of anxiety. For these reasons, our calculation of AD should be considered an approximation. Second, most of the patients At-risk or with HF were taking medication at the time of testing, which could affect the AD measurements, especially in patients HF (212, 213). These could partially be responsible for our finding of a non-significance difference in AD in other groups.

4.5. Conclusion

The association between daily PA and AD may not be similar across the continuum of HF. The comparison of AD in each group across the three ranges of steps/day showed a significant difference only in patients with HFREF, such that patients who recorded the higher range of steps/day had higher AD. The results of the current study might be an additional piece of the puzzle that underscores the different pathways by which PA can impact each of the HF phenotypes. These findings also reinforce previous work which reported a higher volume and intensity of PA may be required to impact the arterial properties in patients with HF.

Acknowledgment

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Table 4-1. Characteristics of study participants

Demographics	**Control (n=32)**	**At-risk (n=42)**	**HFPEF (n=46)**	**HFREF (n=12)**
Age, Mean± SD	69 ± 10 *	65 ± 13	74 ± 9	68 ± 9
Gender, Female, n (%)	22 (69) *	22 (69)	21 (46)	3 (25)
BMI, Mean± SD	25 ± 3.4 *	28 ± 4	30.1 ± 5.8	28.3 ± 3.6
NYHA class I-II/III, n (%)	NA	NA	35 (76)/11 (24)	10 (83)/2 (17) *
LVEF, Mean± SD	63.5 ± 4.5 *	63.9 ± 6.5	60.1 ± 10.3	38.9 ± 8.5
AD, Median [IQR] in 10^{-3} $mmHg^{-1}$	0.86 [0.66-2.6] *	2 [1.2-2.8]	1.2 [0.95-2.4]	1.9 [1.1-3.1]
SWA wearing time (Hrs.), Mean± SD	23.6 ± 0.4	23.6 ± 0.4	23.6 ± 0.6	23.6 ± 0.3
Steps/ day, Median [IQR]	6281 [4514-8676] *	4770 [2443-7891]	2177 [1023-3125]	2949 [1824-6134]
Time >100 Steps/day [a], Median [IQR]	4.5 [1-18] *	3 [0-12]	0 [0-0.6]	0.9 [0-14]
Low step range [b], n (%)	7 (22)	14 (33)	37 (80)	7 (58)
Medium step range, n (%)	10 (31)	15 (36)	6 (13)	3 (25)
High step range, n (%)	15 (47)	13 (31)	3 (7)	2 (17)
SBP Mean± SD	133 ± 18	131 ± 19	126 ± 18	122 ± 28
DBP, Mean± SD	72 ± 11	73 ± 12	72 ± 14	69 ± 6
PP, Mean± SD	61 ± 15	58 ± 16	54 ± 18	53 ± 26
Comorbidities and Cardiovascular History				
HTN, n (%)	4 (13) *	37 (80)	36 (80)	8 (67)
Type II Diabetes, n (%)	0 *	6 (14)	20 (43)	2 (17)
COPD, n (%)	0 *	3 (7)	9 (20)	4 (33)
Past CV procedures [C], n (%)	0 *	4 (10)	9 (20)	3 (25)
Previous MI, n (%)	0 *	9 (21)	12 (26)	7 (58)
Sign and Symptoms				
Dyspnea, n (%)	0 *	5 (12)	25 (54)	5 (42)
Fatigue, n (%)	1 (3) *	7 (17)	22 (48)	7 (58)

Leg Edema, n (%)	0 *	3 (7)	11 (24)	2 (17)
Medications				
ACE inhibitors, n (%)	3 (9)	21 (50)	25 (54)	9 (75)
Angiotensin receptor blockers, n (%)	1 (3)	14 (33)	11 (24)	2 (17)
Anti-Arrhythmic, n (%)	0	1 (2)	10 (22)	1 (8)
Diuretics, n (%)	1 (3)	20 (48)	37 (80)	10 (83)
B-Blockers, n (%)	1 (3)	19 (45)	39 (85)	10 (83)
Calcium channel blockers, n (%)	0	8 (19)	12 (26)	1 (8)
Nitrates, n (%)	1 (3)	1 (2)	9 (20)	4 (33)
Statins, n (%)	6 (19)	19 (45)	32 (70)	8 (67)

AD, Aortic distensibility (10^{-3} $mmHg^{-1}$); IQR, Interquartile range; At-risk, patients at risk of developing Heart failure; HFPEF, heart failure with preserved ejection fraction; HFREF, Heart failure with reduced ejection fraction; BMI, Body mass index; NYHA, New York heart association functional classification; LVEF, left ventricle ejection fraction; SBP, systolic blood pressure (mmHg); DBP, Diastolic blood pressure (mmHg); PP, Pulse pressure (mmHg); HTN, Hypertension; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; MI, Myocardial infarction. Star (*) indicates significant difference across groups, P<0.05. [a] Time in minutes spent in cadence > 100 Steps/day. [b] ≤ 3,500 steps/day, between 3,500 and 7,100 steps/day, and ≥ 7,100 steps/day were categorized as low, medium and high step ranges, respectively. [c] Previous Cardiovascular procedures including; Pacemaker or Implantable Cardioverter Defibrillator, Coronary Artery Bypass Grafting, or Valve surgery

Chapter 5

The Relationship between Daily Physical Activity and Myocardial Stress Biomarkers in Patients with Heart Failure and Preserved Ejection Fraction

5.1. Introduction

At first, natriuretic peptides (NPs) as biomarkers were introduced for the diagnosis of heart failure (HF), however; the usage of both B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) has expanded to include prognosis for patients with HF (214). There is also evidence advocating the use of NPs in screening asymptomatic individuals who are at risk of developing HF (At-risk), such as the elderly with hypertension, diabetes or asymptomatic coronary artery disease (34). The primary stimuli for the synthesis and release of the NPs precursor are ventricular dilatation, hypertrophy or increased wall tension (34). As ventricular systolic dysfunction is typically associated with larger chamber radius and greater wall stress, it has been documented that patients with HF and reduced ejection fraction (i.e., HFREF) typically have a higher level of NPs than those with HF and preserved ejection fraction (i.e., HFPEF) (163, 164). It is well documented that exercise is beneficial for heart health and due to recent advancements in biomarker analyses, new mechanisms by which exercise can impede the progression of cardiovascular (CV) diseases such as HF have been uncovered (215).

A systematic review of 9 studies showed moderate intensity exercise training significantly reduced BNP and NT-proBNP level in HF patients (170). The evidence suggests the volume, intensity and length of the exercise program might play a role in determining the changes of NPs

in patients with HF whereas the frequency and duration of exercise sessions appeared to have no effect (170). However, the referral rate of patients with HF to cardiac rehabilitation is dramatically low (9% for HFPEF vs 12% for HFREF) (183) and even for those who attend CR, adherence to the exercise program has proven to be difficult (12, 13). In fact, one of the major trials on the effects of exercise training in the HF population, HF-ACTION trial (216), failed to show the positive impact on decreasing the rate of adverse CV events (217). The investigators reported less than 70% adherence to complete all exercise sessions and only 25% of patients in exercise treatments arm continued to perform any exercise after two-thirds of trial length (217). On the other hand, due to the complex and heterogeneous nature of HFPEF, early-stage diagnosis is difficult. Therefore, it is unlikely that patients with HFPEF acquire enough awareness and education regarding the importance of being physically active (183, 185). Indeed, promoting daily PA has been suggested as a suitable alternative to structured exercise regimens (16, 218).

Daily physical activity (PA) has been shown to be associated with favorable cardiac structural changes in a healthy adult, elder population (219, 220) and patients with HF (221, 222).deFilippi et al., in a prospective study of older adults free of HF, showed the probability of an increase in NT-proBNP level over 2 to 3 years was inversely related to the level of PA (167). The same negative association was reported between PA and NT-proBNP level in patients with HFPEF (168). The association between daily PA and the level of circulating myocardial stress biomarkers across the healthy controls to those at risk or with HF could highlight the importance of non-exercise daily PA in the prevention and management of patients with HFPEF. Therefore, the purpose of this study is to investigate the association between PA and myocardial stress biomarkers in patients with HFPEF and contrast it with At-risk and healthy controls.

5.2. Methods

5.2.1. Study participants

This was a cross-sectional substudy of the **H**eart Failure **E**tiology and **A**nalysis **R**esearch **T**eam (HEART) research project (177). The HEART project was a prospective observational cohort study aimed to define new diagnostic criteria for patients with HF with preserved EF. The present study was approved by the University of Alberta's health research ethics board, and all participants provided written informed consent. Sample size calculation was performed based on a power of 0.80 and α of 0.05. For the effect size we used correlation coefficient of r=-0.26 (18). Jehn et al. investigated the association between the amount of time/day spent walking measured by accelerometer and NT-proBNP in elderly patients with HF. The total required sample size was calculated to be 114 participants.

All participants were enrolled in the HEART project and were categorized into one of three groups based on their baseline clinical criteria (177). The control group included healthy, age and gender-matched participants with no evidence of hypertension, coronary artery disease (CAD), diabetes mellitus, any organ diseases, or inflammatory or autoimmune conditions. Further, the participants in the control group were not taking any cardiac medications. The At-risk group consisted of patients with preserved left ventricular (LV) systolic function but who had one or more of the following conditions; hypertension (≥3 medications or LV hypertrophy on ECG or LV mass index > gender-matched upper limit normal on an imaging test); diabetes; atrial fibrillation; or obesity (body mass index >30); confirmed acute coronary syndrome >2 weeks; chronic CAD with chest pain/shortness of breath or chronic obstructive pulmonary disease but with no signs

of HF. The HF group included patients with signs and symptoms of HF along with preserved LVEF (HFPEF). The diagnosis of HFPEF was based on the clinical phenotype of symptoms consistent with HF (including dyspnea, fatigue, exertional intolerance) and a LVEF >45%. Exclusion criteria included age <18 years; known malignancy with expected survival <1 year; pregnant or recent pregnancy <6 months; recent event (<2 weeks since Acute Coronary Syndrome, HF or another admission); severe mitral or aortic stenosis or severe pulmonary hypertension (>60 mmHg) (177). For this study, we were able to include 122 participants categorized into the 4 groups who had both biomarkers measurements and PA data.

5.2.2. Outcome Measures

5.2.2.1. Physical Activity.

Daily PA was assessed objectively using the SenseWear™ Mini Armband (SWA; Body Media, Inc. Pittsburgh, PA). In the previous work by our group on the HEART cohort, results indicated that steps/day was the most robust measure to evaluate PA in a HF population (198). Therefore, we used steps/day (from the SWA) as the single measure of PA. Step count was collected for a minimum of 4 consecutive days and averaged over the number of days with valid recording to represent daily PA (198).

5.2.2.2. Myocardial Stress Biomarkers.

Plasma BNP levels were assessed using a Biosite Triage reagent pack (Biosite Inc., San Diego, CA, USA) as previously described in detail (223). In addition, plasma NT-proBNP analysis was performed with the commercially available immunoassay using the Elecsys proBNP assay (Roche Diagnostics GmbH, Manheim, Germany) read in an automated access immunoanalyzer (Beckman-Coulter, Fullerton,CA, USA) at Alberta Health Services Laboratory Services, Edmonton, Alberta.

5.2.3. Statistical Analysis

Descriptive analysis (i.e., mean (standard deviation), median (range), or frequency (proportion)) was used to summarize and compare patients' clinical and demographic characteristics between groups.

Univariable analysis was performed by using the Chi-square test or Fisher's exact test (when small frequencies were present) for categorical variables, while independent T-test was used for continuous variables to assess whether the differences of variables between groups were statistically significant. Assumptions were checked before performing the tests.

Due to the skewed distribution of biomarkers (*BNP* and *NT-proBNP*), we logged transformed the dependent variables (i.e. *Log BNP* and *Log NT-proBNP*). Univariable linear regression and mixed effect model, treating the group as a random effect, were used to analyze the relationship of Log BNP/Log NT-proBNP with each variable individually. The aim was to identify the variables needed to be adjusted.

To assess the relationship between biomarkers and steps/day, and the interaction between groups and steps, the multivariable analysis was performed while adjusting other covariates. The variables representing demographics (i.e., age, gender, BMI) medications, medical history and common sign and symptoms of HF (e.g., dyspnea, fatigue and etc.) that showed to be statistically significant (P-value < 0.05) at Univariable level or clinically significant were used as main covariates in the multivariable linear regression model.

The equation used in order to calculate the magnitude of the association between biomarkers and daily activity (for every 1,000 steps/day) was:

Log Biomarker = (β_1×1,000) + β_2 + (β_3 × 1,000)

Where β_1 is the coefficient of steps, β_2 is the coefficient of the selected group and β_3 is the coefficient of the interaction between the selected group and steps.

All assumptions of the models were satisfied, and P-value < 0.05 was considered as statistically significant. The performance of models was measured by R Square. The analysis was performed by using R 3.4.0 (Vienna, Austria; https://www.R-project.org/) and SAS 9.4 software (SAS Institute Inc. Cary, NC, USA).

5.3. Results

5.3.1. Participant Demographics across Groups

Demographics, comorbidities and medical history of participants are shown in Table 5.1. The HFPEF group was the oldest, and the At-risk group were the youngest. Also, the HFPEF group was more obese than controls (P<0.0001) and there was a similar trend in comparison with At-risk (P=0.0589). In both HFPEF and At-risk groups almost 60% of participants were females in contrast to the control group with only 31% female. In the HFPEF group 78% of patients were classified in NYHA class I-II and their LVEF was 60% and 37%, respectively. The distribution of dyspnea, fatigue, leg edema, atrial fibrillation or flutter, and type II diabetes were higher in HFPEF group compared with both At-risk and control groups.

5.3.2. Physical Activity across Groups

The average daily step count of all participants was 4,523 ± 3,446 steps/day. Across the three groups, the HFPEF group had the lowest step count (2,755 ± 2,682 steps/day compared to

control (6,475 ± 3,344 steps/day, p<0.0001) and the At-risk group (5,262 ± 3,384 steps/day, p <0.001) (Table 5.1). The difference in the daily step count between the At-risk and control groups was not statistically significant.

5.3.3. Myocardial Stress Biomarkers across Groups

Across the groups, there was a significantly higher concentration of both biomarkers in the HFPEF versus the non-HF groups (P<0.001) (Table 5.1). The median levels of BNP and NT-proBNP were not significantly different between the At-risk and controls.

5.3.4. The relation between Physical Activity and Biomarkers

The results of the multivariable regression models revealed that the association of steps and Log BNP in the At-risk group was significantly different from that in HFPEF group (P-value, 0.025) (Appendix B-Table 5-2). In fact, there was a negative association between daily steps and log BNP in At-risk group such that for every 1,000 steps/day corresponded with 1.136 units reduction in Log BNP. In the HFPEF group, every 1,000 steps/day corresponded to 0.2 units decrease in log BNP. Meanwhile, we did not find statistical evidence to show the effect of steps/day on Log BNP within the control group is significantly different from the HFPEF group (P-value is 0.274).

When the association between steps/day and the Log NT-proBNPwas examined, we did not observe any differences when we compared the HFPEF group with the At-risk or control groups (P-values 0.083 and 0.8202, respectively). However, results did suggest a trend in the At-risk group. There was a negative association between daily steps and log NT-proBNP in the At-risk group in which every 1,000 steps/day corresponded with 1.454 units reduction in Log NT-

proBNP. This reduction was only 0.13 units of Log NT-proBNP for every 1,000 steps/day in HFPEF group.

5.4. Discussion

The purpose of the present study was to evaluate the association between daily PA and myocardial stress biomarkers in patients with HFPEF and contrast them with those from the at-risk of HF group and healthy controls. A few studies have documented such a relationship in the elderly population (158, 167) or in patients with HFPEF (168), however; to the best of our knowledge, this is the first attempt to assess this relationship across the three groups (i.e., HFPEF, At-risk, and healthy controls). The findings of the present study are: a) The level of both BNP and NT-proBNP were higher in HFPEF group compared to control and At-risk groups, b) Both non-HF groups took significantly more steps per day than patients with HFPEF and c) In comparison to the HFPEF group, those in the At-risk group had a greater reduction of their BNP level for every 1,000 steps/day completed.

A higher level of NPs in patients with HF compared to the healthy control group is consistent with previous reports (42, 164). However, to the best of our knowledge, this is the first comparison to include an At-risk group. Previous studies have reported a higher level of NPs in those with either hypertension, diabetes or CAD compared to healthy controls (158-160). The result from the present study showed that the level of both myocardial stress biomarkers was comparable for the At-risk and control groups. One explanation could be the fact that our At-risk group had a higher BMI than controls. The inverse relation between NPs and obesity has been shown previously (160, 224).

The findings of the current study showed that for every increment of 1,000 step/day, the reduction in BNP level in the At-risk group was higher than what was observed in the HFPEF group. The association of NPs with daily PA has not been investigated extensively and few studies have used objective measures of PA. In a recent study, Snipelsky et al. reported an inverse relationship between NT-proBNP and both measures of activity they recorded (i.e., average daily accelerometer units and hours active per day) in patients with HFPEF at baseline (168). However, with over a 6 weeks nitrate therapy, there were no significant associations between changes in measures of PA and changes in NT-proBNP. The investigators suggested, compared indices of HF's severity (e.g., 6MWT, NT-proBNP, or NYHA classification) objectively measured PA is more sensitive to the impact of an intervention on the functional status of patients with HFPEF. At 2004 Meyer et al. reported changes in anaerobic threshold of patients with HF after 12 weeks of endurance training was not associated with changes in NT-proBNP (225). Later, Nilsson et al. found no significant association between changes of NT-proBNP and changes in 6MWT after 4 months of high-intensity interval training or at 12-months follow-up in HF patients (226).

Another study by Parsons et al. used objectively measured PA data in more than 1,000 British men without a history of CV disease and found the relationship between NT-proBNP and PA was not linear (158). There was a significant negative association between the level of NT-proBNP and steps/day; however, this relationship was only present when the daily step count was below 4,000. Higher levels of PA did not yield significant associations. In the present study, there was a significant association between Log BNP and PA and a meaningful but not significant association between Log NT-proBNP and PA in At-risk group despite thier 5,262 ± 3,384 steps/day activity level.

Another observation from Parsons's study was that, by stratifying based on hypertension status, the association between PA and NT-proBNP only existed in those with hypertension (158). In addition, these authors reported a higher proportion of those with hypertension were taking statins and anticoagulants, had diabetes, higher BMI and took fewer steps/day compared to normotensive individuals. These characteristics are consistent with our At-risk group and the findings of the present study that showed the relationship between PA and Log BNP was stronger in those At-risk. Also, there was a clinically significant association between NT-proBNP and steps/day in our results in the At-risk group with a trend toward statistical significance (P-value 0.0825). The association between changes in BNP and changes in NT-proBNP in the HF population has shown to be around 52% and up to 58% in those without chronic kidney disease (227).

The importance of these key findings in the clinical setting is multidimensional. First, these results confirm the potential preventive impact of daily PA on reducing the risk of developing HF. Secondly, the improvement of PA could impede the decline in cardiac function and recover detrimental structural changes in patients with HF (228). It is well documented that many established HF risk factors such as obesity, hypertension, diabetes, CAD and etc. are influenced by improving daily PA level (229). Now the recent evidence is emerging that shows promoting daily PA has great positive effects on not only patients with HF but those at-risk of developing HF (158, 168). In fact, recently, Florido et al. in a six-year follow-up study showed even for those with a sedentary lifestyle, each 512 MET×min/week higher PA (e.g., ~ 30 minutes of brisk walking 4 times a week) corresponded with 11% lower risk of HF (230).

5.4.1. Limitations

The interpretation of our findings should be with caution due to the cross-sectional design of this study with a relatively small cohort. However, to the best of our knowledge, this is the first attempt to compare the association of natriuretic peptides with objectively-measured daily PA in healthy controls and those at-risk of HF in comparison to patients with HFPEF. In addition, even though the accelerometer-measured PA is far more valid and reliable than self-reported PA, different devices used in recording and different methods of data transformation might be partially responsible for discrepancies observed in the results of studies (62). High interindividual and intraindividual variations have been reported for NPs in different populations (43, 231, 232), which makes it even more difficult to compare the result of studies.

5.5. Conclusion

Across those with HFPEF, at risk of developing HF or healthy controls, completing more volume of PA have the greatest impact on myocardial stress biomarkers in the At-risk group. As the famous quote says, “prevention is better than cure”. Encouraging those patients A-risk of HF could be more rewarding and practical than asking patients with HF to be more active. Therefore, objective assessment of daily PA simply by recording daily step count could provide a strong tool for identifying those at higher risk and a great benchmark for planning a rehabilitation intervention.

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Table 5-1. Characteristics of study participants

Variable		HFPEF N = 50	At Risk N = 43	P-value At risk vs HFPEF	Control N = 29	P-value Control vs HFPEF
Age	Mean (SD) Median (IQR)	72.80 (9.75) 74.5 (66.0-81.0)	65.09 (12.59) 66.0 (60.0-73.0)	0.0016*	68.45 (10.75) 71.0 (64.0-76.0)	0.0784
Gender	Male	20 (40.00)	18 (41.86)	0.8556	20 (68.97)	0.0131*
BMI	Mean (SD) Median (IQR)	30.97 (6.95) 31.0 (27.4-35.1)	28.56 (5.18) 27.6 (25.5-30.6)	0.0589*	25.00 (3.65) 24.4 (22.6-27.5)	<0.0001*
STEPS	Mean (SD) Median (IQR)	2755.05 (2682.06) 2084.8 (1048.3-3000.3)	5261.61 (3383.70) 4784.5 (2248.3-7753.8)	0.0002*	6474.76 (3343.98) 4146.3 (4399.3-9170.3)	<0.0001*
SWA wearing time (Hrs)	Mean (SD) Median (IQR)	23.6 (0.7) 23.8 (23.4-23.9)	23.6 (0.5) 23.7 (23.4-23.9)	0.954	23.6 (0.4) 23.7 (23.5-23.8)	0.970
BNP	Mean (SD) Median (IQR)	146.74 (116.72) 105.0 (67.0-222.0)	43.56 (45.71) 25.0 (15.0 – 58.0)	<0.0001*	38.69 (24.50) 33.0 (18.0-52.0)	<0.0001
NT-proBNP	Mean (SD) Median (IQR)	114.74 (116.72) 65.5 (32.0-122.0)	16.60 (22.44) 9.00 (4.0-21.0)	0.0005*	13.41 (10.83) 11.0 (5.0-18.0)	0.0003
Log BNP	Mean (SD) Median (IQR)	4.61 (0.97) 4.7 (4.2-5.4)	3.42 (0.81) 3.22 (2.7-4.1)	<0.0001*	3.46 (0.64) 3.5 (2.9-4.0)	<0.0001
Log NT-proBNP	Mean (SD) Median (IQR)	4.10 (1.19) 4.2 (3.5-4.8)	2.24 (1.06) 2.20 (1.4-3.0)	<0.0001*	2.30 (0.80) 2.4 (1.6-2.9)	<0.0001*
Anticoagulants	Yes	23 (46.00)	5 (11.63)	0.0003*	0 (0.00)	<0.0001*
Anti-Hypertensions	Yes	48 (96.00)	40 (93.02)	0.6595	3 (20.69)	<0.0001*
Hypertension	Yes	38 (76.00)	37 (86.05)	0.2215	4 (13.79)	<0.0001*
Dyslipidemia	Yes	31 (62.00)	24 (55.81)	0.5451	6 (20.69)	0.0004*
Cerebrovascular Disease	Yes	5 (10.00)	5 (11.63)	>0.999	0 (0.00)	0.1520
Cirrhosis	Yes	0 (0.00)	0 (0.00)		0 (0.00)	
Cancer	Yes	2 (4.08)	0 (0.00)	0.4974	0 (0.00)	0.5268

History of Alcoholism	Yes	1 (2.00)	0 (0.00)	>0.999	0 (0.00)	>0.999
Atrial fibrillation/Flutter	Yes	26 (52.00)	7 (16.28)	0.0003*	0 (0.00)	<0.0001*
Smoking	Current	4 (8.00)	3 (6.98)	0.9652	0 (0.00)	0.0495*
	Former	18 (36.00)	18 (41.86)		6 (20.69)	
	Never	25 (50.00)	20 (46.51)		23 (79.31)	
	Unknown	3 (6.00)	2 (4.65)		0 (0.00)	
Previous MI	Yes	12 (24.00)	10 (23.26)	0.9329	0 (0.00)	0.0029*
Dyspnea	Yes	26 (52.00)	7 (16.28)	0.0003*	0 (0.00)	<0.0001*
Fatigue	Yes	24 (48.00)	8 (18.60)	0.0029*	1 (3.45)	<0.0001*
Leg Edema	Yes	11 (22.00)	2 (4.65)	0.0161*	0 (0.00)	0.0056*
Other CV procedures	Yes	8 (16.00)	5 (11.63)	0.5444	0 (0.00)	0.0237*
NYHA	I-II / III-IV	49 (78)/ 11 (22)	0 (0.00)		0 (0.00)	
COPD	Yes	12 (24.00)	3 (6.98)	0.0621	0 (0.00)	0.0029*
T2D	Yes	19 (38.00)	6 (13.95)	0.0091*	0 (0.00)	0.0001*
T1D	Yes	1 (2.00)	2 (4.65)	0.5941	0 (0.00)	>0.999

At-risk, patients at risk of developing Heart failure; HFPEF, heart failure with preserved ejection fraction; BMI, Body mass index; BNP, brain natriuretic peptide (pg/ml); NT-proBNP, N-terminal pro-brain natriuretic peptide (pmol/L); NYHA, New York heart association functional classification; LVEF, left ventricle ejection fraction; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; MI, Myocardial infarction. Star (*) indicates significant difference, P<0.05. [a] *Previous Cardiovascular procedures including; Pacemaker or Implantable Cardioverter Defibrillator, Coronary Artery Bypass Grafting, or Valve surgery.* [b] *Antihypertensive medications including beta-blockers, ACE inhibitors, calcium channel blockers, angiotensin II receptor blockers, diuretics, and etc.*

Chapter 6

General Discussion and Conclusion

6.1. General Discussion

One of the key manifestations of heart failure (HF) is diminished exercise capacity meaning the maximum ability to perform physical activity (PA) is reduced. However, having the capacity does not necessarily translate to performing daily PA. Historically, rehabilitation programs targeting patients with HF have addressed reduced aerobic capacity with exercise training. However, there is no consensus on the best mode, volume, and intensity of an exercise program for patients with HF (12). In addition, adherence to these exercise training programs seems to be problematic for the HF population, and hence the sustainability of achieved benefits might decrease or dissipate over time (233). As an alternative to exercise training some investigators suggest that encouraging daily PA might be a viable substitute because it encompasses occupational, leisure, and household activities and can be accomplished throughout the day. Promoting regular PA in patients with HF has shown to reduce hospitalization, disease progression, and mortality while improving function, independence, and quality of life (10, 12, 19). In fact, every 60 min increase in total non-sedentary ambulatory-based movements (i.e., all intensities > 1.5 METs) in patients with HF has been shown to be associated with a 35% reduction in the risk of all-cause mortality (123).

To the best of our knowledge, there is no study that has compared the daily PA of patients with HF and reduced ejection fraction (HFREF) with those with HF and preserved ejection fraction

(HFPEF). Furthermore, the daily volume and patterns of PA in both HF phenotypes contrasted to those at risk of developing HF (At-risk) and healthy controls are unknown. Having a better understanding of the daily volume of PA across the HF continuum could provide a holistic view of the changes in daily PA while the capacity to perform PA diminishes. Identifying the patterns of PA could shed light on daily fluctuations and distribution of PA energy expenditure (PAEE) across the HF continuum. Lack of objective information about the volume and patterns of daily PA across the HF continuum could lead to negative aftereffects including late diagnosis and worst prognosis, higher costs of treatments or failed intervention. In contrast, staring a routine objective assessment of PA as early as the appearance of risk factors such as higher blood pressure, overweight, or myocardial infarction could help to identify those at higher risk of HF sooner. It could also assist health care providers in designing a tailored program for these patients. In addition, daily PA data could provide a perfect foundation for an effective and long-lasting behavioral change intervention which in return may result in lower costs and better quality of life.

Despite the recommendation of several health agencies, such as the American Heart Association, to regularly assess the daily PA as an important risk factor (62), this practice is still far away from reality. The 2018 PA guideline of the American Medical Association reported that almost 80% of US adults and adolescents are insufficiently active compared to the recommended level of PA (107). This is unfortunate since recent advancement in the technology of monitoring devices allows for an accurate assessment of a number of PA measures. Further, these devices are accessible and affordable for the public. There have been a variety of measures reported in the literature that yields objective information about different dimensions of PA (e.g., intensity,

duration, etc.). Although each of these measures adds to the collective information about the volume and patterns of PA, using multiple measures has some drawbacks. For example, it may be harder to compare the results of studies that used different measures (e.g., steps vs counts). In addition, gathering data from several domains of PA would require a more complex and expensive device. Also, using different measures makes it harder to translate the findings to the general audience. Since walking is the most popular form of PA and a functional part of our daily life (108), almost all tracking devices available in the market report the number of steps/day as the most common measure of PA. In fact, the result of our first study revealed step count compared to other measures that represent time or energy spent in different intensities is the most robust measure of PA for patients at risk or with HF. Steps/day has been widely used as a measure to promote PA in healthy and patient populations because it makes it easy to set a goal, track progress and provide feedback for different target populations (155).

For years investigators have tried to calculate the minimum volume and intensity of PA required to achieve different positive health benefits. According to the recent PA guidelines, typically, the higher the intensity and volume of PA the greater the benefits (107). However, it is not clear if in patients with HF performing activities of daily living (i.e. ADL) is associated with favorable changes in prognostic determinants.

The second and third studies in this thesis aimed to not only investigate the association between steps/day and prognostic determinant in patients with HF but also to assess if these associations are different across the HF continuum. Evaluating the associations between the marker of daily PA and aortic distensibility (AD) and myocardial stress biomarkers could also help

in the development of pathways leading to earlier diagnosis, more precise classifications, and better prognosis of patients with HF.

The results of the second study showed that the association between daily step count and AD may not be similar across the continuum of HF. The findings showed there was a direct relationship, such that a higher range of steps/day was associated with a higher AD, but only in our small HFREF group. The fact that the association was only seen in the HFREF group suggest that larger studies are needed to assess the association between AD and steps/day across the spectrum of HF. In fact, the results of a 2019 meta-analysis showed that in older adults, there is a statistically weak but clinically significant correlation between objectively measured daily step count and pulse wave velocity (PWV) (155). Their results showed that for every 1,000 steps/day increase in PA, a 0.18 m/s reduction in PWV was observed (155). This association appeared to be curvilinear whereby the greatest effects on arterial stiffness were observed between those with low-active to an active lifestyle (i.e., from 5,000 to 7,499 steps/day) and those with an active to a very active lifestyle (i.e., from 7,500 to 9,999 steps/day).

The findings of the third study also indicated the associations between steps/day and BNP or NT-proBNP were not comparable across groups; from healthy controls, to those At-risk and with HFPEF. In fact, the association between steps/day and natriuretic peptides (NPs) were more prominent in the At-risk group compared to patients with HFPEF. To the best of our knowledge, this is the first study investigating the relationship between a marker of objectively measured daily PA and NPs while including an At-risk group. We could only find one study assessing the association of daily PA with NT-proBNP in patients with HFPEF (168). In that study, investigators used two markers of accelerometer-measured PA. The first marker was representative of both

intensity and duration (e.g., average daily accelerometer units) while the second marker was the only representative of the total active time. The authors noted that while at baseline, those with higher NT-proBNP showed lower PA in both markers, there were no significant associations between changes in the two markers of PA and changes in NT-proBNP. Systematic reviews about the effects of aerobic exercise training on NPs in patients with HF suggested exercise intensity and the total volume of PAEE during exercise may determine the extent of favorable changes in NPs (170, 234). Smart et al., suggested that a minimum aerobic exercise training volume of approximately 460 Kcal/week might be required to elicit changes in NPs in patients with HF (234).

In summary, the volume of PA, as defined by the product of intensity multiplied by frequency and duration (62), seems to play a crucial role in determining the extent of health benefits in those At-risk or with HF. The results of our first study revealed that the majority of our cohort had a sedentary lifestyle. While those with HF may benefit the most by being more active, according to our results they were the least active across the HF continuum followed by the At-risk group. The daily PA performed by the majority of patients with HF might not reach the minimum volume required to improve AD or reduce NPs. This could partially explain why in the 2nd and 3rd studies we did not find significant associations where previous reports did.

To conclude, the main objective of this thesis was to provide a clearer picture of the functional status of individuals At-risk of HF versus those patients with HF. This information could be used to adjust exercise training targets and establish realistic rehabilitation goals that may, in turn, result in long-term behavior change of the patients and improved outcomes. Generally, behavior change is a function of three components ability, motivation, and trigger (235). To put

it in context, for changing PA behavior of patients At-risk or with HF, not only they should be able to perform the PA tasks but also should be motivated and be prompted to do that.

Therefore, the first question should be, is this target population able to complete the current recommended level of PA? The answer to this question appears to depend on the part of the HF continuum we are targeting. For instance, the results of our first study showed that patients with HF completed the least volume of PA compared to those At-risk and healthy controls. The first study also provided some important insights regarding the patterns of daily PA of two phenotypes of HF. While the energy and time that each HF group spent in light intensity and all moderate-to-vigorous intensity PA (MVPA) (i.e., not limited to bouts of ≥10 min) were comparable, those with HFREF were actually performing 6 times more continuous MVPA lasting for at least 10-minutes than patients with HFPEF. These findings may have implications for individualized strategies to promote PA. First, for patients with HF who are currently engaged in some daily MVPA, increasing the amount of time spent at ≥ 3 METs should be encouraged. A higher volume of MVPA will lead to a greater drop in the risk of mortality and extended health benefits (106). However, insisting on this approach for those patients who are spending the majority of their waking time sedentary or light PA (e.g., ADL), may not bode well for a long-term behavior change. For these patients increasing the volume of the light intensity PA and decreasing the sedentary time should be prioritized over completing MVPA. Reducing the risk of mortality and improving the quality of life is achievable by reducing sedentary time and increasing light intensity PA (106). Secondly, those at risk of developing HF are performing below the recommended level of PA which may soon join the HF population if not encouraged to decrease their sedentary time and spend more time in regular MVPA.

The element of ability was discussed by introducing feasible and progressive strategies to promote PA in this population. Thus, the remaining part of the puzzle is understanding what it takes to get them to do that hence motivation and trigger. In brief, patients should receive clear and customized advice from health care providers regarding why and how to be active as an important part of their standard care (236, 237). Helping patients through the process of adopting positive health behavior by breaking the goals down into smaller achievable steps, correcting patient's perceived costs and benefits, and improving their self-confidence could increase their motivation. In addition, increasing social support and self-efficacy in patients with HF in response to patient's endeavors could help in forming triggers (236, 237). Although the ultimate goal in this population should be meet the current PA recommendations, for a majority of patients it appears to be achievable only through a tailored increase in the volume of PA and continuous support (e.g. reducing barriers, increasing accessibility, social support) to boost their confidence.

The findings of this thesis could further advance our understanding of the significance of PA across the HF continuum. Routine objective assessment of PA is vital. Longitudinal objective data on PA could provide a proper basis for individualized behavioral interventions. In addition, it could be used to motivate and empower patients with detailed feedback for guideline-directed self-care.

Moreover, these findings could provide additional evidence that the response to PA conveys through different pathways across the HF continuum. In other words, PA appears to have a different impact on different groups from healthy to At-risk and HF. One obvious reason is the relative intensity which reflects the different aerobic capacity of these groups. However, despite

an equal reduction of the capacity in the two phenotypes of HF, our results suggest that the effects of PA could differ across HFPEF and HFREF. In fact, there is an emerging trend of evidence suggesting patients with HFPEF would benefit more from PA than their HFREF peers (39). Also, Omar et al. reported a heterogeneous response to exercise training in patients with HF that calls for more individualized approaches in PA promotion (238).

The combined message from the results of these three studies is that regular assessment of PA could be used as an important tool to identify those with a higher risk of HF incidence and to design individualized rehabilitation programs to improve function and prognosis. Although the underlying mechanisms were not studied in this thesis, several other studies have noticed a considerable risk reduction after adopting an active lifestyle (120, 230). In addition, the association between a single marker of PA such as steps/day and important prognostic determinant of HF underscores the importance of regular assessment of this behavior. Despite the different mechanisms by which PA benefits individuals across the HF continuum, it is critical to recognize risk factors associated with a sedentary lifestyle and proper strategies to tackle this issue.

6.2. Limitations

This thesis was a sub-study of a larger Alberta Heart Failure Etiology and Analysis Research Team (HEART) research program, a prospective observational study aimed to define new diagnostic criteria for patients with HFPEF. One of the main limitations of the present thesis was the delayed start, which impacted the sample size of participants, especially for the HFREF group. In addition, although the nature of the Alberta HEART was observational, it still took

approximately 2 years to collect our PA data. Consequently, during that period we recorded the PA data for some participants at Alberta HEART's baseline and for some others at Alberta HEART's follow-up. Although, we used corresponded dates for all variables included in our analysis, it is possible that internal (e.g., signs and symptoms, comorbidities) and external factors (e.g., phases of Alberta HEART, time of year) affected the PA of the some of the participants. One of the challenges of this thesis was the interpretation of the results of 2nd and 3rd studies knowing the majority of the cohort were sedentary. The daily PA performed by the majority of patients with HF may not have reached the minimum volume required to improve AD or reduce NPs.

6.3. Recommendations

Using simple and reasonably accurate activity trackers that can objectively report the number of steps/day should be encouraged in future longitudinal studies. Having information about PA over several time-points along other prognostic markers could provide us with the trend of changes in daily performance over time. The application of universal measures of PA could help to compare the results of different studies and perform stronger systematic reviews or meta-analysis. Having the aerobic capacity of participants could significantly add to the value of the information provided by PA assessment. For example, the relative intensity of daily PA performed could be calculated as the percentage of their VO_2 peak. Our original design included assessments of aerobic capacity and cardiac output to gain a better sense of the functional and cardiac capacity of participants. However, in order to measure both VO2 peak and cardiac output during maximal bike test, we used an Inert Gas Rebreathing machine called Innocor® which required patients to go through complex and difficult procedures. For example, the mouth-piece

was connected to a proportionally heavy apparatus. In order to help participants tolerate this weight, we suspended the apparatus by a ring to a modified serum stand which resulted in restricted head movements. Moreover, saliva retention in the mouth-piece caused discomfort and breathing difficulties. Thus, sub-maximal termination of the test and daily fluctuations of the patient's sign and symptoms might have contributed to not recording enough usable data during exercise tests.

For future studies, comparing the long-term effects of daily PA on prognostic determinants such as AD and NPs across both phenotypes of HF categorized in sedentary and active patients is recommended.

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Appendix A

Ethics Approval

Date:	March 28, 2012
Principal Investigator:	Justin Ezekowitz
Study ID:	Pro00007105
Study Title:	AHFMR Interdisciplinary Team Grant on Understanding and Treating Diastolic Heart Failure: Novel Mechanisms, Diagnostics and Potential Therapeutics
Sponsor/Funding Agency:	AHFMR - Alberta Heritage Foundation for Medical Research AHFMR Prevention of Organ Failure Centre (PROOF)
Approval Expiry Date:	September 1, 2012

Thank you for submitting an amendment request to the Health Research Ethics Board - Biomedical Panel. The following has been reviewed and approved on behalf of the committee: Vascular substudy (without the use of contrast agent) utilizing pulse arterial tonometry and the associated Vascular Substudy Informed Consent Form, 27 Mar 2012; addition of daily energy expenditure measured captured by use of an armband; revised main study Informed Consent Form, 27 Mar 2012; Permission to contact potential participant form, 27 Mar 2012; and Recruitment poster, file dated Feb 2012.

Note: Approval for an **amendment** does not change the original approval date of a study.

Sincerely,

S.K.M. Kimber, MD, FRCPC
Chair, HREB Biomedical

Note: This correspondence includes an electronic signature (validation and approval via an online system).

Appendix B

Table 5-2. The results of multivariable linear regression analysis showing the interaction between groups and steps/day, and the relationship between biomarkers and steps/day while adjusting for covariates

Variable		Coefficient (S.E) (C.I)	EXP Coefficient (S.E) (C.I)	P-value
Log BNP				
Continuous Variable				
Age		0.0205 (0.0073) 0.0060 – 0.0349		0.0059
BMI		0.0070 (0.0152) -0.0233 – 0.0372		0.6488
STEPS		-0.0002 (0.0001) -0.0233 - -0.0001		0.0018
Categorical variable				
Groups	At-risk	-1.068 (0.2903) -1.6437 - -0.4914	0.3439 0.1933 – 0.6118	0.0004
	Control	-0.5161 (0.4696) -1.4473 – 0.4151	0.5968 0.2352 – 1.5146	0.2741
	HFPEF	Reference		
Groups:STEPS Interaction	At-risk:STEPS	0.000132 (0.00006) 0.00001687 – 0.0002487	1.00012 1.0000169 – 1.0002487	0.0252
	Control:STEPS	0.000102 (0.00006) -0.00002491 – 0.0002253	1.00010 0.9999751 – 1.0002253	00.115
	HFPEF:STEPS	Reference		
ANTICOAGULANT	Yes	0.1081 (0.3317) -0.5500 – 0.7221	1.1142 0.5769 – 2.1518	0.7451
	No	Reference		
Anti HTN [b]	Yes	0.1903 (0.2680) -0.3415 – 0.7221	1.2096 0.7107 – 2.1518	0.4793

	No	Reference		
Gender	Male	0.0271 (0.1643) -0.2991 – 0.3532	1.0274 0.7415 – 1.4236	0.8696
	Female	Reference		
Atrial fibrillation flutter	Yes	0.2909 (0.3120) -0.3283 – 0.9100	1.3376 0.7202 – 2.4843	0.3535
	No	Reference		
History of Smoking	Yes	0.1608 (0.1522) -0.1411 – 0.4628	1.1745 0.8684 – 1.5885	0.2931
	No	Reference		
Previous MI	Yes	-0.0066 (0.2232) -0.4495 – 0.4364	0.9934 0.6379 – 1.5471	0.9766
	No	Reference		
Dyspnea	Yes	0.0902 (0.2171) -0.3405 – 0.5210	1.0944 0.7114 – 1.6836	0.6786
	No	Reference		
Fatigue	Yes	-0.0527 (0.1891) -0.4279 – 0.3225	0.9486 0.6518 – 1.3806	0.7809
	No	Reference		
Leg Edema	Yes	0.5910 (0.2722) 0.0508 – 1.1313	1.8058 1.0521 – 3.0997	0.0324
	No	Reference		
Other CV procedures [a]	Yes	0.4487 (0.3484) -0.0443 – 0.9165	1.5663 0.9567 – 2.5642	0.0740
	No	Reference		
T2D	Yes	0.0377 (0.2077) -0.3744 – 0.4498	1.0384 0.6877 – 1.5680	0.8563
	No	Reference		
R-square	0.5672			
Log NTproBNP				

Continuous Variable				
Age		0.02854 (0.0084) 0.01183 – 0.0452		0.0010
BMI		-0.0285 (0.0174) -0.04745 – 0.0217		0.4611
STEPS		-0.00013 (0.0000548) -0.0002353 – -0.00001786		0.0229
Categorical variable				
Groups	atrisk	-1.442 (0.9450) -0.5186 – 3.2305	0.2364 0.1217 – 0.4592	<0.0001
	Control	-0.1598 (0.3346) -2.1060 – -0.7782	0.8523 0.2906 – 2.4993	0.7688
	HFPEF	Reference		
Groups:STEPS Interaction	At-risk:STEPS	0.0001185 (0.0001185) -0.00001556 – 0.0002527	1.0001186 0.9999844 – 1.0002527	0.0825
	Control:STEPS	0.0000166 (0.0000166) -0.00012812 – 0.0001614	1.0000166 0.9998719 – 1.001614	0.8202
	HFPEF:STEPS	Reference		
ANTICOAGULANT	Yes	0.8265 (0.3664) 0.09941 – 1.5536	2.2853 1.1045 – 4.7284	0.0263
	No	Reference		
Anti HTN [b]	Yes	0.5153(0.3095) -0.09886 – 1.1295	1.6742 0.9059 – 3.0942	0.0991
	No	Reference		
Gender	Male	0.1405(0.1807) -0.02181 – 0.4992	1.1509 0.8040 – 1.6474	0.4387
	Female	Reference		
Atrial fibrillation flutter	Yes	0.1390(0.3504) -0.5563 – 0.8342	1.1491 0.5733 – 2.3030	0.6925
	No	Reference		

History of Smoking	Yes	0.1616(0.1756) -0.1868 – 0.5100	1.1754 0.8296 – 1.6654	0.3597
	No	Reference		
Dyspnea	Yes	0.2827(0.2435) -0.2006 – 0.7659	1.3267 0.8183 – 2.1510	0.2485
	No	Reference		
Fatigue	Yes	0.0800 (0.2172) -0.3510 – 0.5109	1.0833 0.7040 – 1.6668	0.7134
	No	Reference		
Leg Edema	Yes	0.1922 (0.3147) -0.4322 – 0.8166	1.2119 0.6491 – 2.2629	0.5427
	No	Reference		
Other CV procedures. [a]	Yes	0.3145 (0.2801) -0.2412 – 0.8703	1.3696 0.7857 – 2.3875	0.2641
	No	Reference		
T2D	Yes	0.1285 (0.2387) -0.3452 – 0.6023	1.1372 0.7081 – 1.8262	0.5915
	No	Reference		
R-square	0.6885			

At-risk, patients at risk of developing Heart failure; HFPEF, heart failure with preserved ejection fraction; BMI, Body mass index; BNP, brain natriuretic peptide (pg/ml); NT-proBNP, N-terminal pro-brain natriuretic peptide (pmol/L); NYHA, New York heart association functional classification; LVEF, left ventricle ejection fraction; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; MI, Myocardial infarction. [a] *Other Cardiovascular procedures including; Pacemaker or Implantable Cardioverter Defibrillator, Coronary Artery Bypass Grafting, or Valve surgery.* [b] *Antihypertensive medications including beta-blockers, ACE inhibitors, calcium channel blockers, angiotensin II receptor blockers, diuretics, and etc.*