The Relationship of Resting Cardiopulmonary Function to Peak and Submaximal Cardiopulmonary Exercise Testing in Older Adults with Heart Failure

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Dedication

I have been able to pursue a bachelor's degree, master's degree, and two doctorates. This dissertation is dedicated to all of the girls and women throughout the world who have been denied higher education and education in general. I hope we can change the world so that no country limits anyone's right to life, liberty, and the pursuit of happiness.

Abstract

Background: Heart failure (HF) is a challenging disease that affects more than five million people, half of whom are at least 75 years old. Peak oxygen consumption (VO_{2peak}), the minute ventilation/carbon dioxide production (VE/VCO_2) slope, and the 6MWT are powerful prognostic indicators of all-cause mortality and cardiovascular-related mortality. VO_{2peak} and the VE/VCO_2 slope, obtained during CPX, have been shown to be useful for monitoring the efficacy of symptom and therapeutic management. Peak cardiac output (Q_{peak}) would also be an excellent prognostic indicator but traditionally it has been difficult to measure since the measurement is usually highly invasive. At the University of Minnesota, we are able to measure Q_{peak} noninvasively using the acetylene washin method. Despite the body of evidence supporting these measures, CPX and the 6MWT are not routinely performed on an outpatient basis as a part of HF symptom assessment and management. Additionally, older patients with HF often do not recognize worsening symptoms which frequently lead to hospitalization. In order for nurses to maximize quality of life for patients with HF and affect morbidity and mortality, usable methods for the evaluation of therapeutic efficacy of symptom management and prescribed treatments must be available. N-terminal prohormone brain natriuretic peptide (NT-pro BNP), New York Heart Association (NYHA) classification, and inspiratory capacity, are all obtainable in an office visit and may explain enough variance in peak Q, VO_2, the VE/VCO_2 slope, 6MWT distance, or all three measurements to be useful in the outpatient setting.

Objective: The purpose of this study was to explore the potential of a model that incorporates resting measures, NT-Pro BNP, NYHA classification, and inspiratory

capacity, for the evaluation of therapeutic efficacy of symptom management and prescribed treatments for older patients with HF. We hypothesized that there is a relationship between Q_{peak}, VO_{2peak}, the VE/VCO_2 slope, and/or 6MWT distance with NT-pro BNP, NYHA classification, and inspiratory capacity.

Method: Twenty-three older patients (mean age 73.6 $\pm$ 4.5 years old) with HF underwent venipuncture, inspiratory capacity measurement, and performed the 6MWT and CPX per standardized protocol. Q_{peak}, VO_2 peak and the VE/VCO_2 slope measurements were recorded during the CPX. NYHA classification was obtained from chart review and assessment.

Results: The strongest relationships were between inspiratory capacity and Q_{peak} ($R = 0.77$, $p < 0.0001$), and between NT-pro BNP and the VE/VCO_2 slope ($R = 0.71$, $p < 0.001$). Additionally, there was a moderate relationship between NT-pro BNP and VO_{2peak} ($R = -0.47$, $p < 0.03$) and between inspiratory capacity and VO_{2peak} ($R = 0.51$, $p < 0.02$). Due to the lack of variance NYHA classification was not included in the regression analysis. The 6MWT distance did not correlate with NT-pro BNP or inspiratory capacity. NT-pro BNP accounted for 22% of variance in VO_{2peak} and 50% of variance in the VE/VCO_2 slope. Mean inspiratory capacity accounted for 59% of variance in Q_{peak} and 26% of variance in VO_{2peak}. The combined measurements of inspiratory capacity and NT-pro BNP explained 42% of the variance in VO_{2peak} (adjusted $R^2 = 0.42$, $F(2, 20) = 8.82$, $p < 0.002$). A model of prediction for either Q_{peak} or the VE/VCO_2 slope could not be constructed since only one predictor variable for each outcome variable was statistically significant.

Conclusion: This study is likely the first investigation into the relationship between Q_{peak} and inspiratory capacity and highlights the potential usefulness of inspiratory capacity measurement, in the management of HF. NT-pro BNP and inspiratory capacity can, either alone or combined, explain between 42% and 59% of variance in key exercise measurements. These measurements are obtainable by clinicians in the office setting to monitor disease and symptom management; they may also be useful in predicting prognosis. Of greater significance, is that inspiratory capacity has the potential to be measured by patients themselves at home.

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List of Abbreviations

ACCF	American College of Cardiology Foundation
ACE-I	Angiotensin Converting Enzyme Inhibitor
AHA	American Heart Association
ARB	Angiotensin Receptor Blocker
ATS	American Thoracic Society
BMI	Body Mass Index
BNP	B-type Brain Natriuretic Peptide
Ca	Systemic Arteries
Cv	Systemic Veins
C-indices	Concordance Indices
CPX	Cardiopulmonary Exercise Testing
CTSI	Clinical and Translational Science Institute
EDV	End-Diastolic Volume
ESV	End-Systolic Volume
HF	Heart Failure
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
HR	Heart Rate
LLCT	Lung-Lung Circulation Time
LVEF	Left Ventricular Ejection Fraction
NT-pro BNP	N-Terminal prohormone B-type Natriuretic Peptide
NYHA	New York Heart Association
O_2	Oxygen
PI	Principal Investigator
6MWT	Six-Minute Walk test
Q	Cardiac Output
Q_{peak}	Peak Cardiac Output
RECOuP-HF	The Relationship of Resting Cardiopulmonary Function to Peak and Submaximal Cardiopulmonary Exercise Testing in Older Adults
REDCap	Research Electronic Data capture

SV	Stroke Volume
v	Systemic Veins
VE/VCO_2	Minute Ventilation/Carbon Dioxide Production
VO_2	Oxygen Consumption
VO_{2peak}	Peak Oxygen Consumption

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Chapter 1: Introduction

Background and Significance

Heart failure (HF) is a devastating syndrome that occurs when the heart is no longer able to generate enough cardiac output to meet the needs of the tissues. More than five million people in the United States have been diagnosed with HF and it is the primary reason for 6.5 million hospital days each year (Mozaffarian, et al. 2016). The total combined direct and indirect cost associated with HF in the United States in 2010 was approximately $32 billion and it is projected that costs will exceed $70 billion by the year 2030. (Heidenreich, et al., 2011). HF is frequently the end result of other cardiovascular disease processes and as such is generally a disease of older age. Therefore, it comes as little surprise that the median age for patients with HF is 75 years old and that two and one half million people in the United States aged 75 or greater have been diagnosed with HF (Thomas & Rich, 2007).

After diagnosis, the overall one-year mortality rate for HF is 20% and fewer than 15% of HF patients survive 8 to 12 years (Mozaffarian et al., 2016). In a retrospective study of Medicare beneficiaries Croft et al. (1999) found that 30% of patients at least 67 years old died within one year after their first hospitalization for HF. From ages 65 -74 the incidence of HF double with each ten-year increase and for women, it triples in the 85 – 94 year old range (National Institute of Health, 2006). Patients with HF have considerable morbidity, including shortness of breath, fatigue, and edema. For older patients with HF, these symptoms are often compounded with frailty and comorbidities such as coronary artery disease, hypertension, diabetes and chronic obstructive pulmonary disease which makes symptom recognition more difficult. Often, older

patients with HF discount symptoms as part of aging which may lead to prolonged periods of worsening symptoms and hospital admission instead of outpatient treatment.

Complexity in the Management of Heart Failure

Management of the disease process and symptoms in HF is complex and can involve lifestyle changes, pharmacotherapy, exercise therapy, device therapy, and possibly transplant. As an example of the complexity of the care and management of HF as a disease, the executive summary of the Heart Failure Society 2010 Comprehensive Heart Failure Practice Guideline is 60 pages long and the 2013 American College of Cardiology Foundation (ACCF)/ American Heart Association (AHA) Guideline for the Management of Heart Failure is 80 pages long (Albert et al., 2010; Yancy et al., 2013). The complexity level increases in older patients with HF due to normal physiologic changes in aging, abnormal physiologic changes in aging which cause comorbidities, and the potential for frailty.

Although physiologic measurements obtained during maximal or peak exercise and submaximal exercise, including peak oxygen consumption (VO_{2peak}), ventilator efficiency as portrayed by the minute ventilation/carbon dioxide production (VE/VCO_2) slope, and Six-Minute Walk Test (6MWT) distance, are significant prognostic indicators and useful for monitoring therapeutic efficacy, these measurements are not routinely used clinically in most settings other than large cardiovascular care centers. Additionally, the gold standard measurement, cardiac output (Q) requires invasive monitoring which is generally only performed in intensive care settings. However, N-terminal prohormone B-type natriuretic peptide (NT-pro BNP), New York Hear Association (NYHA) classification, and inspiratory capacity are measurements that do not require peak

exercise performance and have been shown to correlate with VO_{2peak}, ventilator efficiency VE/VCO_2 slope, and/or 6MWT distance and may provide information useful in assessing therapeutic efficacy of treatments and symptom management. The proposed measurements may also correlate with peak cardiac output (Q_{peak}) which we are able to measure non-invasively at the University of Minnesota using the open-circuit acetylene washin method (Johnson et al., 2000).

Complexity of medication management. In addition to the likelihood of multiple comorbidities and the potential for frailty, many older patients have multiple medications prescribed. Kaufman, Kelly, Rosenberg, Anderson, and Mitchell (2002) found that 44% of men and 57% of women over the age of 65 used at least five medications per week. In a study of 97 patients with HF, Gastelurrutia et al. (2011) found that the average number of medications taken by older patients with HF (mean age 74.5) was 10.2 $\pm$ 3.2 with 147 drug-related negative outcomes. Considering that the risk for an adverse drug event increases from 13% for patients taking two medications to 82% for patients taking more than seven medications, patients with HF are at substantial risk of an adverse drug event and require close monitoring (Goldberg, Mabee, Chan, & Wong, 1997). Often, an adverse drug event in older patients causes falling. Falling at an older age carries considerable risk of morbidity, decreased independence, mortality, and cost.

Other causes for concern in pharmacotherapy in older patients with HF are under-dosing and underutilization. Of the 147 drug-related negative outcomes that Gastelurrutia et al. (2011) found, 24% were due to insufficient dose. Kamajda et al. (2009) followed 741 octogenarians and 2836 younger patients who had been hospitalized for HF for one

year and found that the octogenarians had fewer of the standard medications for HF prescribed than younger patients. Gambassi et al. (2000) reviewed the medication usage of 86,094 patients with HF living in long-term care and found that only 25% of the patients had been prescribed an angiotensin-converting enzyme inhibitor, which is a standard of care for HF (Yancy et al., 2013).

Older patients with HF are at a higher risk for medication interactions, for underutilization, and for under-dosing of standard medications (Maher, Hanlon, & Hajjar, 2014). In order for these patients to receive maximal therapeutic benefits while minimizing risk, it is important to have tools to assess the therapeutic efficacy of disease and symptom management that can be performed in the clinic. It becomes even more important considering that older adults are often under-represented in the research that provides evidence for therapies.

Complexity of Symptom Recognition

Patients often do not recognize symptoms of volume overload which can lead to rapid decompensation and necessitate hospital admission. This is particularly true in older patients (at least 65 years old) with HF who have been found to have difficulty in evaluating and understanding the meaning of shortness of breath (Riegel et al., 2009) and may not comprehend the importance of their symptoms (Jurgens, Hoke, Burns, Reigel 2009; Reigel & Carlson, 2002; Sethares, Sosa, Fischer, Reigel et al, 2009). Additionally, older patients with HF frequently discount symptoms, including shortness of breath, either as not important or as a normal function of aging (Patel Shafazand, Shaufelberger, Ekman, 2007). Prior hospital admission for acute, decompensated HF has not been found to increase symptom recognition (Friedman, 1997; Jurgens, 2006; Jurgens et al., 2009).

Although patients are taught both in the outpatient setting and during a hospitalization to monitor shortness of breath, lower leg swelling, and daily weights, in a study of 5,964 participants from 15 countries Jaarsma et al. (2013) found that less than half of patients with HF weighed themselves regularly.

The national 30-day post-hospital discharge re-admission rate for acute, decompensated HF is 25%; one out of every four patients hospitalized for HF is readmitted within 30 days (Krumholz et al., 2009). In a retrospective study of 83 participants with HF, Schiff et al. estimated that 57% of admissions for acute, decompensated HF could have been prevented if there had been adequate self-monitoring of symptoms (Krumholz et al., 2009). Annema et al. (2009) interviewed patients, caregivers, cardiologists, and HF nurses who believed that 23-31% of readmissions were most likely avoidable and specified treatment nonadherence and delay in requesting help as the most important reasons for readmission.

For patients with HF, hospitalizations affect both quality of life and mortality (Loehr, Rosamond, Chang, Folsom, Chambless, 2008; Falk, Etman, Anderson, Fu, Granger, 2013). In order for nurses to maximize quality of life for patients with HF and affect morbidity and mortality, we need improved methods of symptom recognition. Additionally, methods for the evaluation of therapeutic efficacy of symptom management and prescribed treatments must be available and able to be used in the outpatient setting.

Problem Statement and Purpose

Heart failure is a challenging disease that affects more than five million people, half of whom are at least 75 years old. Q, VO_{2peak}, the VE/VCO_2 slope, and the 6MWT are powerful prognostic indicators and VO_{2peak}, the VE/VCO_2 slope, and the 6MWT are

useful for monitoring the therapeutic efficacy of symptom and disease management. However, despite the body of evidence supporting these measures, cardiopulmonary exercise testing (CPX) and the 6MWT are not routinely performed in the outpatient setting. NT-pro BNP, NYHA classification, and inspiratory capacity, are all obtainable in an office visit and may explain enough variance in peak $Q_{,}$ VO_2, the VE/VCO_2 slope, 6MWT distance, or all three measurements to be useful in the outpatient setting. If a model can be built that explains enough of the variance in Q_{peak} VO_{2peak}, the VE/VCO_2 slope, or 6MWT distance, then these measurements will be useful for nurses for symptom management, determination of therapeutic efficacy, and possibly prognosis for older patients with HF.

Three resting measurements may be able to explain enough variance in Q_{peak} VO_{2peak}, the VE/VCO_2 slope, and/or the 6MWT to be useful in the outpatient management of symptoms and disease progression in patients with HF. One resting measurement, inspiratory capacity, has the potential to be useful not only in the clinical management of symptoms and disease progression, but also in helping older patients with HF in their own home. It has been shown that older patients have difficulty in symptom recognition and often delay care. A tool that could be used at home which allows the patient have a concrete measurement of volume overload would be a significant benefit to our patients and their caregivers in symptom validation and help nurses maximize quality of life for patients with HF.

Purpose

The purpose of this study was to investigate the relationship of Q_{peak}, VO_{2peak}, the VE/VCO_2 slope, and 6MWT distance to NT-pro BNP, NYHA classification, and

inspiratory capacity in older patients with HF. The purpose will be addressed through two specific aims.

Specific aims. The specific aims of this research study are:

1. To investigate the relationship of Q_{peak}, VO_{2peak}, the VE/VCO_2 slope, and/or 6MWT distance with NT-pro BNP, NYHA classification, and inspiratory capacity, in older adults with HF.

   Hypothesis 1: There is a relationship between Q_{peak}, $VO2_{peak}$, the VE/VCO_2 slope, and/or 6MWT distance with NT-pro BNP, NYHA classification, and inspiratory capacity.
2. To explore possible models of predicting peak Q_{peak}, VO_2, the VE/VCO_2 slope, and/or 6MWT distance from NT-pro BNP, NYHA classification, and inspiratory capacity in older adults with HF.

Chapter 2 Literature Review

Pathophysiology of Heart Failure

The pathophysiology of HF is not completely understood. During the cardiac cycle, in the diastolic phase, the ventricles fill. As they fill, they become enlarged and the myocytes stretch, which translates to potential energy for contraction. Generally, the strength of the ventricular contraction is based on the amount of stretch that is achieved during diastole. This physiologic principle, known as the Frank-Starling law of the heart, is the essence of how blood is circulated through the vascular system (Widmaier, Raff, Strang, 2014). Ventricular filling influences the force of ventricular contraction because the force of the ventricular contraction is based on the amount of stretch that has occurred during filling. This principal works well until the ventricles are consistently over-stretched or damaged in some way. Once that point is reached, the ventricles no longer contract as forcefully as they once did no matter how large the stretch load is (Ashrafian, Williams, & Frenneux, 2008). Additionally, the neurohormonal system releases higher amounts of catecholamines in an effort to stimulate the failing heart (Widmaier et al, 2014). As seen in Figure 1, this continuous stimulation often leads to structural remodeling of the ventricle to include misshaping and hypertrophy, both of which lead to worsening pump effectiveness (Ashrafian et al.).

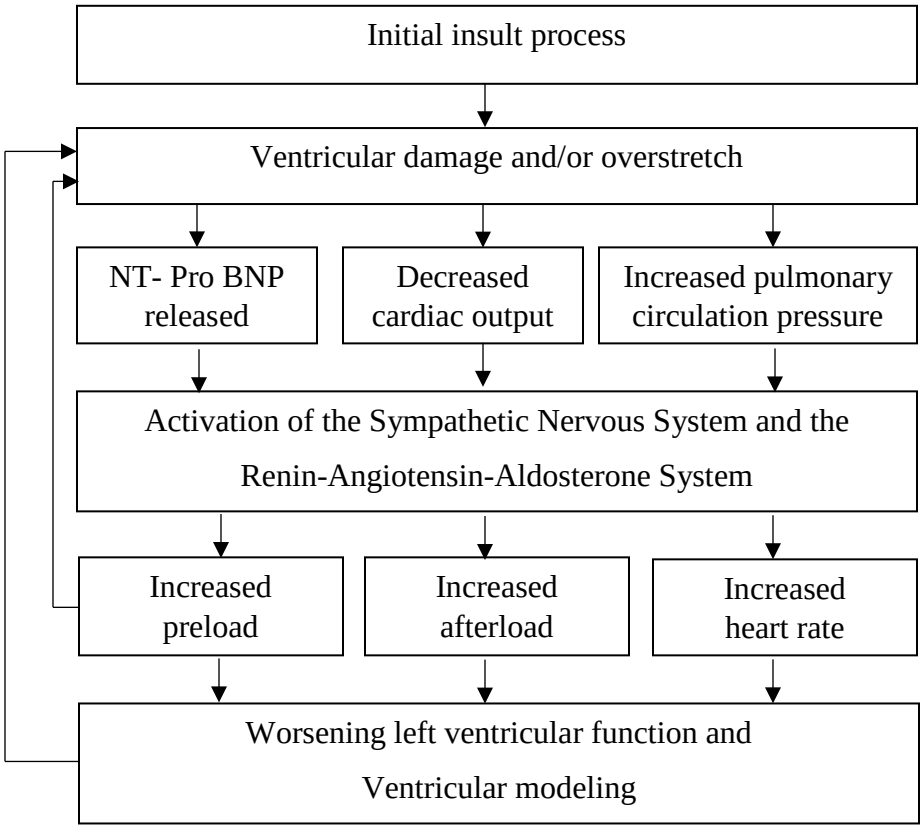

Figure 1. Pathophysiology of Systolic Heart Failure

Current Methods for Predicting Prognosis, Assessing Treatment Efficacy and Symptom Management, and Assessing Functional Capacity

Cardiac output

Heart Failure is a syndrome that occurs when the heart is no longer able to generate enough cardiac output to meet the needs of the tissues. Cardiac output is the amount of blood pumped by the heart in one minute. It is the product of heart rate (HR) and stroke volume (SV) (Q= HR × SV) (Widmaier et al., 2014). Stroke volume is the difference between end-diastolic volume (EDV) and end-systolic volume (ESV) (SV =

EDV – ESV) (Widmaier et al., 2014). The human heart beats 60 – 80 times per minute and is under constant control by the neurohormonal regulation. During exercise, the heart is stimulated to beat faster which, under normal circumstances, helps to increase Q.

End-diastolic volume, a key component in stroke volume, is influenced by venous return to the heart or preload. Cardiac muscle tissue stretches in response to diastolic filling and increased preload increases stretch which ultimately increases the force of the contraction. Again, under normal circumstances, increased filling would increase Q. In systolic HF, the cardiac muscle tissue is no longer able to generate a contraction of appropriate force. Less blood is pumped during systole which leaves a larger amount of blood in the ventricles or a larger end-systolic volume. A larger end-systolic volume means that less blood is able to enter the ventricles during diastole and blood "backs up" in the systemic circulation. In the lungs, the "backup" causes pulmonary congestion which makes diffusion of gases less efficient. It also increases dead space in the lungs.

Peak cardiac output as a prognostic measurement. Currently, the gold standard for measuring Q is thermodilution via pulmonary artery catheterization. The procedure is highly invasive, has multiple associated risks, and is generally performed in an intensive care setting. Thus, surrogate measurements for prognosis, evaluation of treatment efficacy, and assessment of functional capacity include echocardiography, measurements obtained at peak or maximal exercise capacity, and the six-minute walk test distance are used clinically and in research (Yancy et al., 2013).

Although VO_{2peak} has been used as a surrogate measurement for peak Q, there have been concerns that VO_{2peak} does not accurately reflect Q_{peak}. McCole, Davis, & Fueger (2000) studied nine healthy, young participants and found that participants had a

greater maximum Q on a six-minute maximal exercise test than on a twelve-minute maximal exercise test but the maximum VO_2 was similar for both exercise tests. Wilson, Rayos, Yeoh, and Gothard (1995) studied 64 participants who were undergoing evaluation for heart transplant secondary to severe HF and found that more than half of the participants who had a significantly reduced VO_{2peak} had only a mild or moderate reduction in Q_{peak}. The investigators attributed the difference to two causes: skeletal deconditioning and participant motivation during the exercise test. Cardiac Output is a function of stroke volume and heart rate and so would not be affected by skeletal deconditioning in the same way that VO_{2peak} may be.

Most interestingly, Chomsky et al. (1996) studied 185 participants with HF who had been referred for transplantation and compared Q_{peak} to VO_{2preak} as a predictor for one-year survival. Q_{peak} was a more powerful predictor of survival than VO_{2peak} (risk ratio: 4.3, $p< .0009$; risk ratio: 3.3, $p < .001$ respectively). Chomsky and his team also described skeletal deconditioning and patient motivation as factors contributing to the differences between the two variables. Additionally, they described body composition (obesity) as a cause. Chomsky et al. measured Q_{peak} via pulmonary artery catheterization which is highly invasive and requires specialized monitoring and care.

Throughout the last forty years, scientists have worked to measure Q_{peak} noninvasively during exercise testing. Most of these techniques involve rebreathing a mixture of some type of insoluble gas combined with a soluble gas. The soluble gas is dissolved in the capillaries of the lung which is measured continuously by a gas analyzer. Pulmonary blood flow is equal to Q and is measured by the rate of soluble gas dissolving in the pulmonary capillaries (Sackner, Greeneltch, Heiman, Epstein, Atkin, 1975).

Traditionally, variations of this method have been tried but not adopted clinically because of the expertise required to perform the testing and frequent calibrations needed. Additionally, some rebreathing techniques require that the patient learn a specific pattern of breathing which may interfere with the normal breathing of intense exercise (need source here). Lastly, rebreathing occasionally caused a buildup of carbon dioxide which is uncomfortable for the patient and may alter results.

Physiologists at the University of Minnesota and Mayo Clinic refined a technique which does not require rebreathing of the gas mixture and therefore eliminated the problem of carbon dioxide buildup and patients are able to breathe normally (Johnson, Beck, Proctor, Miller, Dietz, Joyner, 2000). The acetylene washin method is available to researchers at the University of Minnesota and has been compared to thermodilution in anesthetized dogs (Gan, Nishi, Chin, Slutsky, 1993), compared to rebreathing techniques in humans (Nielsen, Hansen, Gronlund, 1994; Stout, Wessel, Paul, 1975) and compared to thermodilution in exercising humans (Johnson et al. 2000).

Echocardiography

The 2013 ACCF/AHA Guideline for the Management of Heart Failure (Yancy et al. 2013) recommends a thorough history and physical examination and echocardiography as a part of the initial evaluation of the patient with HF, and serially in patients who have received treatment as a Class I recommendation (level of evidence: C; expert consensus opinion, case studies, or standards of care). Serial echocardiography is performed, among other reasons, to assess and monitor cardiac structure and function, however it is not useful for prognostication and often it does not correlate with the patient's functional status (Williams et al. 2004).

Standard measurements obtained during exercise

***Peak oxygen consumption*.** Oxygen consumption (VO_2) is calculated by the Fick equation: VO_2 is the product of Q and the difference of oxygen (O_2) content between systemic arteries (C_a) and systemic veins (C_v) [$VO_2 = (Q – C_a) \times (Q - C_v)$] (Widmaier et al., 2014). In HF, the ventricles' inability to contract effectively will cause a reduction in Q. Additionally, there is often a diminished heart rate response, which is augmented with beta adrenergic receptor antagonist medications that are used to offset remodeling. Both of these factors decrease cardiac output; a key component in the Fick equation. During exercise, the uptake of oxygen increases. VO_{2peak} is also influenced by vascular function, arteriovenous oxygen difference, and how well skeletal muscles utilize oxygen. A VO_{2peak} value greater than 20 ml/kg/mn is considered normal for patients without cardiovascular disease and traditionally a VO_{2peak} less than or equal to 14 mL/kg/min in patients with HF is considered an indication for consideration of cardiac transplantation (Mancini, Eisen, Kussmaul, Mill, Edmunds, Wilson, 1991).

***Ventilatory Efficiency*.** Ventilatory efficiency is the amount of ventilation needed to eliminate the carbon dioxide in the lungs (Mancini, et al., 1991). The pathophysiology of exercise ventilatory inefficiency is not well-understood however, it is known that the VE/VCO_2 slope is affected by the amount of carbon dioxide produced, the ratio of dead space to tidal volume of the lung, and the partial pressure of arterial carbon dioxide (Tuminello, Guazzi, Lancellotti, & Pierard, 2007). Pulmonary congestion caused by the decreased cardiac output in HF can increase the amount of dead space in the lung. In general, the risk for patient mortality is higher when the VE/VCO_2 slope value is 34 or greater (Gibelin et al 2012).

Prognostic ability of peak oxygen consumption and ventilatory efficiency.

Because thermodilution is impractical, VO_{2peak} obtained during CPX has come to be used as a surrogate measurement for cardiac output. Another measurement obtained during CPX that has shown to be highly prognostic is the VE/VCO_2 slope. Both of these measurements have been shown to be powerful prognostic indicators. In a meta-analysis of 19 articles including 7,319 participants, Cahalin et al. (2013) found that the pooled diagnostic odds ratio for death, heart transplantation, implantation of a left ventricular assist device, or myoplasty for VO_{2peak} was 4.10 (95% CI: 3.16-5.330) with a high level of heterogeneity (Cochran-Q 60.57, I^2 70.3%). Cahalin et al. (2013) also reviewed 15 articles on the VE/VCO_2 slope for a total of 5,044 participants and calculated the pooled diagnostic odds ratio for the previously mentioned endpoints as 5.40 (94% CI: 4.17-6.99) with a modest level of heterogeneity (Cochran-Q statistic 26.22, I^2 46.6%). Swank et al. (2012) had 1620 participants with systolic HF perform CPX at baseline and after three months of unsupervised exercise training. The investigators found that every 6% increase in VO_{2peak} was associated with a 5% lower risk of the primary end point of time to all-cause mortality or all-cause hospitalization (hazard ratio= 0.95; CI= 0.93-0.98; $p <$ 0.001), a 4% lower risk of the secondary end point of time to cardiovascular death or cardiovascular hospitalization (hazard ratio= 0.96; CI= 0.94- 0.99; $p < 0.001$), an 8% lower risk of cardiovascular mortality or hospitalization for HF (hazard ratio= 0.92; CI= 0.88-0.96; $p < 0.001$) and a 7% lower all-cause mortality (hazard ratio= 0.93; CI= 0.90-0.97; $p < 0.001$).

Clearly, these two measurements during CPX are highly valuable; Cahalin et al. recommended that CPX be included in the clinical assessment of patients with HF.

However, CPX requires expensive specialized equipment, equipment calibration and upkeep, and staff training and is often not utilized for the standard management of HF. Additionally, older patients with HF often are not physically able to perform exercise testing.

Usefulness of peak oxygen consumption and ventilatory efficiency in assessing therapeutic efficacy. Traditionally, CPX has been used in the evaluation of patients with HF to determine candidacy for transplant or to evaluate when symptoms of HF do not seem to match the objective findings in HF (Yancy, et al. 2013). Arena, Myers, and Guazzi (2008) performed an evidence-based review and cited numerous intervention studies, to include pharmacological, exercise training, and inspiratory muscle training which used measurements of peak exercise capacity as an endpoint. Arena et al. (2011) reviewed articles that included these two measurements to assess therapeutic efficacy and found that both VO_{2peak} and the VE/VCO_2 slope were able to detect improvements from pharmacological interventions to include inhibition of the renin-angiotensin system and beta-adrenergic receptor blockade. They recommended that CPX should be used as part of the overall evaluation for patients with HF who are not yet at the point of being considered for transplant.

VO_{2peak} is not part of the selection criteria for cardiac resynchronization therapy but is part of the selection criteria for left ventricular assist devices and transplant (Lietz & Miller, 2009). The European Association for Cardiovascular Prevention and Rehabilitation and the American Heart Association released a joint scientific statement in 2012 which recommended expanding the use of CPX in patients with HF, but did not signify a level of recommendation (Guazzi et al, 2012). Despite these findings and

recommendations, the use of CPX often is not a standard part of clinical evaluation of patients with HF, most likely because of the costly specialized equipment needed and the specialized training for staff. Also, older patients with HF may not physically be able to perform exercise testing. Therefore, resting measurements would be beneficial clinically; especially for older patients.

Six Minute Walk Test. The 6MWT is simply a measurement of how far a patient can walk on a flat surface in six minutes. The test is an inclusive assessment of exercise capacity and as such does not provide individual information on any one component. Normal values for the 6MWT distance have only recently been established. Casanova et al. (2011) conducted a study of 444 healthy participants from seven countries and found that the mean distance walked was 570 $\pm$ 90 meters and males walked on average 30 meters more than females. The test is limited by age and comorbidities. The landmark SOLVD study established that walking less than 300 meters during the 6MWT has been shown to be predictive of death, all-cause hospitalization, and hospitalization for HF (Bittner, et al., 1993).

The Six-minute walk test is a measurement of exercise tolerance that is comprised of multiple factors that may influence the ability to exercise. The test is influenced by the patient's ability to ventilate and perfuse tissues, metabolize oxygen in the muscles, and the patient's muscle strength and conditioning (Pichurko, 2012). The test has been used for more than 40 years in the evaluation of exercise tolerance in multiple disease processes, most notably heart and lung diseases. Recently, Forman et al. (2012) established the prognostic value of the 6MWT in its own right. In a study composed of 2,054 participants with systolic HF, the investigators compared the prognostic values of

the 6MWT, VO_{2peak}, and the VE/VCO_2 slope and found that the 6MWT and measures of peak exercise capacity performed similarly in predicting all-cause hospitalization/mortality and all-cause mortality.

Validity of the Six Minute Walk Test as compared to peak oxygen consumption and ventilatory efficiency. Forman et al. calculated the concordance indices (C-indices) of the 6MWT, VO_{2peak}, and the VE/VCO_2 slope to determine the ratio of pairs of participants who had differing outcomes, where the participant who actually experienced the adverse outcome had a higher predicted probability of the outcome happening. The C-indices for the 6MWT were 0.58 (95% CI: 0.57- 0.60) and 0.65 (95% CI: 0.62- 0.68) respectively; and the C-indices for VO_{2peak} were 0.61 (95% CI: 0.59- 0.62) and 0.68 (95% CI: 0.65- 0.71) respectively. The C-indices for the VE/VCO_2 slope were 0.56 (95% CI: 0.55- 0.58) and 0.65 (95% CI: 0.61- 0.68) respectively. Although the 6MWT does not require specialized equipment, it does require staff training and space to perform the test. It is frequently used in research, but often clinically it is not commonly used for the management of HF.

Proposed Resting Measurements for Predicting Prognosis, Assessing Treatment Efficacy and Symptom Management, and Assessing Functional Capacity

During the past decade, investigators have found relationships between NT-Pro BNP and NYHA classification with VO_{2peak} (Williams et al., 2005; Kallistratos, Dritsas, Laoutaris, & Cokkinos, 2007). Additionally, in the recent past research groups have investigated inspiratory capacity and its correlation to VO_{2peak}.

N-terminal prohormone B-type natriuretic peptide. When cardiac myocytes experience pressure or volume overload which causes excessive stretching, B-type

natriuretic peptide (BNP) and NT-Pro BNP are secreted. Neither measurement is specific to HF however, higher levels of both are likely to be caused by HF. Clinically, there is very little difference between the values, however NT-Pro BNP is stable at room temperature for a longer period of time. In a study of 100 patients with HF, Kallistratos et al. (2007) found a significant correlation between VO_{2peak} and NT-Pro BNP (r =0.77, p < 0.001). Williams et al. (2005) studied 86 patients with HF and found significant correlations between VO_{2peak} and NT-pro BNP levels (r =0.64, p < 0.001) and NYHA class (r =0.76, p <0.001). In multivariate regression modelling to predict a VO_{2peak} value of less than 20 ml/kg/min, NYHA and log NT-pro BNP accounted for 61.9% of variance (p <0.0005.) Passino et al. (2006) studied 154 patients with HF and found that NT-pro BNP correlated with VO_{2peak} (r =0.53, p <0.001) and the VE/VCO2 slope (r =0.58, p <0.001). These three studies, with a total of 340 patients with HF, show a strong correlation between NT-pro BNP levels and VO_{2peak}. Williams et al. were able to account for 61.9% of variance in VO_{2peak} when NT-Pro BNP levels were combined with NYHA classification, and Passino et al. included a correlation with the VE/VCO2 slope. Based on these results, it is reasonable to investigate the relationship of NT-pro BNP to VO_{2peak}, and the VE/VCO_2 slope, to see if it adds value to a model for prediction.

New York Heart Association classification. The NYHA functional classification system was developed in an era when medical imaging was rudimentary to categorize patients with HF based on functional limitation. The classes progress from Class I, mild with no functional limitation, to class IV; severe, unable to perform any activity of daily living without symptoms. The classification is determined by a cardiologist or clinician with experience in HF after the history and physical examination

has been done. Researchers have investigated the relationship between VO_{2peak} and NYHA classification for some time (Williams et al., 2005).

In addition to the correlation between VO_{2peak} and NYHA found by Kallistratos et al. (2007), Meyer, Karamanoglu, Ehsani, and Kovacs (2004) examined the role of left ventricular (LV) chamber stiffness and NYHA classification as a factor in VO_{2peak} during exercise testing in 41 patients with HF. They found that LV chamber stiffness accounted for 55% (r=-0.75, p<0.001) and NYHA classification accounted for 43% (r=-0.67, p<0.001) of variance in VO_{2peak}. Davies, Francis, Piepoli, Scott, Ponikowski, & Coats (2000) studied 50 older patients with HF (75.9 $\pm$ 4.5 years) and upon multivariate Cox proportional hazard analysis found that NYHA classification was a predictor of two-year mortality (X^2 6.57, p <0,01). These three studies, for a total of 177 patients, show a relationship between VO_{2peak} and NYHA classification. Additionally, in the study by Davies et al., the patients had a mean age of 76 years old and NYHA was predictive of mortality. Thus, the relationship between NYHA classification, VO_{2peak}, the VE/VCO_2 slope, and 6MWT distance will be investigated further in this study.

Inspiratory capacity. Inspiratory capacity is the maximal inspiration possible after normal exhalation and can be a component of pulmonary function testing. The relationship of exercise capacity and inspiratory capacity has been investigated in patients with chronic obstructive pulmonary disease (COPD) and cystic fibrosis.

Diaz et al. (2000) investigated the relationship of maximal oxygen consumption to inspiratory capacity and other measures in 52 patients with COPD and found that inspiratory capacity and forced vital capacity were the only independent predictor of maximal oxygen consumption (r =-0.54, -0.55 respectively, p <0.0001). Perpati et al.

(2010) investigated the relationship of VO_{2peak} to inspiratory capacity and other resting measures in 18 patients with cystic fibrosis and 11 healthy patients and found that inspiratory capacity was the only independent predictor of VO_{2peak} ($r = 0.67$, $p < 0.007$). Nanas et al. (2003) investigated the role of resting pulmonary function as a predictor of exercise capacity in 51 patients with HF. The researchers found that inspiratory capacity was the only independent predictor of VO_{2peak} ($r = 0.71$, $p < 0.0001$) and explained 50% of the variance in VO_{2peak}. Morris et al. (2007) studied the relationship between lung-lung circulation time (LLCT) and inspiratory capacity and VO_{2peak} in 30 patients with HF and found that both LLCT and inspiratory capacity were univariate correlates oVO_{2peak}, but on multiple regression LLCT was the only independent predictor of peak VO_{2peak} ($r = -0.75$, $p < 0.001$), and explained 54% of the variance in VO_{2peak}. It is possible that 30 participants was too low a number to accurately perform stepwise regression or that inspiratory capacity and LLCT are highly correlated.

Although there have not been studies published on the correlation between the VE/VCO_2 slope and inspiratory capacity, it is reasonable that there should be a correlation between these two measurements. The increased VE/VCO_2 slope in patients with HF is made up of two mechanisms, increased physiologic dead space and alveolar hyperinflation (Robertson, 2011). Physiologic dead space is made up of two components, air that remains in the airways (does not reach the alveoli) and air that reaches the alveoli but does not perfuse to the bloodstream. Perfusion may be limited for a variety of reasons, but in HF it is typically blocked acutely because of pulmonary edema as a result of increased hydrostatic pressure due to volume overload.

The pulmonary capillary wedge pressure is a highly invasive measurement which is done during thermodilution via pulmonary artery catheterization and is used to estimate left atrial pressure. As heart failure progresses, left atrial pressure increases due to worsening stroke volume. Left atrial pressure directly affects the pulmonary vasculature since it is by nature highly compliant. Pulmonary edema is thought to occur when the pulmonary capillary wedge pressure is greater than 20mmHg (Klabunde, 2015). Increased left atrial pressure is a direct indication of increased pulmonary capillary hydrostatic pressure. Increased pulmonary hydrostatic pressure causes pulmonary edema and decreased gas diffusion capacity. Pulmonary edema increases dead space within the lungs which directly decreases inspiratory capacity. Since inspiratory capacity measures the maximal possible inspiration, it is decreased when there is increased physiologic dead space in the lungs. Figure 1 depicts the relationship between HF, volume overload, and inspiratory capacity. It is this mechanism that makes inspiratory capacity potentially useful for measurement in clinic and eventually in the patient's home.

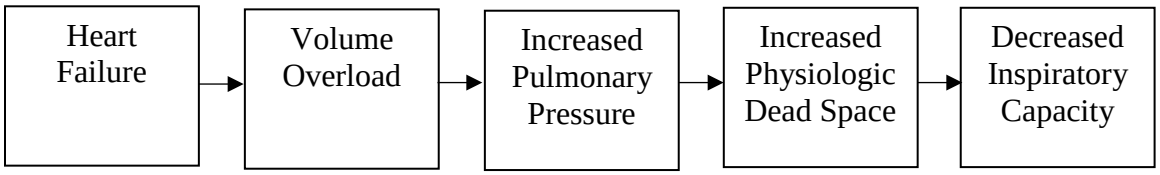

Figure 2. Relationship between heart failure, volume overload, and inspiratory capacity

In a study with 40 participants with HF, Ries et al. found a correlation between pulmonary capillary wedge pressure and total lung capacity (r= -0.5, p<0.01) (Ries, Gregoratos, Friedman, &Clausen, 1986). Total lung capacity is largely affected by the amount of physiologic dead space in the lungs, which is also measured by inspiratory

capacity. Nanas et al. (2003) also found a weak correlation between pulmonary capillary wedge pressure and inspiratory capacity (r= -0.34, p< 0.02). In a study of 57 patients with HF, Reindl et al. (1998) found that pulmonary artery pressure and pulmonary capillary wedge pressure correlated with the VE/VCO_2 slope (r= 0.69, p< 0.001; r= 0.52, p< 0.001 respectively). These three studies, for a total of 148 participants, give basis for seeking a correlation between inspiratory capacity and the VE/VCO_2 slope.

Inspiratory capacity is a resting measurements that can be performed by patients who are not able to ambulate well. Often, older patients with HF have multiple comorbidities that limit performing CPX, the 6MWT, or both. Although there are only a few studies of inspiratory capacity, their correlation coefficients have been relative high and if there is significant correlation between VO_{2peak}, the VE/VCO_2 slope, and 6MWT distance to inspiratory capacity, it will add value to for monitoring treatment efficacy and symptom management in any patient that is unable to ambulate well.

Gap

VO_{2peak}, the VE/VCO_2 slope, and 6MWT distance have been shown to be powerful prognostic indicators and useful in monitoring the efficacy of therapeutic management in HF. Despite the strong evidence behind these measurements, CPX is not routinely performed clinically and generally is used for the evaluation for transplant or when symptoms do not match objective findings. It is possible that CPX is not performed because it requires specialized equipment and specialized training for staff. Additionally, there is a portion of the population of patients with HF that are unable to perform exercise testing. The 6MWT is also underutilized, possibly because the test requires some staff training and a physical location to perform the test. Therefore, clinically useful prognostic

indicators are needed and NT-Pro BNP, NYHA classification, and inspiratory capacity have the potential to provide that information. If these resting values could be shown to correlate with the established powerful prognostic predictors and assessments of therapeutic efficacy, this would be incredibly valuable to the clinician in an outpatient clinical setting and may be useful for research.

Chapter 3 Research Method

Design

This was a correlational study designed to examine the relationships of measurements that can be obtained during a resting state with measurements that must be obtained while the patient is exercising. The study took place in the Exercise and Applied Physiology Laboratory located in the School of Nursing at the University of Minnesota.

Specific Aims

The specific aims of this research study were to:

1. To investigate the relationship of Q_{peak}, VO_{2peak}, the VE/VCO_2 slope, and/or 6MWT distance with NT-pro BNP, NYHA classification, and inspiratory capacity, in older adults with HF.

   Hypothesis 1: There is a relationship between Q_{peak}, $VO2_{peak}$, the VE/VCO_2 slope, and/or 6MWT distance with NT-pro BNP, NYHA classification, and inspiratory capacity.

2. To explore possible models of predicting peak Q_{peak}, VO_2, the VE/VCO_2 slope, and/or 6MWT distance from NT-pro BNP, NYHA classification, and inspiratory capacity in older adults with HF.

Study Population

Setting

Study participants were recruited via use of the Clinical Data Repository within the University of Minnesota's Clinical and Translational Science Institute (CTSI). The Clinical Data Repository contains the electronic health records of more than two million patients who obtain health care in the Fairview-University system and is available to

investigators. A nurse informaticist employed by CTSI worked with the principal investigator to identify patients who met the study inclusion and exclusion criteria. Once patients were identified, recruitment letters which were approved by the University of Minnesota Institutional Review Board were sent from the University of Minnesota CTSI to eligible participants (Appendix G). Participants who were interested in the study were encouraged to contact the investigator for more information about the study.

Sample size

Considering that correlations would be determined using multiple regression analysis, the sample size is based on the results of Knofczynski & Mundfrom (2007), who used a Monte Carlo simulation to determine minimum sample sizes for varying numbers of predictor variables in multiple regression analysis. In order for the regression of three predictor variables to have a good prediction level with the squared population multiple correlation coefficient set at .50, the study needed 45 participants. Because not all older patients with HF may be able to complete a CPX, we attempted to recruit 55 participants with an expected possible attrition rate of 20%.

Sample

We recruited English-speaking adults who were at least 65 years old with HF who had an ejection fraction of 40% or less at time of diagnosis. Table 1 describes inclusion and exclusion criteria.

Table 1

Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Age greater than or equal to 65 years old • Ability to read and write in English • Ejection fraction less than or equal to 40% per echo or other imaging at time of diagnosis • NYHA classification recorded in the last 3 months • Stable HF; no event or hospitalization in the last three months	• Diagnosed chronic obstructive pulmonary disease • Comorbidity that limits treadmill exercise testing • Left-ventricular assist device in situ • Cardiac resynchronization therapy in situ for less than one year • EKG changes consistent with ischemia induced by exercise

NYHA = New York Heart Association, HF = heart failure, EKG = electrocardiogram

Variables and Measurements

Demographic and health information. Demographic and health information was obtained per chart review and verified by the participant. Data collected included past medical history, current medications, ejection fraction, NYHA classification, coronary angiography or other tests relating to the possibility of coronary ischemia during exercise if available, and prior results of exercise testing if available (Appendix M). Additionally, information on age, gender, and ethnicity was collected.

Cardiopulmonary exercise testing

After familiarization with the procedure and verbal encouragement to exercise to the point of exhaustion, participants performed symptom-limited exercise testing using a modified Bruce protocol (Appendix P). Treadmill exercise testing was overseen by a board-certified cardiologist who was on-site. Participant's electrocardiograms were continuously monitored by trained personnel and their blood pressures were monitored and recorded every two minutes by sphygmomanometry. Gas exchange was measured by

the participant breathing through a low- resistance valve with nose clamp. VO_2 and the respiratory exchange ratio were measured on a breath-by-breath basis and averaged over 15-second intervals. The highest average VO_2 was recorded as the VO_{2peak}. Cardiac output was calculated via the metabolic cart's software based on breath-by-breath analysis once adequate acetylene washin was obtained (Johnson, Beck, Proctor, Miller, Dietz, Joyner, 2000). The highest Q was recorded as the Q_{peak}. The VE/VCO_2 slope was calculated via the metabolic cart's software by formulating a graph of ventilation and carbon dioxide production and fitting a linear regression equation to the model. The lowest VE/VCO_2 slope was used for model formulation.

Six Minute Walk Test. Participants received verbal instruction on the test as directed by the American Thoracic Society (2002) protocol (Appendix Q). Participants were then be directed to walk on a marked course in the hall with the researcher or trained staff observing. The distance walked in six minutes was recorded in meters.

Predictor variables.

N-Terminal prohormone B-type natriuretic peptide measurement and New York Heart Association functional class. After initial check-in, venipuncture was performed and a blood sample was collected into plastic tubes containing ethylene-diamintetra-acetate, placed on ice, and transported to the laboratory for analysis. The participant's most recent NYHA classification was obtained from chart review.

Inspiratory capacity. The procedure for obtaining inspiratory capacity was explained to each participant and demonstrated by the physiology lab staff (Appendix O). As recommended by the ATS (2005), participants were relaxed in a seated position and breathed regularly through a mouthpiece until they had reached a steady end-expiratory

volume. After normal end-exhalation, the participants were directed to take as big a breath in as possible and hold it for three seconds. Participants did this at least three times and up to five times per ATS protocol. Participants were seated during the testing in order to be consistent with Nanas et al. (2003). The average of three attempts which were within 10% of each other was used.

Procedure

Potential participants who had received a letter from the University of Minnesota and opted to contact the principal investigator (PI), underwent initial telephone screening to ensure they met study inclusion criteria (Appendices I and J). The PI then arranged to meet with the potential participant. During the meeting the PI explained the study, including risks and benefits of study participation, assessed the participant's understanding of the study (Appendix J), and if potential participants continued to be interested in taking part in the study, had them sign an Informed Consent document and Health Insurance Portability and Accountability Act (HIPAA) document (Appendices K and L). The PI acted as the witness for the signing of the informed consent. During this meeting, the PI and the participant scheduled a testing date and time.

Prior to the testing dates, the PI reviewed the participant's medical records and pertinent data were recorded. On the day of exercise testing, participants underwent venipuncture in the phlebotomy lab and then walked to the School of Nursing Exercise Physiology lab accompanied by the researcher or research assistant. Once in the physiology lab, participants had their height and weight measured, rested as needed for up to 15 minutes, and then performed spirometry measurement following the American Thoracic Society (ATS) protocol (Miller et al.) After 15 minutes of rest, participants

performed cardiopulmonary exercise testing per protocol, during which time VO_2 peak, the VE/VCO_2 slope, and cardiac output measurements were recorded. The participants rested again for at least 45 minutes. Once this resting period was finished, they performed the 6MWT following the ATS 6MWT protocol (ATS, 2002). The Exercise and Applied Physiology Laboratory had an established protocol for emergencies (Appendix N).

Diabetic population. Due to the increased risk of cardiopulmonary exercise testing to participants with diabetes, these participants were asked to bring their glucometers with them on the day of testing. Per the School of Nursing Physiology lab protocol, participants with diabetes checked their blood glucose level prior to CPX. If their blood glucose level was less than 130 mg/dl, then participants were provided with a source of carbohydrates to consume. Participant's blood glucose levels were then rechecked after a period of 10 minutes. This was repeated as needed until their blood glucose level was at least 130 mg/dl to ensure that they were safe to perform vigorous physical activity. Participants with diabetes whose blood glucose was higher than 300 mg/dl were not allowed to perform CPX and were referred to their primary care provider.

Ethical Considerations

The research prospectus was reviewed and approved by the author's doctoral committee. Additionally, it was approved by the Institutional Review Board of the University of Minnesota (Appendices A – F). Participation in the study was completely voluntary and participants had the voluntary nature of the study explained to them prior to consenting to the study. Additionally, participants were told that they have the right to withdraw at any point during the study.

Vulnerable and underrepresented populations. The investigation involved participants who were at least 65 years of age. Although this population is not considered a "vulnerable population" as defined by the National Institute of Health, it is an underrepresented group in research (NIH, 2009). It is well-known that older persons are often excluded from Randomized, controlled trials, commonly due to multiple comorbidities or frailty (Heiat, Gross, & Krumholz, 2002; Masoudi et al., 2003). This study intentionally included the age group that is likely to be diagnosed with HF.

Protection against Potential Risks

In exercise testing, there are certain risks. It is possible for participants with undiagnosed coronary artery disease to develop ischemia during exercise testing. Additionally, it may be possible for a participant to feel dizzy, lightheaded, or fall during exercise testing. In this population, the participants were already diagnosed with HF. Upon initial diagnosis of HF, it is a standard of care to evaluate for coronary artery disease, since coronary artery disease is a leading cause of HF (Yancey et al. 2013). The participants underwent continuous electrocardiogram monitoring throughout the CPX, and blood pressure measurement occurred every two minutes. Chest pain, dizziness, and electrocardiogram changes consistent with ischemia were indications for immediately discontinuing the CPX. In the event of an emergency, the researcher had a protocol in place to activate the emergency medical system and ensure rapid transport to the Fairview-University emergency department. The CPX was be performed by trained staff under the supervision of a cardiologist.

All potential participants were told that this is a research experiment, had the purpose of the research study explained to them, and were given an explanation of how

participants are recruited (Lo, 2007). Explanations included procedures for venipuncture, chart review of their medical records for the obtainment of verification of diagnosis of HF, NYHA classification, medical history, angiography, and prior stress tests, walking for six minutes with rest if needed, and standard CPX to the point of maximal exercise as able. Additionally, the potential participants had the risks of the procedures explained to them which could include infection from venipuncture and cardiac ischemia as a result of maximal exercise. The risk of infection from venipuncture is low; it was performed by a trained laboratory technician. The risk of ischemia has been addressed previously. The researcher explained how the CPX was supervised, including trained staff, continuous EKG monitoring, and on-site cardiologist supervision.

The potential participants also had the benefits of the research explained to them which included clinical measurements that may be useful for prediction and how well treatments are working. The research study did not have personal benefits for individual participants. Once these steps were completed, potential participants had the opportunity to ask questions and have them answered. Next, when potential participants verbalized understanding of the investigation, the risks and benefits of the research, completed the Assessment of Participant Understanding form (Appendix I), and agreed to participate, they signed a consent form (Appendix J).

Data Security

It is the responsibility of the researcher to ensure confidentiality of data (Lo, 2007). Confidentiality was protected by assigning an identifying number to each participant. Data with identifying markers was collected by hand and stored in a locked office. Only the researcher and her advisor, Dr. Diane Treat-Jacobson, had access to data

with identifying markers. Cleansed data was identified by the participant's assigned number and was stored in the Research Electronic Data Capture (REDCap) cloud storage system accessed via the University of Minnesota's Clinical and Translational Science Institute. The researcher, her advisor, and a University of Minnesota School of Nursing statistician had access to data stored in REDCap. Once the research investigation is completed, data with identifying markers will be destroyed. Non-identifiable data will be stored for two years after the completion of the research.

Chapter 4: Results

Sample

Eligible patients with HF (N=35) were recruited over a period of two years (January 2014 to December 2015) to participate in the study. Of these, four participants had medical events (acute gastrointestinal bleed, cerebral vascular accident, lumbar spine dysplasia, new onset anemia) that occurred after consent was obtained, but prior to exercise testing, that made them ineligible to participate; and three participants failed exercise testing (significant arrhythmia, substantial dyspnea, chest discomfort). Thus, 28 participants completed the study. The results of five participants who underwent testing were excluded due to NT-pro BNP levels which were greater than two standard deviations above the mean. The final number of participants available for study analysis was 23.

Demographics and health data. Participant demographics and medical data for the final sample (N=23) used in the analyses are summarized in Table 2. All of the participants were Caucasian males with a mean age of 73.6 ($\pm$ 4.5) years old. All were classified as having NYHA Cass II HF and the mean left ventricular ejection fraction was 44.5% ($\pm$ 8). In general, the participants were well-managed; 96% were taking beta-adrenergic receptor antagonist (beta-blockers) type medications and 70% were taking either angiotensin-converting enzyme inhibitor type medications or angiotensin receptor blocking type medications which is consistent with the 2013 ACCF/AHA Guideline for the Management of Heart Failure (Albert et al., 2010; Yancy et al., 2013. Half of the participants had a history of either coronary artery disease (52%) or hypertension (38%),

which is most likely normal in this patient population since both diagnoses are risk factors for the development of HF (Yancy et al.). No participants were current smokers.

Table 2

Participant Demographic and Medical Characteristics

	Mean (SD) or n (%)	
Age (years)	73.6	(4.5)
Gender (male)	23	(100%)
Ethnicity		
Caucasian	23	(100%)
NYHA Functional Class		
Class II	23	(100%)
LVEF	44.5	(8)
BMI (kg/m^2)	29.9	(4.2)
Medications		
ARB/ACE-I	23	(100%)
Beta-Blockers	16	(70%)
Diuretics	22	(96%)
Digoxin	11	(48%)
Medical History		
Atrial Fibrillation	1	(4%)
Coronary Artery Disease	12	(52%)
History of Acute Myocardial Infarction	8	(28%)
Hypertension	11	(38%)

NYHA = New York Hear Association, LVEF = Left Ventricular Ejection Fraction, BMI = Body Mass Index, ARB = Angiotensin Receptor Blocker, ACE-I = Angiotensin Converting Enzyme Inhibitor

Resting and exercise measurement values are described in Table 3. The mean inspiratory capacity, 2.9 $\pm$ 0.8 L, was comparable to established lung volume reference values for generally healthy older adults (age 72 $\pm$ 5 years old; inspiratory capacity 2.45 L $\pm$ 0.73) (Garcia-Rio et al., 2009). The mean Q_{peak} was 7.9 $\pm$ 2.4 L/min which is significantly less than normal reference values for maximum Q (25 L/min for healthy, sedentary males), however most reference values have been calculated from a significantly younger population (Sagiv, 2012). Direct measurement of peak or maximum

Q in older adults has not been studied extensively. One group did report a mean Q_{max} of 20 L/min for generally healthy older adult males (age 29-72) (Rodeheffer, et al., 1984). Additionally, there are no established reference values for patients with HF. In this study, the lower mean Q_{peak} was to be expected, considering the nature of HF. As NT-pro BNP is highly individualized, and followed as a trend for each patient, there are no standard reference values.

The mean peak VO_2 was 18.2 $\pm$ 3.8 mL/min/kg. Normal values for VO_{2max} for generally healthy sedentary older adults (65 – 74 years old) are 23.1 $\pm$ 6.3 mL/min/kg (Herdy & Uhlendorf, 2010). Historically, patients with HF with a peak VO_2 of 10 – 14 mL/min/kg have a very poor prognosis and may be listed for cardiac transplant (Mancini et al., 1991). The mean VE/VCO_2 slope was 35.0 $\pm$ 4.6. The normal range for the VE/VCO_2 slope is 20 -30, with 34 generally considered a cut point for poor prognosis (Gibelin, Aldossari, Moceri, & Hugues, 2012). The mean 6MWT distance was 452.3 $\pm$ 63.3 meters. The mean 6MWT distance for generally healthy adults (aged 40- 80 years) is 571 $\pm$ 90 meters (Casanova et al., 2011). Multiple studies have reported an increased mortality rate for patients with HF who walk less than 300 meters during the 6MWT (Bittner et al., 1993, Cahalin, Mathier, Semigran, Dec, & DiSalvo, 1996; Rostagno et al. 2002).

Table 3

Resting and Exercise Values

Resting Measurements	Mean (SD) or n %	
Inspiratory Capacity	2.9	(0.8)
NT-pro BNP (pg/mL)	372.8	(254.6)
NYHA class II (n, %)	23	100%
Exercise Measurements	**Mean (SD)**	
Q_{peak} (L/min)	7.9	(2.4)
VO_{2peak} (mL/min/kg)	18.2	(3.8)
VE/VCO_2 slope	35.0	(4.6)
6MWT (M)	452.3	(63.3)

NT- pro BNP = N-terminal Prohormone Brain Natriuretic Peptide, NYHA = New York Heart Association, Q_{peak} = Peak Cardiac Output, VO_2 peak = Peak Oxygen Consumption, VE/VCO_2 slope = Ventilatory Efficiency

Aim 1: Investigation of the Relationships between Established Measurements and Proposed Measurements

Table 4 displays the correlations between the resting measurements and the exercise measurements. The strongest relationships were between inspiratory capacity and Q_{peak} and between NT-pro BNP and the VE/VCO_2 slope. Additionally, there was a moderate relationship between NT-pro BNP and VO_{2peak} and between inspiratory capacity and VO_{2peak}. All participants in the study were categorized as NYHA functional class II patients. Due to the homogeneity of the variable, NYHA classification was not included in the regression analysis. The 6MWT distance did not correlate with NT-pro BNP or inspiratory capacity. Figures 3 and 4 show the correlation coefficients between the 6MWT distance and NT-pro BNP and mean inspiratory capacity, respectively.

Table 4

Pearson Correlation Coefficients between Peak Cardiac Output, Peak Oxygen Consumption, Ventilatory Efficiency, Six-Minute Walk Test Distance and Inspiratory Capacity and N-terminal Prohormone Brain Natriuretic Peptide.

Resting Measurements	Exercise Measurements			
	Q_{peak} *R (p)*	VO_{2peak} *R (p)*	VE/VCO_2 slope *R (p)*	6MWT distance *R (p)*
NT-Pro BNP	-0.25 (0.25)	-0.47 (<0.03)	0.71 (<0.001)	-.08 (0.73)
Mean Inspiratory Capacity	0.77 (<0.0001)	0.51 (<0.02)	-0.23 (<0.29)	0.0002 (0.98)

Q_{peak} = Peak Cardiac Output, VO_2 peak = Peak Oxygen Consumption, VE/VCO_2 slope = Ventilatory Efficiency, 6MWT = 6-Minute Walk Test, NT- pro BNP = N-terminal Prohormone Brain Natriuretic Peptide

Figures 5, 6, 7, and 8 depict the coefficients of determination between the exercise measurements and the resting measurements where the correlations were found to be statistically significant. NT-pro BNP is able to account for 22% of variance in VO_{2peak} and 50% of variance in the VE/VCO_2 slope. Mean inspiratory capacity is able to account for 59% of variance in Q_{peak} and 26% of variance in VO_{2peak}.

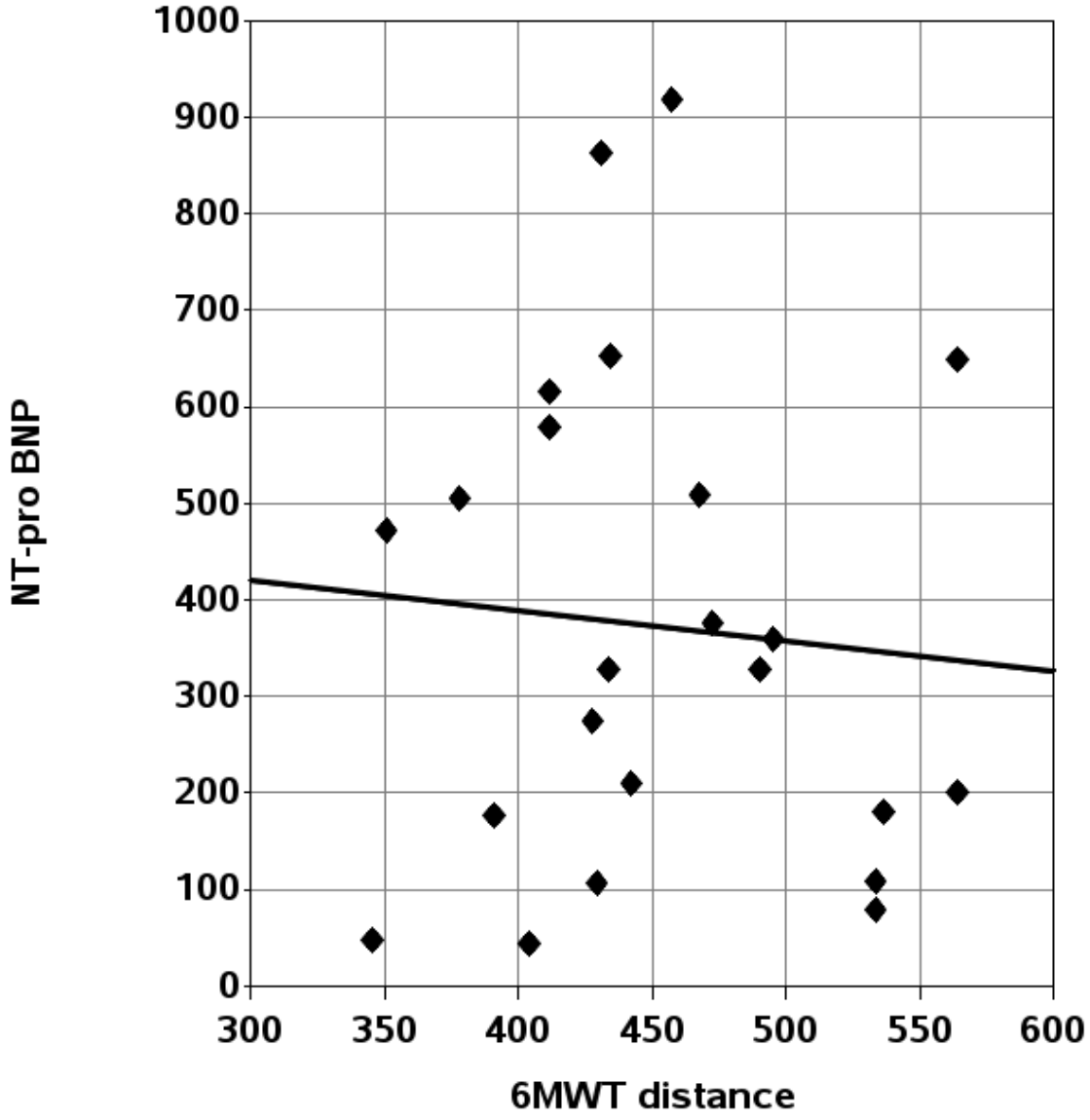

Figure 3. The relationship between N-terminal prohormone brain natriuretic peptide (NT-pro BNP) and Six-Minute Walk Test (6MWT) distance (*R* not statistically significant).

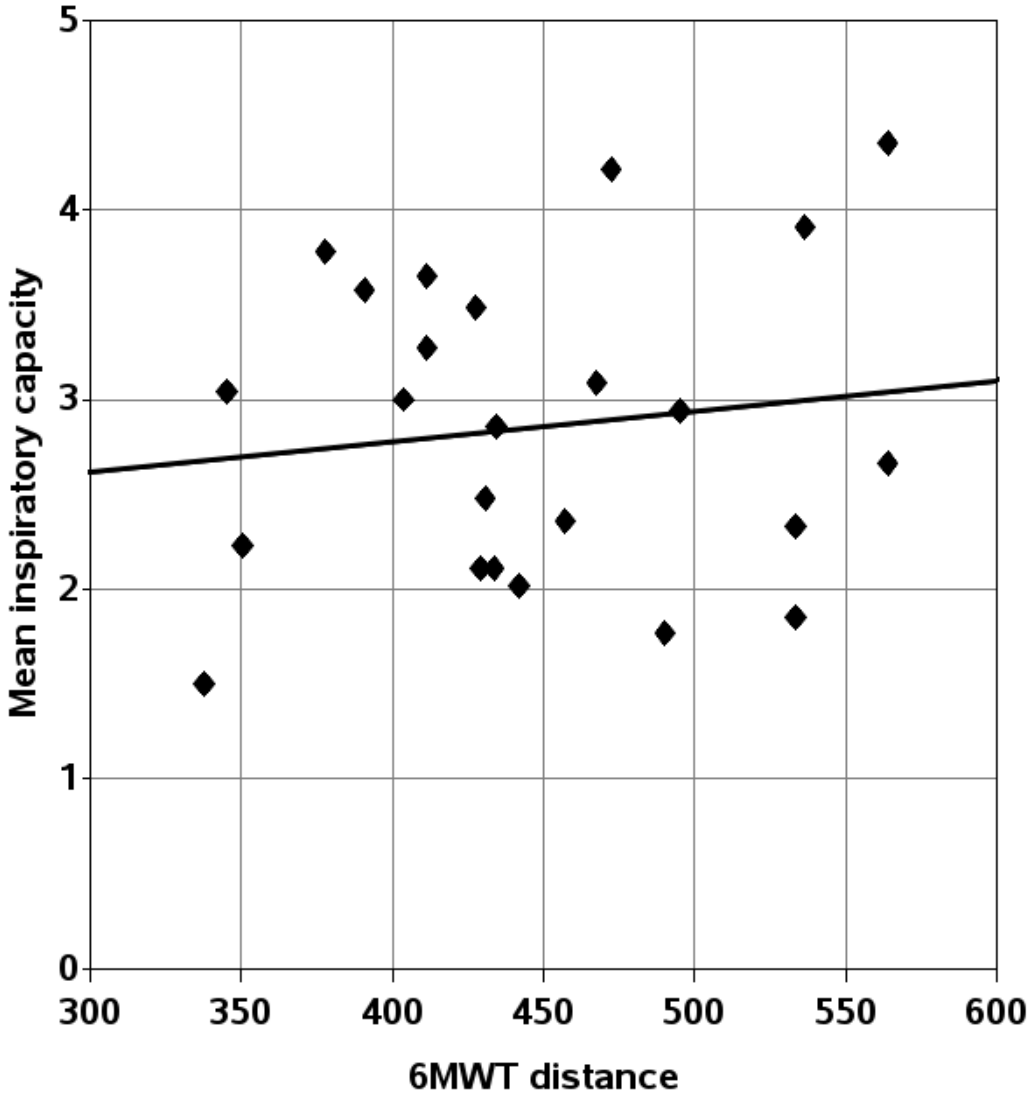

Figure 4. The relationship between mean inspiratory capacity and Six-Minute Walk Test (6MWT) distance (*R* not statistically significant).

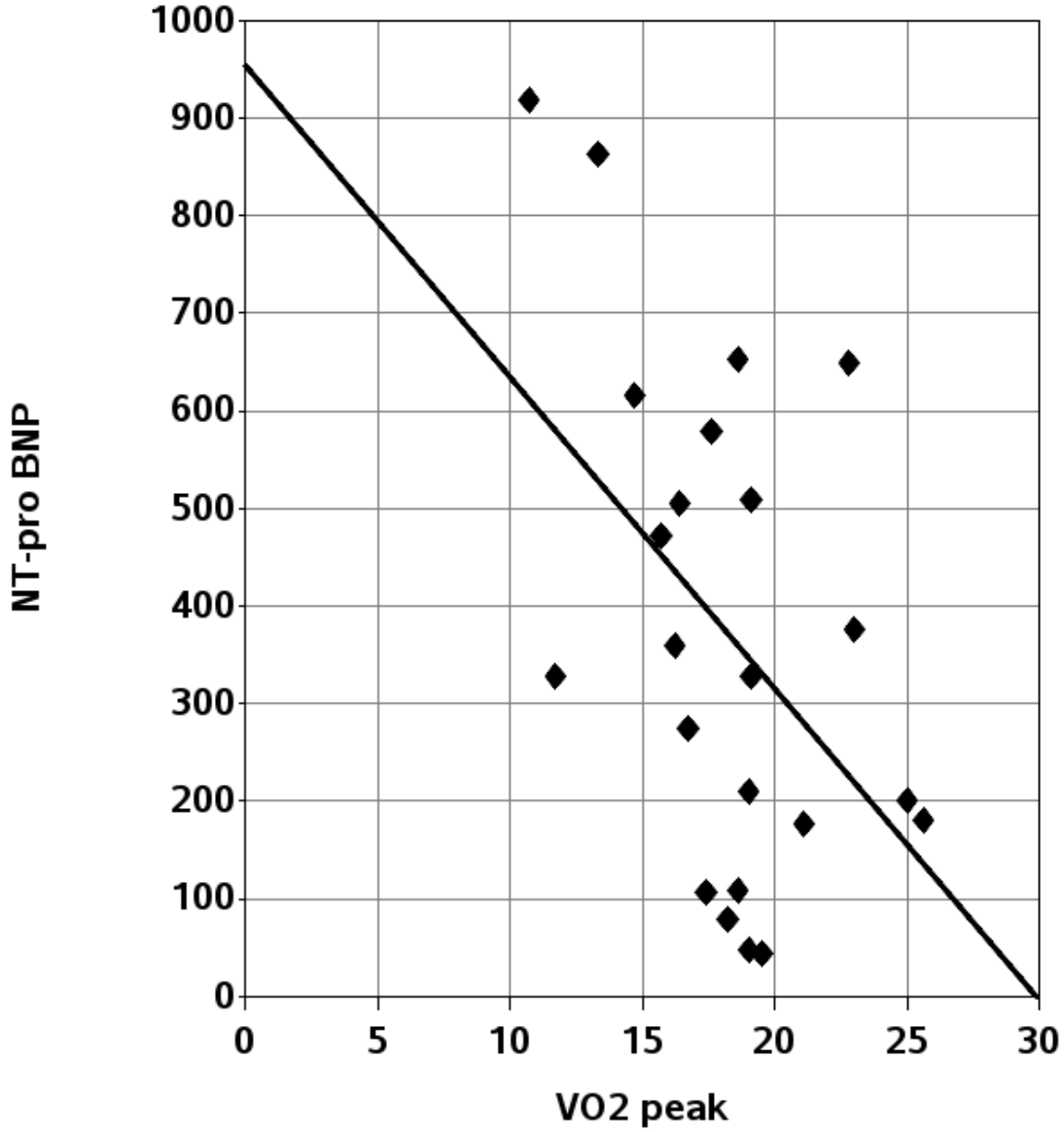

Figure 5. The relationship between N-terminal prohormone brain natriuretic peptide (NT-pro BNP) and peak oxygen consumption (VO_{2peak}). $R^2 = 0.22$ ($p < 0.03$).

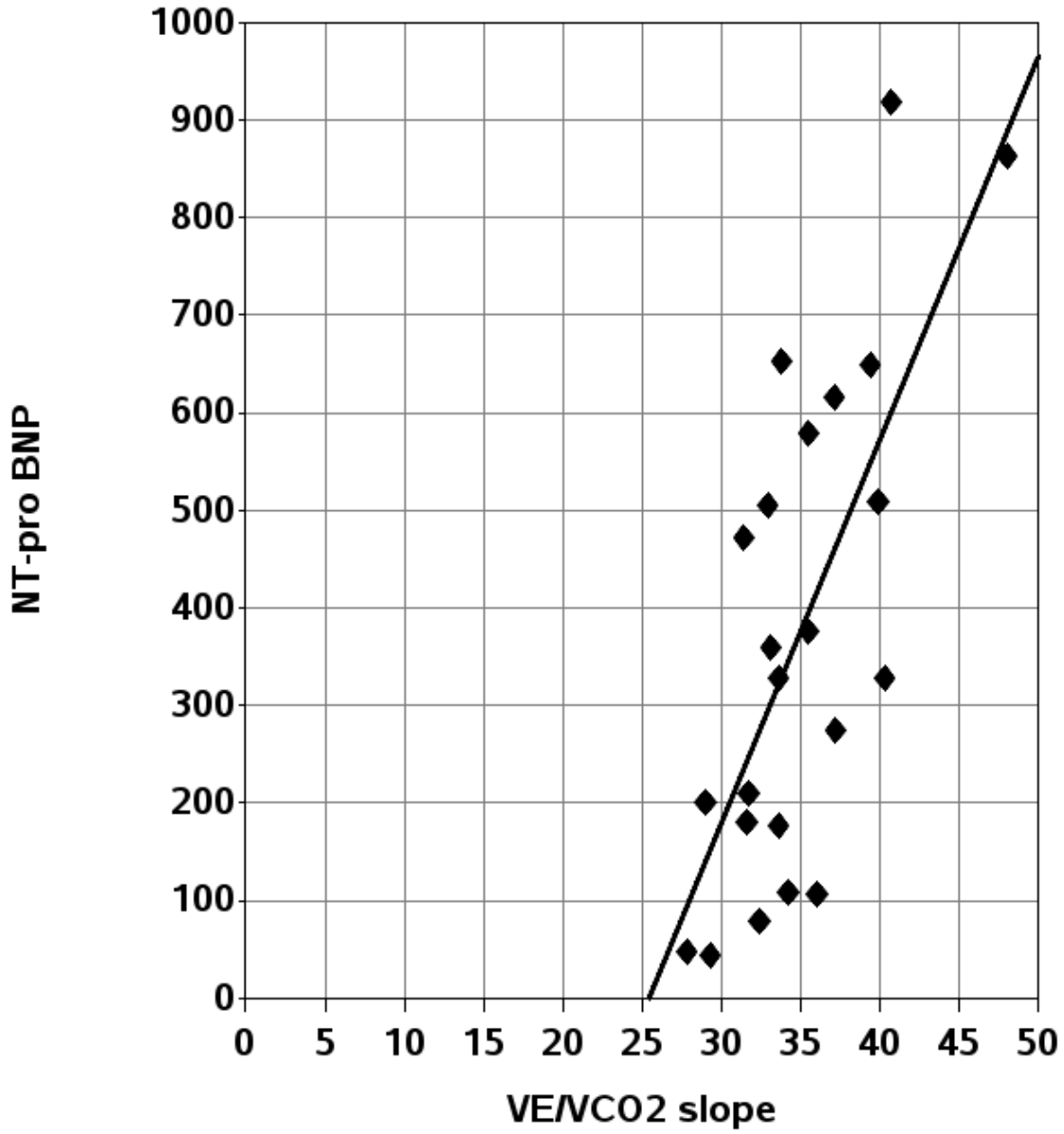

Figure 6. The relationship between N-terminal prohormone brain natriuretic peptide (NT-pro BNP) and Ventilatory Efficiency (VE/VCO_2 slope). $R^2 = 0.50$ ($p < 0.001$)

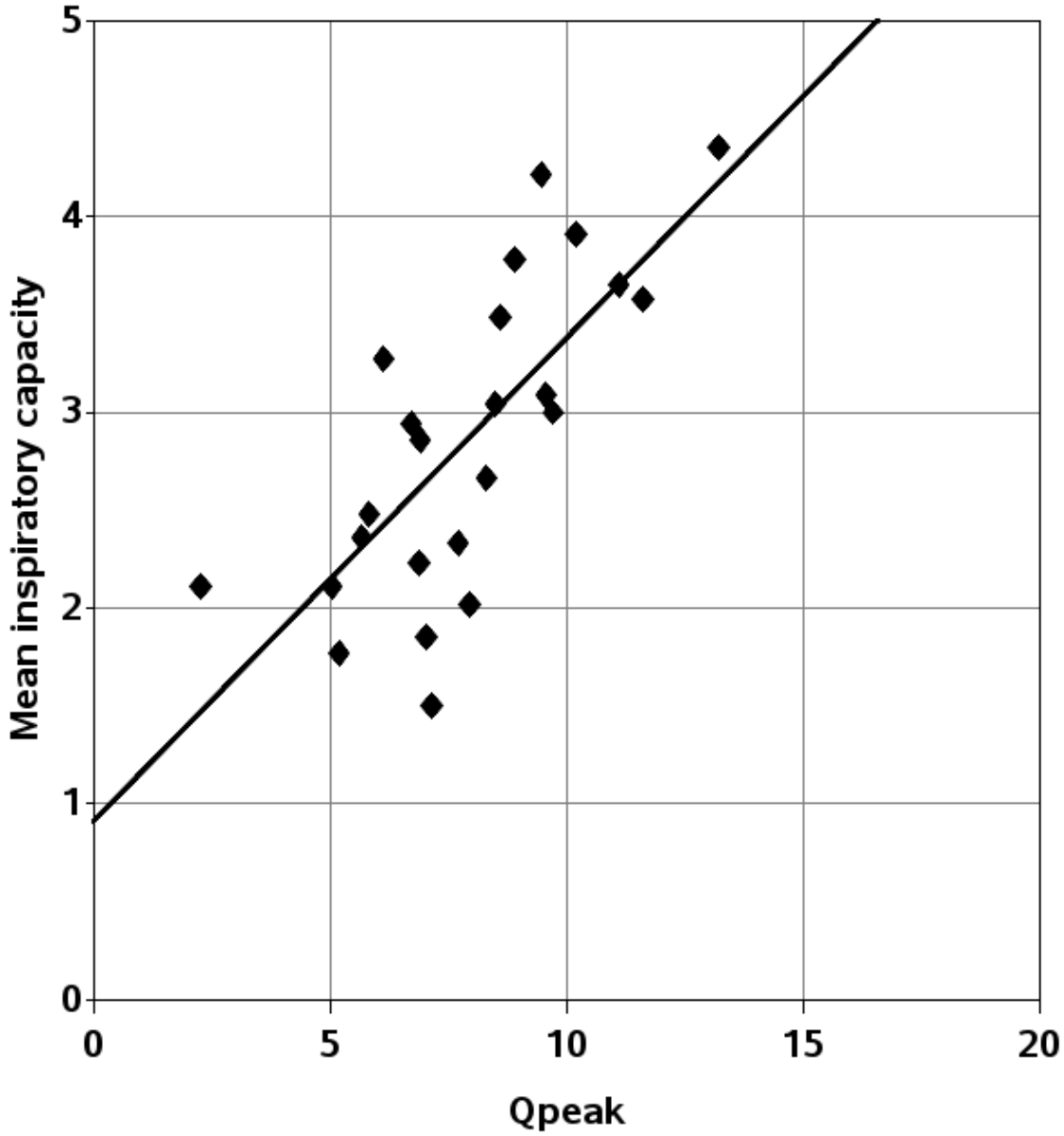

Figure 7. The relationship between mean inspiratory capacity and peak cardiac output (Q_{peak}). R^2 = .59 (p <0.0001)

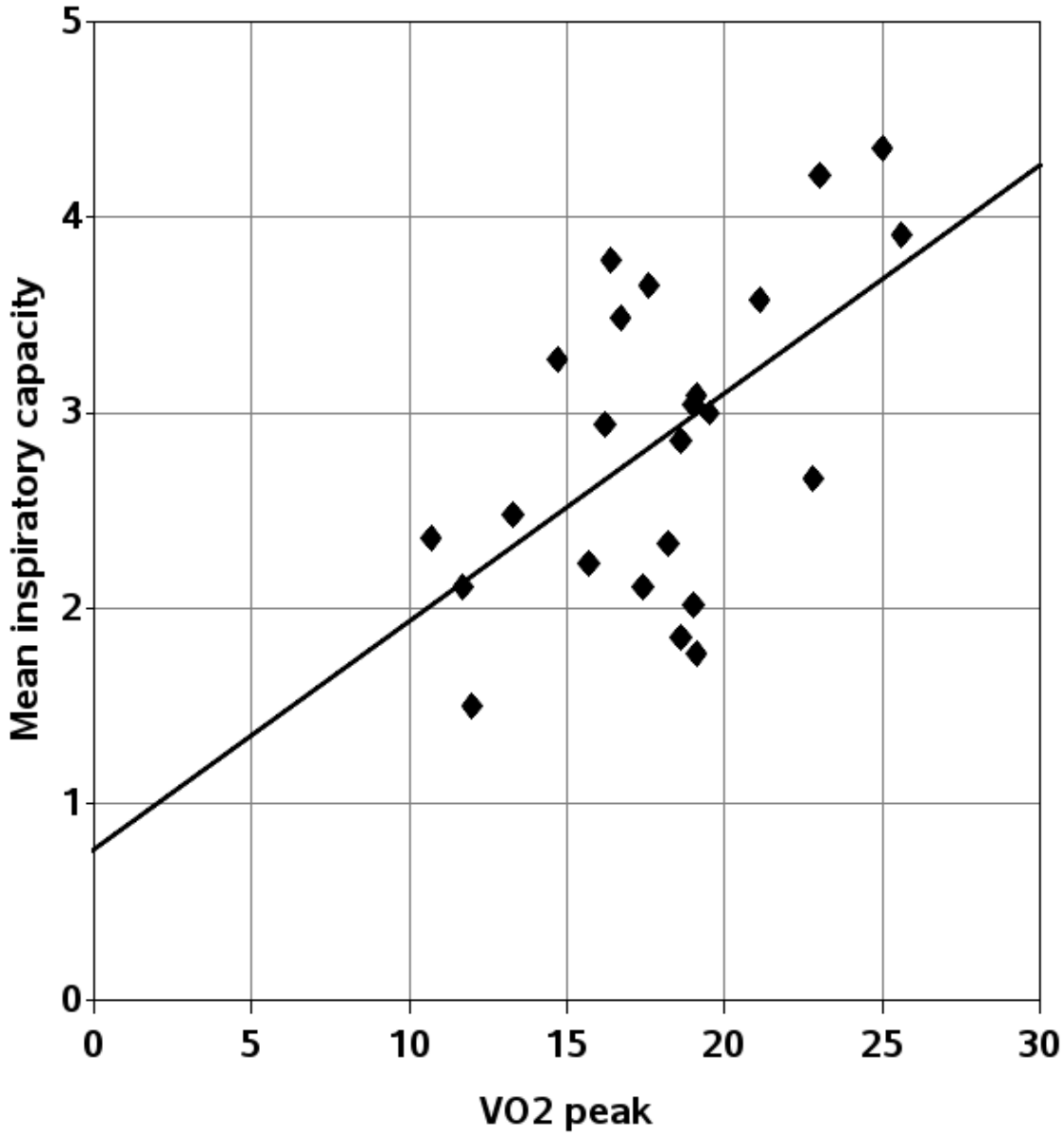

Figure 8. The relationship between mean inspiratory capacity and peak oxygen consumption (VO_{2peak}). $R^2 = 0.26$ ($p < 0.02$)

Hypothesis testing. The proposed relationship between Qpeak, VO_{2peak}, the VE/VCO_2 slope, and/or 6MWT distance with NT-pro BNP, NYHA classification, and inspiratory capacity was partially confirmed. The evidence from this study did not support a relationship between 6MWT distance, NT-pro BNP, and/or inspiratory capacity. The relationship of Q_{peak}, VO_{2peak}, and the VE/VCO_2 slope with NYHA classification could not be tested due to the homogeneity of the sample.

Aim 2: Construction of a Model to Predict Established Measurements from Proposed Measurements

Multiple regression analysis was used to test whether inspiratory capacity and NT-pro BNP significantly predicted VO_{2peak}. The results of the regression indicated the resting measurements explained 42% of the variance in the exercise measurement (adjusted $R^2 = 0.42$, $F(2, 20) = 8.82$, $p < 0.002$). As there was very little overlap between the two variables, NT-pro BNP and inspiratory capacity together explain substantially more of the variance than either do alone. A model of prediction for Q_{peak} or the VE/VCO_2 slope could not be constructed since only one predictor variable for each outcome variable was statistically significant. Both inspiratory capacity and NT-pro BNP were moderately correlated with VO_{2peak}. Additionally, a model for the prediction of 6MWT distance could not be constructed since there was no correlation between 6MWT distance and the predictor variables. Tables 5 and 6 summarize the analysis of variance and the parameter estimates of VO_2 peak as predicted by NT-pro BNP and inspiratory capacity. There was no significant correlation between NT-pro BNP and inspiratory capacity as depicted in Table 7.

Table 5

Analysis of Variance of Peak Oxygen Consumption as Predicted by N-terminal Prohormone Brain Natriuretic Peptide and Inspiratory Capacity

Source	DF	Sum of Squares	Mean Square	F-value	Pr > F
Model	2	145.30	72.65	8.82	0.0018
Error	20	164.74	8.24		
Corrected Total	22	310.01			
R-Square	0.47				
Adjusted R-Square	0.42				

DF = degrees of freedom, Pr > F = significance probability

Table 6

Parameter Estimates for Peak Oxygen Consumption as predicted by N-terminal Prohormone Brain Natriuretic Peptide and Inspiratory Capacity

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	1	13.63	2.59	5.27	<0.0001
NT-pro BNP	1	-0.007	0.002	-2.82	0.0105
Mean IC	1	2.44	0.80	3.05	0.0063

NT- pro BNP = N-terminal Prohormone Brain Natriuretic Peptide, IC = Inspiratory Capacity

Table 7

Pearson Correlation Coefficient Between N-terminal Prohormone Brain Natriuretic Peptide and Inspiratory Capacity

	NT-pro BNP *R (p)*
Mean Inspiratory Capacity	-0.02 (0.93)

NT- pro BNP = N-terminal Prohormone Brain Natriuretic Peptide

Observations

During data analysis, there was a statistically significant correlation between VO_{2peak} and 6MWT distance as shown in Table 9. The moderate correlation between these two exercise measurements has long been established in the literature; most recently by Forman et al. (2012). These investigators studied 2,030 patients with HF and reported a statistically significant, moderate correlation between VO_{2peak} and 6MWT distance ($R = 0.54$, $p < 0.0001$). While the 6MWT is an exercise measurement, and does require office space and training of personnel, it is possible to have patients with HF perform a 6MWT as an outpatient visit. Table 8 depicts the 6MWT as a predictor variable. It may be warranted in future research to include the 6MWT as a predictor variable instead of an outcome variable.

Table 8

Pearson Correlation Coefficients between Peak Cardiac Output, Peak Oxygen Consumption, Ventilatory Efficiency, and Inspiratory Capacity, N-terminal Prohormone Brain Natriuretic Peptide, and Six-Minute Walk Test Distance.

Predictor Measurements	Outcome Measurements		
	Q_{peak}	VO_{2peak}	VE/VCO_2 slope
	R (p)	*R (p)*	*R (p)*
NT-Pro BNP	-0.25 (0.25)	-0.47 (<0.03)	0.71 (<0.001)
Mean Inspiratory Capacity	0.77 (<0.0001)	0.51 (<0.02)	-0.23 (<0.29)
6MWT distance	0.13 (0.55)	**0.46 (<0.03)**	0.06 (0.78)

Q_{peak} = Peak Cardiac Output, VO_2 peak = Peak Oxygen Consumption, VE/VCO_2 slope = Ventilatory Efficiency, 6MWT = 6-Minute Walk Test, NT- pro BNP = N-terminal Prohormone Brain Natriuretic Peptide

Chapter 5: Discussion

Heart failure is a challenging disease that affects more than five million people, half of whom are at least 75 years old (Thomas & Rich, 2007). Many patients with HF experience symptoms such as shortness of breath and fatigue which limit their ability to perform activities of daily living. Often, older adults with HF have worsening dyspnea for days prior to hospitalization and do not realize the significance (Friedman, 1997; Jurgens, 2006; Jurgens et al. 2009). Frequently, older adults living with HF have comorbidities which also limit their activities of daily living, and result in complicating their medication regimen even further (Riegel & Carlson, 2003; LeCorvoisier et al. 2015). Many older adults with HF have reported a relatively poor health-related quality of life (Falk et al., 2013). A barrier to management of their heart failure is that older adults often either do not realize when a symptom occurs or worsens, or may not attribute the symptom to HF (Carlson, Riegel, & Moser, 2001; Reigel et al. 2009; Sethares et al., 2014). Therefore, older adults living with HF need tools which will help them discern symptoms and alert them when symptoms worsen.

HF is a complex disease with a complicated therapeutic regimen. Currently, there are three evidence-based measurements for evaluation of the efficacy of therapies and for prognostication: VO_{2peak}, the VE/VCO_2 slope, and the 6MWT. All three tools require some staff training and a physical location in which to perform the test. Because of this, these measurements are infrequently used clinically for the general management of HF, and measurements obtained during echocardiography combined with patient symptoms are often used to guide treatment. One problem with this approach is that these measurements are not precise and often do not correlate with each other. Clinicians need

tools that can be used in the clinic setting which help them discern treatment efficacy and symptom management.

Peak VO_2, the VE/VCO_2 slope obtained during CPX, and the 6MWT are powerful prognostic indicators and are useful for monitoring the therapeutic efficacy of symptom and disease management. However, despite the body of evidence supporting these measures, CPX and the 6MWT are not routinely performed in the outpatient setting. NT-pro BNP, NYHA classification, and inspiratory capacity, all obtainable in an office visit, can potentially explain enough variance in Q_{peak}, VO_{2peak}, the VE/VCO2 slope, and/or 6MWT distance to be useful clinically and potentially useful in the patient's home environment.

The purpose of this study was to investigate the relationship of Q_{peak}, VO_{2peak}, the VE/VCO_2 slope, and 6MWT distance to NT-pro BNP, NYHA classification, and inspiratory capacity in older patients with HF. The specific aims of the study were to 1) investigate the relationship of Q_{peak}, VO_{2peak}, the VE/VCO_2 slope, and/or 6MWT distance with NT-pro BNP, NYHA classification, and inspiratory capacity, in older adults with HF and 2) explore possible models of predicting peak Q_{peak}, VO_2, the VE/VCO_2 slope, and/or 6MWT distance from NT-pro BNP, NYHA classification, and inspiratory capacity in older adults with HF. The sample comprised older men with NYHA class II HF with expected comorbid conditions, resting measurements, and exercise measurements.

Aim 1: Investigation of the Relationships between Established Measurements and Proposed Measurements

N-Terminal prohormone B-type natriuretic peptide measurement as a predictor variable.

N-Terminal prohormone B-type natriuretic peptide in relation to peak cardiac output. The weak negative relationship between NT-pro BNP and Q_{peak} in this study was not statistically significant. Cardiac output is a function of heart rate and stroke volume. Considering that stroke volume is the difference of end-systolic volume subtracted from end-diastolic volume, in a failing heart, stroke volume decreases initially due to an increased end-systolic volume and, as the disease progresses to a decreased end-diastolic volume (Sagiv, 2012). In HF, NT-pro BNP is excreted by the overstretched ventricles, therefore the inverse relationship between NT-pro BNP and Q_{peak} does seem logical. However, although the results of this study showed a weak (-0.25) negative correlation, this was not statistically significant. The lack of statistical significance may have been affected by the study's relatively low power. The study would have needed at least 60 participants for a correlation of -0.25 to be statistically significant. Of note, 96% of the participants were taking beta-blockers. The purpose of beta-blocking medications is to decrease structural remodeling of the ventricles, with the ultimate goal of preserving or increasing the ejection fraction (Mozzafarian, 2016). It may be possible that the effect of beta-blockers confounded the results and withholding beta blockers may have produced different results. No other studies have reported investigating the relationship between Q_{peak} and NT-pro BNP.

N-Terminal prohormone B-type natriuretic peptide in relation to peak oxygen consumption. The study demonstrated a moderate negative correlation ($r = -0.47$, $p < 0.03$) between VO_{2peak} and NT-pro BNP. Considering that cardiac output is a function of stroke volume (which is partially a function of ventricular stretch), and that cardiac output is a component of VO_2 and that NT-pro BNP release is contingent upon excessive

ventricular stretch, it seems counter-intuitive that the correlation between Q_{peak} and NT-pro BNP was weak and not significant while there was a moderate statistically significant correlation between VO_{2peak} and NT-pro BNP. However, VO_2 is also a function of the difference of venous oxygen concentration subtracted from arterial oxygen concentration. It is likely that with increased pulmonary congestion, the diffusion of oxygen from arteriole to capillary is decreased, which would decrease arterial oxygen concentration. It is also likely that cellular extraction of oxygen remains the same which would mean that venous oxygen concentration would remain the same. Therefore, the difference between arterial and venous oxygen concentration would be less, which would decrease VO_2. Increased ventricular stretch causes ventricles to release NT-pro BNP and leads to decreased stroke volume. Decreased stroke volume leads to pulmonary congestion which negatively affects diffusion of oxygen from the alveoli to the capillary. This physiologic process most likely explains why there is a statistically significant moderate negative relationship between VO_{2peak} and NT-pro BNP but not between Q_{peak} and NT-pro BNP.

In patients with HF, Kallistratos, et al. (2007) found a strong correlation between VO_{2peak} and NT-Pro BNP ($r = -0.77$, $p < 0.001$). Williams et al. (2005) also demonstrated a moderate correlation between VO_{2peak} and NT-pro BNP levels ($r = -0.64$, $p < 0.001$). Investigative teams of Passino et al. (2006) and Maeder, Wolber, Rickli, Meyers, Hack, Riesen et al. (2007) both reported a moderate relationship between VO_{2peak} and NT-pro BNP levels ($r = -0.53$, $p < 0.001$; $r = -.53$, $p < 0.01$, respectively). The results of this study are consistent with prior literature and show a moderate to strong relationship between NT-pro BNP and VO_{2peak}.

N-Terminal prohormone B-type natriuretic peptide in relation to ventilatory efficiency. The results of this study provide evidence for a strong positive correlation (r = 0.71, p <0.001) between NT-pro BNP and the VE/VCO_2 slope. The VE/VCO_2 slope is a function of arterial carbon dioxide pressure and the physiologic dead space- tidal volume ratio (Sun et al, 2002). Again, ventricular overstretch and resultant failure leads to decreased SV and increased pulmonary congestion. Increased pulmonary congestion is a factor in increased pulmonary physiologic dead space. It may also negatively affect tidal volume.

The correlation found in this study is stronger than previously reported by other investigators. Passino et al. (2006) found a moderate correlation between NT-pro BNP and the VE/VCO_2 slope (r = 0.49, p <0.02). Maeder, et al. (2006) described a negative relationship between NT-pro BNP and the VE/VCO_2 slope (r = 0.53, p <0.01).

N-Terminal prohormone B-type natriuretic peptide in relation to the Six-Minute Walk test. This study did not find a relationship between the 6MWT distance and NT-pro BNP. There is no prior literature comparing the 6MWT distance to NT-pro BNP. The 6MWT is an assessment of the patient's overall response to submaximal exercise. As such, it is a function of cardiovascular system performance, pulmonary system performance, and musculoskeletal system performance. It is possible that this global assessment is influenced by many factors which may be more powerful predictors of 6MWT distance than specific physiologic variable such as NT-pro BNP.

New York Heart Association classification as a predictor variable. In this study, all of the participants were categorized as having NYHA class II HF. Although participants were documented as having varying classifications of HF in their electronic

health record, upon review and assessment by the principle investigator, all participants were categorized as having NYHA class II HF. It is possible that although the patient's electronic health record showed the classification, it may not have been re-assessed and recorded in a systematic fashion. Due to the difficulty of recruiting participants, it was not feasible to for the study to stratify participants based on NYHA classification. The lack of variation in NYHA in this sample made it unusable in regression analysis. Williams et al. (2005) and Meyer et al. (2004) reported a strong correlation ($r = 0.76$, $p < 0.001$; $r = 0.67$, $p < 0.001$) between VO_{2peak} and NYHA classification.

Inspiratory capacity as a predictor variable.

Inspiratory capacity in relation to peak cardiac output. This study demonstrated a strong and highly significant relationship ($r = 0.77$, $p < 0.0001$) between Q_{peak} and inspiratory capacity, which supported the hypothesis. Nanas et al. (2003) reported strong correlations between VO_{2peak}, inspiratory capacity, and pulmonary capillary wedge pressure. The authors reported a direct inverse correlation between inspiratory capacity and pulmonary capillary wedge pressure, both of which correlate with physiologic pulmonary dead space. Nanas et al. (2003) performed a stepwise regression analysis which showed that inspiratory capacity and PCWP were able to explain 58% of the variance in VO_{2peak}. Nanas et al. did not measure Q_{peak} as an outcome variable. It stands to reason that inspiratory capacity has a stronger correlation with Q_{peak} since Q is a function of SV and HR and VO_{2peak} is a function of Q and the avO_2 difference. There are fewer variables in Q than in VO_{2peak}. Considering that there are no prior investigations in the literature which investigated the correlation between Q_{peak} and inspiratory capacity, this is a substantial strength of the present study.

Inspiratory capacity in relation to peak oxygen consumption. There was a moderate correlation ($r = 0.51$, $p < 0.02$) between VO_{2peak} and inspiratory capacity, which supported the original hypothesis. This was not unexpected in that both measurements are known to be affected by pulmonary physiologic dead space. In patients with lung disease, Diaz et al. (2000) and Perpati et al. (2010) found a moderate relationship ($r = 0.54$, $p < 0.0001$; $r = 0.67$, $p < 0.007$) between VO_{2peak} and inspiratory capacity. In patients with HF, Nanas et al. (2003) reported a strong correlation ($r = 0.71$, $p < 0.0001$) and Morris et al. (2007) reported a moderate correlation ($r = 0.41$, $p < 0.05$) between VO_{2peak} and inspiratory capacity.

Inspiratory capacity in relation to ventilatory efficiency and Six Minute Walk Test distance. The present study did not find a correlation between either the VE/VCO_2 slope or 6MWT distance and inspiratory capacity. Since the VE/VCO_2 slope is a function of pulmonary physiologic dead space and alveolar inflation, it seemed reasonable that there would be a correlation between it and inspiratory capacity, which is affected by physiologic dead space. It is possible that the study was not adequately powered for the modest relationship seen to reach statistical significance. Once again, the 6MWT is a function of multiple body systems and one physiologic variable may not correlate with a measurement of global functioning. Inspiratory capacity is only one of numerous factors contributing to this broad functional assessment.

Aim 2: Construction of a Model to predict Established Measurements from Proposed Measurements

Considering that the NYHA classifications were homogeneous and there was no significant correlation between Q_{peak}, the VE/VCO_2 slope, and 6MWT distance and at

least two predictor variables, there could not be model construction for these outcome variables. This investigation demonstrated a moderate statistically significant correlation between VO_{2peak}, NT-pro BNP, and inspiratory capacity. In the model, the combination of NT-pro BNP and inspiratory capacity was able to explain 42% of the variance in VO_{2peak}. Mean inspiratory capacity alone was able to explain 59% of the variance in Q_{peak} and NT-pro BNP was able to explain 50% of the variance in the VE/VCO_2 slope. From the present study, these two resting measurements can, either alone or combined, explain between 42% and 59% of variance in key exercise measurements.

Limitations

This investigation was limited by several factors. First, as noted earlier, the sample size was small. It is difficult to have conclusive outcomes with a small sample size. However, the regression analysis was limited to two predictor variables. In the Knofczynski & Mundfrom (2007) reckoning, the regression of two predictor variables with a good prediction level with the squared population multiple correlation coefficient set at .50, the study needed 35 participants. The actual squared population multiple correlation coefficient between VO_{2peak}, inspiratory capacity, and NT-pro BNP was 0.42, which needed at least 45 participants. The investigation did not control for participants with chronic kidney disease. There has been ongoing research in NT-pro BNP levels and chronic kidney disease which have indicated that NT-pro BNP may not only be affected by a decreased glomerular filtration rate but also by the cardio-renal syndrome which often occurs in HF (Anwaruddin, Lloyd-Jones, Baggish, Chen, Krauser, &, Tung, 2006; Santos-Araujo, Leite-Moreira, & Pestana, 2015). Excluding patients with CKD may have

decreased the number of participants who had NT-pro BNP levels higher than two standard deviations from the mean.

The study population had marked homogeneity. All of the participants were categorized as having NYHA functional class II HF. It is possible that the electronic health record of each participant was not updated to reflect changes in NYHA classification. Lastly, exercise testing including CPX and 6MWT is always dependent on participant effort.

Implications for Research

This investigation augments prior evidence of the usefulness of NT-pro BNP and the potential usefulness of inspiratory capacity measurement in the management of HF. In this study, investigators were able to compare resting measurements to Q_{peak}, which has not been done in most other studies. This warrants further investigation considering that the best-known surrogate measurement, VO_{2peak}, is affected by skeletal deconditioning and potentially other factors that do not affect Q_{peak} is not affected by (Wilson et al., 1995; Chomsky et al. 1996). The need for further investigations which include Q_{peak} is substantial.

Although this investigation was not able to include NYHA classification in the model, prior studies have reported a relationship between NYHA classification and VO_{2peak} (Kallistratos et al., 2007; Meyer et al., 2004; Davies et al., 2000). NYHA classification remains a factor in future model development for prediction and disease management.

Inspiratory capacity is a promising, relatively new measurement in HF. This study showed a strong correlation between Q_{peak} and inspiratory capacity and a moderate

correlation between VO_{2peak} and inspiratory capacity. This is likely the first study to show a correlation between Q_{peak} and inspiratory capacity. This study also supports prior HF research on the correlation between VO_{2peak} and inspiratory capacity (Nanas et al., 2003; Morris et al., 2007). Although the study sample was small, the data can be used to inform further research. Additionally, all of the resting measurements, but particularly inspiratory capacity, may be useful in predicting prognosis.

Implications for practice

This study has significant implications for practice. Clinicians should be encouraged to use measurements that are obtainable in the office setting to monitor disease and symptom management. These measurements may also be useful in predicting prognosis. Of greater significance, is that inspiratory capacity has the potential to be measured by patients themselves at home. Much research has shown that patients with HF often discount symptoms or do not do not understand the implication of symptoms that lead to hospitalization (Riegel et al., 2009; Jurgens et al., 2009; Reigel & Carlson, 2002; Sethares et al., 2014). This is particularly true in older patients with HF (Patel et al., 2007). Having the ability to monitor inspiratory capacity at home when symptoms change may help patients recognize worsening congestion and seek appropriate care earlier.

Conclusion

This study is likely the first investigation into the relationship between Q_{peak} and inspiratory capacity and showed the potential usefulness of a model using NT-pro BNP and inspiratory capacity in the prediction of VO_{2peak}. The investigation has both generated

new knowledge and added to the body of knowledge regarding resting measurements and their ability to be used in the management of HF.

The added knowledge will be useful both in implications for further research and disease and symptom management. Once further developed, both clinicians and patients will be able to use these measurements in their management of HF. Clinicians may be able to use the measurements alone or as part of a model in prediction of prognosis.

Heart failure is a difficult syndrome which progressively worsens over time. Patients with HF live with complex symptoms which can be difficult to distinguish from other disease processes. The resting measurements in this study offer promise to assist in the management of HF and its symptoms for both clinicians and patients.

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Office of the Vice President for Research

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MMC 820
Minneapolis, MN 55455

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E-mail: irb@umn.edu or ibc@umn.edu
Website: http://research.umn.edu/subjects/

December 2, 2014

Marjorie Webb
3197 State Road 29
Wilson, WI 54027

RE: ""The Relationship of Resting Cardiopulmonary Function to Maximal and Submaximal Cardiopulmonary Exercise Testing in Older patients with Heart Failure" Funded by the American Nurses Foundation"
IRB Code Number: **1410M54584**

Dear Dr. Webb

The Institutional Review Board (IRB) received your response to its stipulations. Since this information satisfies the federal criteria for approval at 45CFR46.111 and the requirements set by the IRB, final approval for the project protocol date November 20, 2014 is noted in our files. Upon receipt of this letter, you may begin your research.

IRB approval of this study includes the consent form version dated November 20, 2014 (received November 23, 2014) and recruitment materials received October 29, 2014.

The HIPAA Authorization version dated November 26, 2014 has been approved.

The IRB would like to stress that subjects who go through the consent process are considered enrolled participants and are counted toward the total number of subjects, even if they have no further participation in the study. Please keep this in mind when calculating the number of subjects you request. This study is currently approved for 70 subjects. If you desire an increase in the number of approved subjects, you will need to make a formal request to the IRB.

For your records and for grant certification purposes, the approval date for the referenced project is November 5, 2014 and the Assurance of Compliance number is FWA00000312 (Fairview Health Systems Research FWA00000325, Gillette Children's Specialty Healthcare FWA00004003). Research projects are subject to continuing review and renewal; approval will expire one year from that date. You will receive a report form two months before the expiration date. If you would like us to send certification of approval to a funding agency, please tell us the name and address of your contact person at the agency.

As Principal Investigator of this project, you are required by federal regulations to:

*Inform the IRB of any proposed changes in your research that will affect human subjects, changes should not be initiated until written IRB approval is received.
*Report to the IRB subject complaints and unanticipated problems involving risks to subjects or others as they occur.
*Inform the IRB immediately of results of inspections by any external regulatory agency (i.e. FDA).
*Respond to notices for continuing review prior to the study's expiration date.
*Cooperate with post-approval monitoring activities.

Information on the IRB process is available in the form of a guide for researchers entitled, What Every Researcher Needs to Know, found at http://www.research.umn.edu/irb/WERNK/index.cfm

The IRB wishes you success with this research. If you have questions, please call the IRB office at 612-626-5654.

Sincerely,

Andrew Allen

Digitally signed by Andrew Allen
DN: c=US, st=Minnesota, l=Minneapolis, ou=Human Research Protection Program, emailAddress=allen0302@umn.edu, o=University of Minnesota, cn=Andrew Allen
Date: 2014.12.02 22:36:14 -06'00'

Andrew Allen, CIP
Research Compliance Supervisor
AA/bw

CC: Ruth Lindquist, Diane Treat-Jacobson

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Route this form to: See instructions below

Revised October 2013

Change In Protocol Request

Instructions:

Use this form when submitting change requests to approved IRB protocols. This form is for use when the changes are initiated by the PI. Do not use this form to respond when changes are requested by the IRB. Please do not use this form when responding to changes requested in a stipulation or deferral letter.

Submit this form to the Human Research Protection Program:

U.S. Mail Address: or
Human Research Protection Program
MMC 820
420 Delaware St. SE
Minneapolis, MN 55455-0392

Electronic Submission:
Submit to: irb@umn.edu
PI must submit request using University of Minnesota e-mail Account.

FOR IRB USE ONLY:

The UMN IRB reviewed and APPROVED this submission including all attachments listed on this form via full committee review

Andrew Allen

Digitally signed by Andrew Allen
DN: c=US, st=Minnesota, l=Minneapolis, ou=Human Research Protection Program, email=alle0302@umn.edu, o=University of Minnesota, cn=Andrew Allen
Date: 2015.01.23 15:56:44 -06'00'

IRB Protocol Information

IRB Study Number:	**1410M54584**
Principal Investigator:	Marjorie Webb
Primary Study Title:	The Relationship of Resting Cardiopulmonary Function to Maximal and Submaximal Cardiopulmonary Exercise Testing in Older Patients with Heart Failure
Date of this Submission	12/17/2014
Study Includes	☐ Drug(s) / Biologic(s) ☐ Device(s)

Indicate the type of change(s)	Additional information/requirements
☒ Change(s) to Study Procedures/Protocol Amendment Protocol VersionNov 20 2014, DatedNov 20 2014	**Does the change affect study design, change the study endpoint(s) or change the statistical method?** ☒ **No** ☐ Yes **Is this protocol under Masonic Cancer Center's Cancer Protocol Review Committee (CPRC) review?** ☒ No ☐ Yes, CPRC # If "Yes" is checked for *both* questions above, this submission (Change in Protocol form and any supporting documentation) must be reviewed by CPRC (CCPRC@umn.edu) prior to review by the IRB. CPRC will forward this submission to the IRB after CPRC approval. Submission to CPRC must meet the IRB signature requirement (signed by the PI or sent from the PI's x.500 UMN email account).
☐ Notice of Closure to Accrual	
☐ Recruitment changes/Advertisements	Attach a copy of the revised material (flyer, script, etc.) with the submission
☐ Revised Investigator Brochure	Version , Dated
☒ Updated consent form	Include both an updated form with changes highlighted and a "clean" version
☒ Other	Briefly Describe:change to protocol

1. **Briefly summarize the change(s). For protocol amendments, do not say "See summary of changes provided with amendment." Rather, summarize the nature of the significant revisions.**

Changes:
1. change measurement of inspiratory capacity to spirometry which includes inspiratory capacity, forced vital capacity, and forced expiratory volume in one second.
2. add two questionnaires: Functional Assessment of Chronic Illness Therapy- Dyspnea and Functional Assessment of Chronic Illness Therapy- Fatigue
3. add measurement of cardiac output to measurments obtained during cardiopulmonary exercise testing.
4. change the order in which testing will be performed
5. change amount of time between tests
6. change cardiopulmonary testing from bicycle testing to treamill testing

2. **Describe the rationale for the change(s):**

1.Including full spirometry does not significantly change the length of the test, and these other measurements may correlate with the measurements obtained during exercise.
2. dyspnea and fatigue are hallmark symptoms of heart failure. Will compare subjective results with measurements obtained at rest and during exercise.
3. cardiac output is an important measurement that usually requires invasive equipment. The Laboratory of Clinical Physiology equipment has the capacity to obtain this measurement during cardiopulmonary exercise testing (newer method that is non-invasive). The cardiac output will be calculated based on measurements obtained during the test.
4. upon "dry run" of the procedures, it was determined that cardiopulmonary exercise testing (GXT) should be performed before the 6 MWT. During GXT, the participant's heart rate, blood pressure, and EKG are recorded. If there is any ischemia with exertion it will be noted by the cardiologist. These mesurements are not recorded during a 6 MWT. Therefore, we felt it would be safer for the participant to perform a monitored test before an unmonitored one.
5. upon review of other exercise testing protocols, 2 hours between tests was found to be excessive for recovery time. the resting intervals have been changed to 15 minutes between non-strenuous tests (spirometry, venipuncture) and 45 minutes between exercise tests (GXT and 6 MWT).
6. upon review of other exercise testing which included older adults, it was found that they are better able to walk on a treadmill than ride a bike. also, many participants with knee replacements are not able to bend their knees to the degree needed for bicycling.

3. **How will these changes affect the overall risk to subjects in this study?**

There is no change in the overall risk.

4. **Do the changes to the study prompt changes to the consent form(s)?**

☐ **No.**
☒ **Yes. If yes:**
- **Attach a copy of the revised consent form(s) with changes tracked or highlighted as well as a clean copy.**

4.1 Will currently enrolled subjects will be notified of the changes?
☒ **No**
☐ **Yes, explain below how they will be notified** (i.e. subjects will be re-consented with the updated form once approved, subjects will be provided with an information sheet, subjects will be told of changes at next study visit, etc.).

N/A

5. **List and attach all documents included with this request, including version dates:**

1.Webb_ consent form (clean copy) dated 12/17/2014
2. Webb_consent form (highlighted copy) dated 12/17/2014
3.Webb_research proposal for IRB dated 12/17/2014
4. Functional Assessment of Chronic Therapy-Dyspnea
5. Functional Assessment of Chronic Therapy- Fatigue

Marjie A. MD — 12/17/2014

Principal Investigator's Signature — **Date**

Cancer Protocol Review Committee (CPRC) Use Only:

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Route this form to: See instructions below
Revised October 2013

Change In Protocol Request

Instructions:

Use this form when submitting change requests to approved IRB protocols. This form is for use when the changes are initiated by the PI. Do not use this form to respond when changes are requested by the IRB. Please do not use this form when responding to changes requested in a stipulation or deferral letter.

FOR IRB USE ONLY:

Submit this form to the Human Research Protection Program:

U.S. Mail Address: or
Human Research Protection Program
MMC 820
420 Delaware St. SE
Minneapolis, MN 55455-0392

Electronic Submission:
Submit to: irb@umn.edu
PI must submit request using University of Minnesota e-mail Account.

IRB Protocol Information

IRB Study Number:	**1410M54584**
Principal Investigator:	Marjorie Webb
Primary Study Title:	The Relationship of Resting Cardiopulmonary Function to Maximal and Submaximal Cardiopulmonary Exercise Testing in Older patients with Heart Failure
Date of this Submission	1/26/2015
Study includes	☐ Drug(s) / Biologic(s) ☐ Device(s)

Indicate the type of change(s)	Additional information/requirements
☐ Change(s) to Study Procedures/Protocol Amendment Protocol Version , Dated	**Does the change affect study design, change the study endpoint(s) or change the statistical method?** ☒ **No** ☐ Yes **Is this protocol under Masonic Cancer Center's Cancer Protocol Review Committee (CPRC) review?** ☒ No ☐ Yes, CPRC # If "Yes" is checked for *both* questions above, this submission (Change in Protocol form and any supporting documentation) must be reviewed by CPRC (CCPRC@umn.edu) prior to review by the IRB. CPRC will forward this submission to the IRB after CPRC approval. Submission to CPRC must meet the IRB signature requirement (signed by the PI or sent from the PI's x.500 UMN email account).
☐ Notice of Closure to Accrual	
☐ Recruitment changes/Advertisements	Attach a copy of the revised material (flyer, script, etc.) with the submission
☐ Revised Investigator Brochure	Version , Dated
☐ Updated consent form	Include both an updated form with changes highlighted and a "clean" version
☒ Other	Briefly Describe:I incorrectly checked "NO" on section 12.3.3. Phlebotomy

	services will be provided by the Fairview Health Service (UMMC East Bank). Per question in section 12.3.3: this study does not meet Medicare criteria for a qualifying clinical trial.

1. **Briefly summarize the change(s). For protocol amendments, do not say "See summary of changes provided with amendment." Rather, summarize the nature of the significant revisions.**

Patients will undergo phlebotomy performed by Fairview Health Service; TASCS 150001.

2. **Describe the rationale for the change(s):**

Not a change, original IRB application was incorrect.

3. **How will these changes affect the overall risk to subjects in this study?**

No change

4. **Do the changes to the study prompt changes to the consent form(s)?**

☒ **No.**
☐ **Yes. If yes:**
- **Attach a copy of the revised consent form(s) with changes tracked or highlighted as well as a clean copy.**

4.1 Will currently enrolled subjects will be notified of the changes?
☐ **No**
☐ **Yes, explain below how they will be notified** (i.e. subjects will be re-consented with the updated form once approved, subjects will be provided with an information sheet, subjects will be told of changes at next study visit, etc.).

5. **List and attach all documents included with this request, including version dates:**

TASCS billing grid

Principal Investigator's Signature **Date** 1/26/2015

Cancer Protocol Review Committee (CPRC) Use Only:

UNIVERSITY OF MINNESOTA

Route this form to: See instructions below
Revised October 2013

Change in Protocol Request

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420 Delaware St. SE
Minneapolis, MN 55455-0392

Electronic Submission:
Submit to: irb@umn.edu
PI must submit request using University of Minnesota e-mail Account.

IRB Protocol Information

IRB Study Number:	**1410M54584**
Principal Investigator:	Marjorie Webb
Primary Study Title:	The Relationship of Resting Cardiopulmonary Function to Maximal and Submaximal Cardiopulmonary Exercise Testing in Older patients with Heart Failure
Date of this Submission	3/20/2015
Study Includes	☐ Drug(s) / Biologic(s) ☐ Device(s)

Indicate the type of change(s)	Additional information/requirements
☒ Change(s) to Study Procedures/Protocol Amendment Protocol Version1/26/2015, Dated1/26/2015	**Does the change affect study design, change the study endpoint(s) or change the statistical method?** ☒ **No** ☐ Yes **Is this protocol under Masonic Cancer Center's Cancer Protocol Review Committee (CPRC) review?** ☒ No ☐ Yes, CPRC # If "Yes" is checked for *both* questions above, this submission (Change in Protocol form and any supporting documentation) must be reviewed by CPRC (CCPRC@umn.edu) prior to review by the IRB. CPRC will forward this submission to the IRB after CPRC approval. Submission to CPRC must meet the IRB signature requirement (signed by the PI or sent from the PI's x.500 UMN email account).
☐ Notice of Closure to Accrual	
☐ Recruitment changes/Advertisements	Attach a copy of the revised material (flyer, script, etc.) with the submission
☐ Revised Investigator Brochure	Version , Dated
☐ Updated consent form	Include both an updated form with changes highlighted and a "clean" version
☐ Other	Briefly Describe:

1. **Briefly summarize the change(s). For protocol amendments, do not say "See summary of changes provided with amendment." Rather, summarize the nature of the significant revisions.**

change exclusion criteria from "Left-ventricular assist device or cardiac resynchronization therapy in situ" to "Left-ventricular assist device in situ" and "Cardiac resynchronization therapy in situ for less than one year"

2. **Describe the rationale for the change(s):**

Prior studies indicate that the benefits obtained from cardiac resynchronization therapy (CRT) occur in the first year. Therefore, if CRT has been in place longer than one year, the patient has reached a new baseline and the CRT will not affect the comparisons in the study.

3. **How will these changes affect the overall risk to subjects in this study?**

No change

4. **Do the changes to the study prompt changes to the consent form(s)?**

☒ **No.**
☐ **Yes. If yes:**

- **Attach a copy of the revised consent form(s) with changes tracked or highlighted as well as a clean copy.**

4.1 Will currently enrolled subjects will be notified of the changes?

☒ **No**
☐ **Yes, explain below how they will be notified** (i.e. subjects will be re-consented with the updated form once approved, subjects will be provided with an information sheet, subjects will be told of changes at next study visit, etc.).

5. **List and attach all documents included with this request, including version dates:**

revised research proposal 3_20_2015, revised research proposal with change highlighted, reference list

Maryjo K. Wells — **Principal Investigator's Signature**

3/20/2015 — **Date**

Cancer Protocol Review Committee (CPRC) Use Only:

UNIVERSITY OF MINNESOTA

Route this form to: See instructions below | Revised October 2013

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MMC 820
420 Delaware St. SE
Minneapolis, MN 55455-0392

Electronic Submission:
Submit to: irb@umn.edu
PI must submit request using University of Minnesota e-mail Account.

FOR IRB USE ONLY:

The UMN IRB reviewed and APPROVED this submission including all attachments listed on this form by expedited review

Melissa Nowicki

Digitally signed by Melissa Nowicki
DN: c=US, st=Minnesota, l=Minneapolis, ou=Human Research Protection Program, email=mcke0390@umn.edu, o=University of Minnesota, cn=Melissa Nowicki
Date: 2015.07.08 16:28:59 -05'00'

IRB Protocol Information

IRB Study Number:	**1410M54584**
Principal Investigator:	Marjorie Webb
Primary Study Title:	The Relationship of Resting Cardiopulmonary Function to Maximal and Submaximal Cardiopulmonary Exercise Testing in Older patients with Heart Failure
Date of this Submission	5/15/2015
Study Includes	☐ Drug(s) / Biologic(s) ☐ Device(s)

Indicate the type of change(s)	Additional information/requirements
☒ Change(s) to Study Procedures/Protocol Amendment Protocol Version5/15/2015, Dated5/15/2015	**Does the change affect study design, change the study endpoint(s) or change the statistical method?** ☒ **No** ☐ Yes **Is this protocol under Masonic Cancer Center's Cancer Protocol Review Committee (CPRC) review?** ☒ No ☐ Yes, CPRC # **If "Yes" is checked for *both* questions above, this submission (Change in Protocol form and any supporting documentation) must be reviewed by CPRC (CCPRC@umn.edu) prior to review by the IRB. CPRC will forward this submission to the IRB after CPRC approval. Submission to CPRC must meet the IRB signature requirement (signed by the PI or sent from the PI's x.500 UMN email account).**
☐ Notice of Closure to Accrual	
☐ Recruitment changes/Advertisements	Attach a copy of the revised material (flyer, script, etc.) with the submission
☐ Revised Investigator Brochure	Version , Dated
☒ Updated consent form	Include both an updated form with changes highlighted and a "clean" version
☐ Other	Briefly Describe:

1. **Briefly summarize the change(s). For protocol amendments, do not say "See summary of changes provided with amendment." Rather, summarize the nature of the significant revisions.**

Change consent form to exclude the exercise physiologist from being present during the cardiopulmonary exercise testing. Page two of the consent form will be changed to state "During the exercise test you will be monitored by a cardiologist and the physiology lab staff." This change does not affect the study protocol

2. **Describe the rationale for the change(s):**

The cardiologist has the responsibility for participant safety during the cardiopulmonary exercise test. The exercise physiologist generally makes exercise training recommendations based on the test outcome and his/her presence does not increase safety or add benefit to the test. The participants will not do any exercise training as a part of this study.

3. **How will these changes affect the overall risk to subjects in this study?**

No change

4. **Do the changes to the study prompt changes to the consent form(s)?**

☐ **No.**
☒ **Yes. If yes:**
- **Attach a copy of the revised consent form(s) with changes tracked or highlighted as well as a clean copy.**

4.1 Will currently enrolled subjects will be notified of the changes?
☒ **No**
☐ **Yes, explain below how they will be notified** (i.e. subjects will be re-consented with the updated form once approved, subjects will be provided with an information sheet, subjects will be told of changes at next study visit, etc.).

5. **List and attach all documents included with this request, including version dates:**

RECOuP-HF Consent form with highlighted changes, RECOuP-HF consent form clean copy

Marjie A Mill — **Principal Investigator's Signature**

6/15/2015 — **Date**

Cancer Protocol Review Committee (CPRC) Use Only:

Appendix F

UNIVERSITY OF MINNESOTA

Twin Cities Campus

Human Research Protection Program
Office of the Vice President for Research

D528 Mayo Memorial Building
420 Delaware Street S.E.
MMC 820
Minneapolis, MN 55455
Office: 612-626-5654
Fax: 612-626-6061
E-mail: irb@umn.edu or ibc@umn.edu
Website: http://research.umn.edu/subjects/

10 November 2015

Marjorie G Webb
3197 State Road 29
Wilson, WI 54027-2710

RE: "The Relationship of Resting Cardiopulmonary Function to Maximal and Submaximal Cardiopulmonary Exercise Testing in Older patients with Heart Failure" Funded by the American Nurses Foundation"
IRB Code Number: **1410M54584**

Dear Dr. Webb,

The Institutional Review Board (IRB) received your response to its stipulations for renewal. Since this information satisfies the conditions set by the IRB, approval for the recent renewal is confirmed in our files.

The consent form version dated 9 July 2015 is also approved.

For your records and for grant certification purposes, the approval date for the referenced project is 14 October 2015 and the Assurance of Compliance number is FWA00000312 (Fairview Health Systems Research FWA00000325, Gillette Children's Specialty Healthcare FWA00004003). Approval for the project will expire one year from that date. You will receive a report form two months before the expiration date.

As Principal Investigator of this project, you are required by federal regulations to inform the IRB of any proposed changes in your research that will affect human subjects. Changes should not be initiated until written IRB approval is received. Unanticipated problems and adverse events should be reported to the IRB as they occur. Results of inspections by any external regulatory agency (i.e. FDA) must be reported immediately to the IRB. Research projects are subject to continuing review.

If you have any questions, please call the IRB office at 612-626-5654.

The IRB wishes you continued success with your research.

Sincerely,
Melissa Nowicki
Digitally signed by Melissa Nowicki
DN: cn=Melissa Nowicki, o=University of Minnesota, ou=Human Research Protection Program, email=mcka0390@umn.edu, c=US
Date: 2015.11.10 16:51:22 -06'00'
Melissa Nowicki, CCRP
Research Compliance Supervisor
MN/ac

CC: Ruth Lindquist, Diane Treat-Jacobson

Driven to DiscoverSM

Appendix G

Date

This letter is intended to inform you of a research study that is being conducted at the University of Minnesota. Participation in this research study is strictly voluntary and your decision to participate or not in no way affects your relationship with the University of Minnesota Hospital or Clinics.

The University of Minnesota is seeking volunteers to participate in a research study. Patients who are at least 65 years old and have been diagnosed with heart failure are eligible to participate. This is a 1-year study funded by the American Nurses Foundation. Marjorie Webb, DNP, RN, is a PhD candidate in the School of Nursing and is the principal investigator of this study. Diane Treat-Jacobson, PhD, RN, Associate Professor in the School of Nursing, is Dr. Webb's faculty advisor.

The purpose of this study is to compare measurements that are obtained at rest with measurements that are obtained during exercise testing to see whether the resting measurements give comparable information to the exercise measurements. Individuals who agree to participate will be asked to perform a measure of breathing capacity, undergo venipuncture for one vial of blood, walk for six minutes on a flat surface, and undergo an exercise test. During the exercise test participants will be monitored by a cardiologist. All of the tests will be performed on the same day and should take less than at total of 4 hours.

Recruitment for this study began in 2014 and will continue for 1 year. Individuals who participate in the study receive a $40.00 gift card at the end of the testing day. Also, parking for all visits is included at no charge.

If you are interested in this study or would like additional information, please contact Dr. Marjorie Webb at any of the following:

- 715-928-0196 (cell)
- 651.793.1398 (message line)
- mohrx108@umn.edu

Sincerely,

The Relationship of Resting Cardiopulmonary Function to Maximal and Submaximal Cardiopulmonary Exercise Testing in Older patients with Heart Failure
(RECOuP-HF)

You are invited to participate in a research study which involves people over the age of 65 who have been diagnosed with heart failure. Often, it is hard to assess how bad your symptoms are based only on your weight and how you feel. The measures that tell us the most involve an exercise test and are often hard for older people with heart failure to do. Because of this, we want to compare measures that can be done in your health care provider's office with measures that are obtained during exercise testing. We would like to find out whether measurements obtained at rest can be used to assess your symptoms and how well your treatment is working. You were selected as a possible participant because you have been diagnosed with heart failure and you are at least 65 years old. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

This study is being conducted by Marjorie Webb, PhD candidate, DNP, RN, ACNP and her academic advisor, Diane Treat-Jacobson, PhD, RN, at the University Of Minnesota School Of Nursing. It is funded by the American Nurses Foundation.

Study Purpose
The purpose of the study is to verify whether resting measurements can be used to assess whether symptoms are being managed well and assess whether treatments are really working in older patients with heart failure.

We will compare measurements that can be obtained at rest:

- New York Heart Association classification. Cardiologists classify the severity of your heart failure based on your physical ability. We will obtain this information by viewing your medical record.
- NT-pro BNP. (Hormone secreted into your blood stream by your heart when your heart is under stress). This will be collected by venipuncture.
- Spirometry; Inspiratory capacity, forced vital capacity, and Forced expiratory volume in one second. (measurements of how much air you inhale, how much air you exhale, and how quickly you are able to exhale air) We will have you breathe in and out through a tube connected to a machine.
- 2 Functional Assessment of Chronic Illness Therapy Questionnaires. The questionnaires will ask you to rate how often shortness of breath and fatigue affect your daily living.

To measurements obtained during exercise:

- Six-Minute Walk Test Distance. (The distance that you can walk on level ground in six minutes).
- Peak Oxygen Uptake. (The highest amount of oxygen used.) This usually occurs when you are exercising hard). This measurement will be obtained near

the end of your exercise test.

- Minute Ventilation/Carbon Dioxide Production Slope. (How well you get rid of carbon dioxide.) This measure will be calculated once we get information from your cardiopulmonary exercise test.
- Cardiac Output. The amount of blood that your heart pumps in one minute). This measure will be calculated once we get information from your cardiopulmonary exercise test.

Study Procedures

If you agree to participate in this study, you would come to our testing site once. The visit should last between 3 and 4 hours. During the visit, we would ask you to do the following:

1. Complete 2 questionnaires that ask about how shortness of breath and fatigue affect your day-today life. The questionnaires should take you less than 20 minutes to finish.

2. Perform spirometry measurement while at rest. We will ask you to breathe in and out through your mouth using a tube. Once you have regulated your breathing this way (should take about 15 seconds), you will be asked to breathe in as much as possible (inspiratory capacity), out as much as possible (forced vital capacity), and breath out rapidly (forced expiratory volume). We will record these measurements. We will probably ask you to perform this procedure at least twice and possibly three times.

3. Undergo venipuncture. A small gauge needle will be used to withdraw a small sample (approximately 1 teaspoon) of blood from a vein in your arm. We will measure the laboratory value NT-pro BNP which is an indication of how much your ventricles are stretching to pump your blood.

4. Undergo a six-minute walk test. You will be monitored by our research staff while you walk for six minutes on a flat surface such as a hallway. You will be encouraged to walk at a quick pace, but you can stop and rest if needed. The distance you walk in six minutes will be recorded.

5. Undergo exercise testing. You will be asked to walk on a treadmill while your electrocardiogram (ECG, a tracing of the electrical activity of the heart) and blood pressure are monitored. Additionally, you will be asked to breathe through a mouthpiece that will be connected to a device that measures the amount of oxygen you exhale. You will begin walking at the lowest workload and on a level surface. Every three minutes the speed of the treadmill will increase and the incline on which you are walking will get steeper. This process will be repeated until you are unable to continue and must stop. The maximal amount of work you are able to

achieve will be recorded. The entire test usually takes approximately 15 minutes. During the exercise test you will be monitored by staff, a nurse, and a cardiologist. You will also be monitored by the staff for approximately 15 to 30 minutes after the test, depending on how you feel. If you experience shortness of breath or chest pain that makes it uncomfortable for you to continue, or if your ECG shows signs that your heart is being excessively strained, the exercise test will be stopped immediately.

Risks of Study Participation

The study has the following risks:

1. The risks associated with this study are primarily related to exercise. Your blood pressure will be assessed prior to exercise testing while seated and while standing. Your heart rate and ECG will be evaluated prior to starting exercise. These measures will be taken to help ensure that is it safe for you to perform the exercise test. Exercise can change blood pressure, heart rate, and rhythm, therefore, heart rate and rhythm will be monitored continuously during exercise and blood pressure will be monitored every 3 minutes during the exercise test. Exercise testing carries a small risk (1 in 10,000) of heart attack or death. In an effort to minimize this risk, only patients who are without known unstable heart disease will be permitted to participate in this study. All appropriate equipment and trained personnel will be available to deal with any unusual situations should they arise. The exercise test will be stopped if you have shortness of breath or chest pain that makes it uncomfortable for you to continue, or if you ask that it be stopped. There is a risk of bruising of the skin at the blood draw site. The individual who perform this procedure are trained in venipuncture so that this risk is minimized.

2. We will have access to your private health information and will need to use some of your information for the research. The risk here is that your information may not be kept private. Your health information will be linked to the results of your studies (for example, we will know your name and your name will be linked with your blood draw). We plan to protect your health information by using a coding process. Your name and private information for example your age) will be recorded in one place and we will use an identifier (such as a series of numbers) to distinguish information obtained during research.

Benefits of Study Participation

There are no direct benefits to you for participating in this research. The overall benefits include: the potential development of a model that your provider can use (using resting measurements) to better assess heart failure symptoms and how well treatments are working for older people with heart failure. We also hope that people eventually be able to measure inspiratory capacity at home to help them know when to contact their provider when they are not feeling well.

Study Costs/Compensation
This study should not cost you anything. We will compensate you for your time by giving you a $40.00 gift card at the end of the testing day. Additionally, we will pay for your parking on the test day.

Research Related Injury
In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury, let the study physicians know right away.

Confidentiality
The records of this study will be kept private. In any publications or presentations, we will not include any information that will make it possible to identify you as a subject. Your record for the study may, however, be reviewed by departments at the University with appropriate regulatory oversight. To these extents, confidentiality is not absolute. Study data will be encrypted according to current University policy for protection of confidentiality.

Protected Health Information (PHI)
Your PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this information.

Voluntary Nature of the Study
Participation in this study is voluntary. Your decision whether or not to participate in this study will not affect your current or future relations with the University. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

Contacts and Questions
The researcher conducting this study is Dr. Marjorie Webb. You may ask any questions you have now, or if you have questions later, **you are encouraged to** contact them at:

Dr. Marjorie Webb: 715.928.0196
Dr. Diane Treat-Jacobson (Dr. Webb's academic advisor): 612.624.7613

If you have any questions or concerns regarding the study and would like to talk to someone other than the researcher(s), you are encouraged to contact the Fairview Research Helpline at telephone number 612-672-7692 or toll free at 866-508-6961. You may also contact this office in writing or in person at *Fairview Research Administration, 2344 Energy Park Drive, St. Paul, MN 55108.*

Appendix I

RECOuP-HF Participant Face Sheet

(This side to be completed as part of initial candidate screening)

Name: _____ Date: _____

Age: _____ DOB: _____

Study Screening

Do you have heart failure? _____

If you know your ejection fraction what it is? _____

Can you read and write in English? _____

Have you stayed overnight or longer in the hospital in the last 3 months? _____

Do you have Chronic Obstructive Lung Disease (COPD)? _____

Do you have a biventricular pacemaker (also called cardiac resynchronization therapy)?

_____

Do you have any problems that would limit exercising on a treadmill for at least 10 minutes?

_____

Personal Information

Name: _____ Date Contacted: _____

Address: _____

City, State: _____ Zip Code: _____

Phone: (H) _____ (cell) _____

Subject Namecode _____ Staff Initials _____

Subject ID _____

Date _____

Page 1 of 2

RECOuP-HF Participant Face Sheet

(This side to be completed once the participant consents to participate in the study)

Emergency Contacts:

Name:_____ Relation:_____

Phone: (H)_____ (cell)_____

Name:_____ Relation:_____

Phone: (H)_____ (cell)_____

Physicians:

Cardiovascular_____

Clinic affiliation_____

Phone_____

Primary _____

Clinic affiliation _____

Phone_____

Identifier:

Assigned Namecode: _____

Assigned Numerical Identifier: _____

Subject Namecode _____ Staff Initials_____

Subject ID_____

Date _____

Page 2 of 2

Appendix J

RECOuP-HF Assessment of Participant Understanding

The Relationship of Resting Cardiopulmonary Function to Maximal and Submaximal Cardiopulmonary Exercise Testing in Older patients with Heart Failure

Name _____ Date _____

What is your understanding of the purpose of this research?

What is your understanding of spirometry?

How is spirometry obtained?

What is the purpose of a six-minute walk test?

What is your understanding of cardiopulmonary exercise testing?

How long do you expect the tests to take?

What risks are there to you if you agree to take part in the study?

What benefits are there if you agree to take part in the study?

RECOuP-HF Assessment of Participant Understanding

Understanding was assessed by_____
Participant appears to understand the consent form.

Consent form signed (prior to any study procedure) on_____

Consent form copy given to subject by_____on_____

Investigator signature_____

Subject Identifier_____

Subject Namecode _____

Date _____

Appendix K

The Relationship of Resting Cardiopulmonary Function to Maximal and Submaximal Cardiopulmonary Exercise Testing in Older patients with Heart Failure
CONSENT FORM

You are invited to participate in a research study which involves people over the age of 65 who have been diagnosed with heart failure. Often, it is hard to assess how bad your symptoms are based only on your weight and how you feel. The measures that tell us the most involve an exercise test and are often hard for older people with heart failure to do. Because of this, we want to compare measures that can be done in your health care provider's office with measures that are obtained during exercise testing. We would like to find out whether measurements obtained at rest can be used to assess your symptoms and how well your treatment is working. You were selected as a possible participant because you have been diagnosed with heart failure and you are at least 65 years old. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

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the end of your exercise test.

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If you agree to participate in this study, you would come to our testing site once. The visit should last between 3 and 4 hours. During the visit, we would ask you to do the following:

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Your PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this information.

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Contacts and Questions
The researcher conducting this study is Dr. Marjorie Webb. You may ask any questions you have now, or if you have questions later, **you are encouraged to** contact them at:

Dr. Marjorie Webb: 715.928.0196
Dr. Diane Treat-Jacobson (Dr. Webb's academic advisor): 612.624.7613

If you have any questions or concerns regarding the study and would like to talk to someone other than the researcher(s), you are encouraged to contact the Fairview Research Helpline at telephone number 612-672-7692 or toll free at 866-508-6961. You may also contact this office in writing or in person at *Fairview Research Administration, 2344 Energy Park Drive, St. Paul, MN 55108.*

You will be given a copy of this form to keep for your records.

Statement of Consent

I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

Signature of Subject_____ Date _____

Signature of Person Obtaining Consent_____ Date _____

HIPAA[1] AUTHORIZATION TO USE AND DISCLOSE INDIVIDUAL HEALTH INFORMATION FOR RESEARCH PURPOSES

---

1. Purpose. As a research participant, I authorize Dr. Marjorie Webb and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research project entitled "The Relationship of Resting Cardiopulmonary Function to Maximal and Submaximal Cardiopulmonary Exercise Testing in Older patients with Heart Failure" Funded by the American Nurses Foundation" , 141M54584.

2. Individual Health Information to be Used or Disclosed. My individual health information that may be used or disclosed to conduct this research includes: Name, age, gender, medical history (to include comorbidities), ejection fraction, New York Heart Association classification, NT-pro BNP (obtained via venipuncture), inspiratory capacity, cardiopulmonary exercise testing results (to include peak oxygen consumption and minute ventilation/carbon dioxide production slope results), and six-minute walk test distance.

3. Parties Who May Disclose My Individual Health Information. The researcher and the researcher's staff may obtain my individual health information from:

Hospitals: _____

Clinics: _____

Other Providers: _____

Health Plan: _____

and from hospitals, clinics, health care providers and health plans that provide my health care during the study.

4. Parties Who May Receive or Use My Individual Health Information. The individual health information disclosed by parties listed in item 3 and information disclosed by me during the course of the research may be received and used by Dr. Marjorie Webb and the researcher's staff and Diane Treat-Jacobson, PhD, RN, Ruth Lindquist, PhD, RN, and Ulf Bronas, PhD, ATC. Also, if I receive compensation for participating in this study, identifying information about me may be used or disclosed as necessary to provide compensation.

5. Right to Refuse to Sign this Authorization. I do not have to sign this Authorization. If I decide not to sign the Authorization, I may not be allowed to participate in this study or receive any research related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

6. Right to Revoke. I can change my mind and withdraw this authorization at any time by sending a written notice to Dr. Marjorie Webb 700 E. 7th St. St. Paul MN 55106 to inform the researcher of

---

[1] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information.

my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

7. Potential for Re-disclosure. Once my health information is disclosed under this authorization, there is a potential that it will be re-disclosed outside this study and no longer covered by this authorization. However, the research team and the University's Institutional Review Board (the committee that reviews studies to be sure that the rights and safety of study participants are protected) are very careful to protect your privacy and limit the disclosure of identifying information about you.

7A. Also, there are other laws that may require my individual health information to be disclosed for public purposes. Examples include potential disclosures if required for mandated reporting of abuse or neglect, judicial proceedings, health oversight activities and public health measures.

This authorization does not have an expiration date.

I am the research participant or personal representative authorized to act on behalf of the participant.

I have read this information, and I will receive a copy of this authorization form after it is signed.

signature of research participant or research participant's personal representative	date
printed name of research participant or research participant's personal representative	description of personal representative's authority to act on behalf of the research participant

RECOuP-HF Health History Questionnaire

NAME			
DOB:	**Age:**	☐ M ☐ F	Currently smoke? ☐ Y ☐ N
Ethnicity (circle): White (non-Hispanic) Hispanic African-American Asian Other			
Medications: prescribed drugs and over-the-counter drugs			

Medication	Dose	Frequency	Indication	Drug Class

CARDIOVASCULAR DISEASE HISTORY

HEART HISTORY			CURRENT SYMPTOMS		
Coronary Artery Disease	☐ Yes	☐ No	**Angina**	☐ Yes	☐ No
Heart Attack	☐ Yes	☐ No	**Shortness of Breath**	☐ Yes	☐ No
Atrial Fibrillation	☐ Yes	☐ No	**Fatigue**	☐ Yes	☐ No
Valvular Heart Disease	☐ Yes	☐ No	**Lightheaded/dizziness**	☐ Yes	☐ No
Cardiac Surgery		Year	**Details:**		
	☐ Coronary bypass				
	☐ Coronary stents				
	☐ Implanted pacemaker				
	☐ Implanted defibrillator				
	☐ Other				

RECOuP-HF Health History Questionnaire

GENERAL HEALTH HISTORY		
Diabetes	☐ Yes	☐ No
If yes- Type:		
Hypertension (high blood pressure)?	☐ Yes	☐ No

List any other medical problems that other doctors have diagnosed	

		Date		Date
Ejection Fraction				
NYHA class				

Coronary Angiography Date_____

Subject Namecode_____ Staff Initials_____

Subject ID_____ Health Hist - Rev. 11/20/2014

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Appendix N

RECOuP-HF Emergency Action Plan

The RECOuP-HF study personnel will follow the School of Nursing Laboratory of Clinical Physiology (SoN LCP) as posted in the SoN LCP (Moos Tower 1-210) which is as follows:

Supervisor determines the need to activate the EMS using 911.

Supervisor stays with subject and directs staff until EMS or higher trained personnel arrives to take over.

PHONE: Supervisor direct staff to Call 911—Give your name, state emergency (adult or pediatric), University of Minnesota Moos Health Science tower, 515 Delaware St. SE Minneapolis, MN 55455. Enter at 2nd door in the parking circle. Room 1-210. Tell EMS that staff will meet the EMS responders at the door to direct them to the Laboratory.

- Supervisor directs one staff member to meet EMS on the third floor by the entrance to Moos Tower (parking circle) to direct the EMS responders to the Laboratory.
- Place subject in area with easy access for EMS and to allow for proper CPR to be delivered
- Follow BLS guidelines for assessing and maintaining airway, breathing, circulation
- Place AED and follow voice automated commands.
- Place and obtain blood pressure if not already in progress
- Have subject's medication and medical history ready for the EMS responders
- Staff to call listed emergency contact
- Staff or supervisor to follow to ER if requested
- Supervisor documents the adverse event and prepares the report to IRB, and notifies the Laboratory Director (Dr. Bronas and the PI).

RECOuP-HF Spirometry Protocol

(Based on the ATS/ERS position statement: "Standardisation of Spirometry")

FEV_1 and FVC Maneuver

1. Calibration completed
2. Participant history obtained
3. Height and weight obtained
4. Instruct the participant about test technique to include:
    a) Posture
    b) Inhale rapidly and completely
    c) Exhale with maximal force
5. (Technician) demonstrate appropriate technique
6. Participant perform maneuver
    a) Correct posture
    b) Attach nose clip, place mouthpiece (with lips closed around mouthpiece)
    c) Inhale (completely and rapidly)
    d) Brief pause (<1 sec) once TLC is reached
    e) Exhale forcefully until no more air can be breathed out (while standing upright)
    f) Repeat at least 2 times until 2 adequate maneuvers have been completed
7. (Technician) record largest FEV_1 and FVC

FEV_1 and FVC **Within and between- maneuver acceptability criteria**	
Within maneuver	**Between maneuver** (at least 3 tests)
• Artefact-free Examples of artifact: ▪ Cough during 1st second ▪ Glottis closure that influences measurement ▪ Early termination ▪ Etc. • Good start (Extrapolated volume < 5% of FVC or 0.15L; whichever is greater) • Satisfactory exhalation Criteria: duration of ≥ 6 seconds or a plateau in the volume-time curve or the participant cannot or should not continue to exhale	• 2 largest values of FVC are within 0.150 L of each other • 2 largest values of FEV_1 are within 0.150 L of each other Both criteria must be met Relative contraindications for continuing: • Participant has undergone 8 trials Absolute contraindication for continuing: • Participant cannot or should not continue (dizziness, etc.)

RECOuP-HF Spirometry Protocol

IC Maneuver

1. Calibration completed
2. Participant history obtained
3. Height and weight obtained
4. Instruct the participant about test technique to include:
    a) Seated position
    b) Relaxed posture
    c) They will be asked to breathe regularly (with nose-clip in place) for several breaths until end-expiratory lung volume is stable
    d) Once end-expiratory lung volume is stable, they will be told to take a deep breath to TLC (with no hesitation)
5. (Technician) demonstrate appropriate technique
6. Participant perform maneuver
    a) Correct posture
    b) Attach nose clip
    c) Breathe regularly until lung volume stable
    d) Take a deep breath in until TLC is reached
    e) Repeat at least 2 times until 2 adequate maneuvers have been completed
7. (Technician) record largest IC

Inspiratory Capacity **Within and between- maneuver acceptability criteria**	
Within maneuver	**Between maneuver** (at least 3 tests)
• Artefact-free Examples of artifact: ▪ Cough during 1st second ▪ Glottis closure that influences measurement ▪ Early termination ▪ Etc. • Good start (Extrapolated volume < 5% of FVC or 0.15L; whichever is greater) • Satisfactory exhalation Criteria: duration of ≥ 6 seconds or a plateau in the volume-time curve or the participant cannot or should not continue to exhale	• If difference in IC between the largest and next largest maneuver in > 1.50 L, the participant should continue undergoing trials Relative contraindications for continuing: • Participant has undergone 8 trials Absolute contraindication for continuing: • Participant cannot or should not continue (dizziness, etc.)

RECOuP-HF Exercise Testing Protocol

(Based on the ATS/ACCP Statement on Cardiopulmonary Exercise Testing and the AHA Scientific Statement: "Exercise Standards for Testing and Training")

Indications for Stopping the Test

- Participant request
- Chest pain suggestive of ischemia
- Ischemic EKG changes
- Complex ectopy
- Second or third degree heart block
- Fall in systolic pressure > 20 mmHg from the highest value during the test
- Hypertension (> 250 mmHg systolic > 120 mmHg diastolic)
- Severe desaturation: ≤ 80% when accompanied by symptoms and signs of severe hypoxemia
- Sudden pallor
- Loss of coordination
- Mental confusion
- Dizziness or faintness
- Signs of respiratory failure
- Cardiologist expert opinion

Cardiopulmonary Exercise Testing

1. Calibration completed
2. Instruct the participant about test and test technique to include:
    - Explanation of Borg scale (participant's perception of exertion)
    - How to cue the technician that the participant wants to stop
3. Place EKG electrodes
4. Obtain baseline EKG and blood pressure (seated)
5. Obtain standing control torso-lead EKG, blood pressure, heart rate, and end-tidal CO_2
6. Obtain 2 standing cardiac outputs
7. Notify cardiologist
8. CPX with modified Bruce Protocol and monitored by cardiologist

Stage	Duration (min)	Speed (MPH)	Grade (%)
0	3	1	5
1	3	1.7	10
2	3	2.5	12
3	3	3.4	14
4	3	4.2	16
5	3	5	18
6	3	5.5	20
7	3	6	22

RECOuP-HF Exercise Testing Protocol

9. Continuous EKG monitoring
10. Obtain/record EKG, blood pressure, heart rate, and cardiac output every 3 minutes
11. Obtain/record participant's perception of exertion (Borg scale) every 3 minutes

Indications for Stopping the Test

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- Dizziness or faintness
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- Cardiologist expert opinion

12. Participant reaches exhaustion- CPX terminated
13. Technician calculates peak cardiac output, peak oxygen consumption, and ventilatory efficiency
14. Cool down (as needed)
15. Participant may sit/rest
16. Post-test monitoring
    - Blood pressure and heart rate 1 minute post exercise, 3 minutes post-exercise, and 6 minutes post-exercise and every 3 minutes thereafter until participant has returned to near baseline
17. Once post-test monitoring completed, offer water bottle
18. Participant to rest for 45 minutes prior to 6MWT

RECOuP-HF 6MWT Protocol

(Based on the ATS position statement: "Guidelines for the Six-Minute Walk Test")

Indications for Stopping the Test

- Chest pain
- Intolerable dyspnea
- Leg cramps
- Staggering
- Diaphoresis
- Pale or ashen appearance

6MWT

1. Course marked
2. Chair available
3. Rest time completed
4. Observer ready to mark laps on RECOup-HF 6MWT Assessment Form
5. Timer set for 6 minutes
6. Participant instructions:

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

   Demonstrate by walking one lap yourself. Walk down corridor and back briskly.

   "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog."

   "Start now or whenever you are ready."

7. When participant starts walking, start the timer
8. Mark the lap on the assessment form each time the participant completes one lap (once down and once back is 2 laps)

RECOuP-HF 6MWT Protocol

Indications for Stopping the Test

- Chest pain
- Intolerable dyspnea
- Leg cramps
- Staggering
- Diaphoresis
- Pale or ashen appearance

9. During the test:
    - After the first minute, tell the participant the following (in even tones): "You are doing well. You have 5 minutes to go."
    - When the timer shows 4 minutes remaining, tell the participant the following: "Keep up the good work. You have 4 minutes to go."
    - When the timer shows 3 minutes remaining, tell the participant the following: "You are doing well. You are halfway done."
    - When the timer shows 2 minutes remaining, tell the participant the following: "Keep up the good work. You have only 2 minutes left."
    - When the timer shows only 1 minute remaining, tell the participant: "You are doing well. You have only 1 minute to go."

    Do not use other words of encouragement (or body language to speed up).

    - If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the participant stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.
    - When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."
    - When the timer rings (or buzzes), say this: "Stop!" Walk over to the participant. Consider taking the chair if he/she looks exhausted. Mark the spot where he/she stopped (leave measuring tape at the spot).
10. Count the number of tick marks on the assessment form and record in the "total laps" space

RECOuP-HF 6MWT Protocol

Indications for Stopping the Test

- Chest pain
- Intolerable dyspnea
- Leg cramps
- Staggering
- Diaphoresis
- Pale or ashen appearance

11. Monitor blood pressure immediately post-test, 1 minute post-test, 3 minutes post-test, and 6 minutes post-test
12. Thank or encourage the participant for his/her good effort.
13. Offer bottled water.
14. Record the additional distance covered (the number of feet in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest foot, and record it on the worksheet.
15. Convert total distance walked to meters.