2012

A Comparison of Maximal Exercise Responses among Patients with a Total Artificial Heart, a Left Ventricular Assist Device, or Advanced Heart Failure

Justin M. Canada

Virginia Commonwealth University

Follow this and additional works at: https://scholarscompass.vcu.edu/etd

Part of the Medicine and Health Sciences Commons

© The Author

Downloaded from https://scholarscompass.vcu.edu/etd/340
A Comparison of Maximal Exercise Responses among Patients with a Total Artificial Heart, a Left Ventricular Assist Device, or Advanced Heart Failure

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Health & Movement Sciences at Virginia Commonwealth University

by

Justin McNair Canada

Bachelor of Science

Old Dominion University – 1997

Director: Ronald K. Evans, PhD

Associate Professor

School of Education

Health and Human Performance Department

Virginia Commonwealth University

Richmond, Virginia

May, 2012
Acknowledgement

The author wishes to thank several people. First and foremost, I would like to thank my wife, Amy, for her enduring support in this endeavor. I would like to thank my beautiful baby girls, Raegan and Reese for the long nights away from daddy while I was completing this project. I would like to thank my patient advisor, Dr. Ronald Evans for continuing to support me when this task became much longer than I/ we thought. In addition, I would like to thank Dr. Edmund Acevedo for his advice and willingness to serve on my committee. Lastly, I would like to thank Dr. Keyur Shah for his interest in exercise physiology, vigorous support of our exercise testing laboratory, and consummate advice.
# Table of Contents

List of Tables ......................................................................................................................... iv  
List of Figures .......................................................................................................................... v  
List of Abbreviations .............................................................................................................. vi  
Thesis Abstract ......................................................................................................................... viii  
Thesis Introduction .................................................................................................................... 1  
Review of Literature .................................................................................................................. 6  
Manuscript ................................................................................................................................ 65  
  Abstract ................................................................................................................................. 65  
  Introduction .......................................................................................................................... 66  
  Methodology ......................................................................................................................... 70  
  Results ................................................................................................................................. 80  
  Discussion ........................................................................................................................... 92  
  Manuscript Bibliography ...................................................................................................... 97  

Appendix 1  
  Thesis Bibliography .............................................................................................................. 103  

Appendix 2  
  Significant Differences of CPET Variables between HF groups ................................................. 116  

Appendix 3  
  Institutional Review Board Approval ....................................................................................... 117
List of Tables

Review of Literature

1. Weber Functional Classification Scale ................................................................. 29

Manuscript

1. Clinical Characteristics of Heart Failure Groups ......................................................... 82

2. MCS Device Specific Variables .................................................................................. 83

3. Standard Exercise Test Variables ............................................................................... 85

4. Descriptive CPET Variables ...................................................................................... 87

5. Weber Functional & Ventilatory Class Schema .......................................................... 89

Appendix 2

1. Significant Differences of CPET Variables between HF groups ............................... 116
List of Figures

Review of Literature

1. Activation of the renin-angiotensin-aldosterone system (RAAS) ............................................. 16

2. HeartMate I – XVE LVAD ...........................................................................................................43

3. Internal Workings of HeartMate II LVAD .................................................................................. 44

4. Thoratec HeartMate II LVAD .................................................................................................... 46

5. Artificial Heart in Comparison to Human Heart .......................................................................... 48

6. TAH with Big-Blue Console ...................................................................................................... 50

7. TAH with SynCardia Freedom Driver Console .......................................................................... 51

Manuscript

1. Peak VO₂ by HF Group .............................................................................................................. 88
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF</td>
<td>Heart Failure</td>
</tr>
<tr>
<td>TAH</td>
<td>SynCardia Total Artificial Heart</td>
</tr>
<tr>
<td>HMII</td>
<td>Thoratec HeartMate II</td>
</tr>
<tr>
<td>LVAD</td>
<td>Left-ventricular assist device</td>
</tr>
<tr>
<td>CPET</td>
<td>Cardiopulmonary Exercise Test</td>
</tr>
<tr>
<td>MCS</td>
<td>Mechanical Circulatory Support</td>
</tr>
<tr>
<td>VO₂</td>
<td>Ventilatory Oxygen Consumption</td>
</tr>
<tr>
<td>VCO₂</td>
<td>Ventilatory Carbon Dioxide Production</td>
</tr>
<tr>
<td>VE</td>
<td>Minute Ventilation</td>
</tr>
<tr>
<td>VAT</td>
<td>Ventilatory Anaerobic Threshold</td>
</tr>
<tr>
<td>OUES</td>
<td>Oxygen Uptake Efficiency Slope</td>
</tr>
<tr>
<td>RER</td>
<td>Respiratory Exchange Ratio</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean Arterial Pressure</td>
</tr>
<tr>
<td>EDV</td>
<td>End Diastolic Volume</td>
</tr>
<tr>
<td>LV</td>
<td>Left Ventricle</td>
</tr>
<tr>
<td>6MWD</td>
<td>Six-Minute Walk Distance</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary Artery Disease</td>
</tr>
</tbody>
</table>
AICD  Automatic Internal Cardioverter Defibrillator
PetCO2  Partial Pressure End-tidal Carbon Dioxide
BMI  Body Mass Index
MET  Metabolic Equivalent
HTx  Heart Transplant
ESHF  Advanced Heart Failure
NICM  Non-Ischemic Cardiomyopathy
ICM  Ischemic Cardiomyopathy
CHD  Congenital Heart Disease
Hgb  Hemoglobin
BTT  Bridge to Transplant
BTD  Bridge to Decision
DT  Destination Therapy
bpm  beats per minute
RPE  Rating of Perceived Exertion
RPD  Rating of Perceived Dyspnea
Abstract

A COMPARISON OF MAXIMAL EXERCISE RESPONSES AMONG PATIENTS WITH A TOTAL ARTIFICIAL HEART, A LEFT VENTRICULAR ASSIST DEVICE, OR ADVANCED HEART FAILURE

By Justin McNair Canada, BS

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Health & Movement Sciences at Virginia Commonwealth University.

Virginia Commonwealth University, 2012.

Major Director: Ronald K. Evans, PhD, Associate Professor, School of Education, Health and Human Performance Department

The purpose of this study was to evaluate graded exercise responses to treadmill exercise in patients with a total artificial heart (SynCardia, Tucson, AZ). Additionally, this study sought to compare the exercise response in total artificial heart (TAH) patients to both advanced heart failure (HF) patients on medical management only and HeartMate II (Thoratec Corp., Pleasanton, CA) left-ventricular assist device (HMII) patients. For patients with biventricular heart failure the TAH is a viable option to bridge patients until transplant becomes available. Its demonstrated improvement in mortality and increasing usage necessitates a shift in focus to quality of life in the TAH patient including functional ability. The evaluation of cardiorespiratory responses to graded exercise provides an objective measure of functional ability. There is very limited information in the literature on the exercise response of the
mechanical circulatory support (MCS) device patient, particularly the TAH patient. A review was performed on MCS patients who underwent symptom-limited cardiopulmonary exercise testing (CPET) following device implant of either TAH or HMII. ANOVA was performed to compare differences between the two device groups and HF patients listed for heart transplant. Fourteen TAH patients underwent CPET (9 male, 5 female) with peak oxygen consumption ($\dot{V}O_2$) of 0.926 ± .168 L·min, 36 ± 8% % predicted, 11.0 ± 2.3 ml.kg.min or 3.1 ± 0.7 METs. Ventilatory anaerobic threshold (VAT) was 0.706 ± .181 L·min. Peak $\dot{V}O_2$, % pred. $\dot{V}O_2$ and VAT were significantly lower in the TAH compared with HMII and advanced HF ($p = 0.0012$, $p = 0.0106$, $p = 0.0009$, respectively). Peak RER was significantly higher ($p < .0001$) and OUES was significantly lower ($p = 0.0004$) in the TAH. Exercise capacity is significantly reduced in the TAH patient below that observed in HMII LVAD and advanced HF patients. This provides a baseline for expected functional status and has implications on the ADL tolerance of these individuals. The next step is to develop strategies to ameliorate this continued exercise intolerance.

The documents herein contain a review of literature including a background in heart failure and the use of the exercise response in the heart failure patient. An overview is also presented on the use of MCS describing physiology, device function, and exercise physiology of the MCS device patient. A manuscript has also been included detailing a cross-sectional review of the effects of graded exercise in the TAH patient and comparing it to the HMII and advanced HF patient.
Introduction

Heart failure, which is a syndrome that includes circulatory congestion and/or inadequate tissue perfusion, can be caused by any type of condition that damages the heart and typically leads to debilitating symptoms of dyspnea, fatigue, and exercise intolerance. It carries attributable risks, increasing incidence, an ominous prognosis, complex pathophysiology, and can be a challenge to manage.\(^1\) The American Heart Association estimates that there are 5.7 million Americans living with heart failure and 600,000 new cases are diagnosed annually.\(^2\) Lifetime risk of heart failure development is 1 in 5 for both men and women, and hypertension is associated with 75% of all heart failure cases.\(^3,4\) Furthermore, the incidence is highest among African-Americans and it increases with advancing age.\(^5,4\) Risk factors for the development of heart failure include coronary artery disease, hypertension, cardiomyopathy, myocardial infarction (MI), obesity, diabetes, dyslipidemia, valvular heart disease, renal insufficiency, sleep-disordered breathing, and tachycardia.\(^1,6\) Antecedent MI and hypertension are the most attributable risk factors.\(^3,7\) Approximately 50% of those diagnosed with heart failure will die within 5 years and it carries a mortality risk that is four times that of the general population of like age.\(^7,8\) Lastly, heart failure is the most common hospital discharge diagnosis and consumes more Medicare dollars than any other diagnosis.\(^2,7\)
Advanced heart failure therapies are available for patients with end-stage disease who are refractory to conventional medical management. This includes the use of inotrophic agents, heart transplantation, and mechanical circulatory support (MCS) devices. Heart transplantation remains the definitive therapy for those with refractory end-stage heart failure. Unfortunately, the demand for heart transplants continues to significantly exceed the supply of donor hearts. This has led to the increasing use of mechanical circulatory support devices to keep patients alive until heart transplant. To date, the majority of MCS devices implanted are left-ventricular assist devices (LVAD) which unload the native heart’s left ventricle and improve survival and quality of life. However, there is a subset of patients with advanced heart failure that are not appropriate candidates for LVAD therapy due to right-sided heart failure or biventricular failure. For these patients, the SynCardia Total Artificial Heart (TAH) is the most effective treatment therapy as a bridge to heart transplant. The TAH consists of two pneumatically driven pumps that orthotopically replace the failing hearts native ventricles.

Typically, clinical evaluation of the heart failure patient includes identification of causes, description of symptoms, evaluation of cardiac structure, and quantification of functional status. Patients are stratified according to heart failure risk, presence of cardiac structural changes, functional status, and presence of symptoms. This allows determination of prognosis and guides management. In heart failure, cardiopulmonary exercise testing (CPET)
has proven to be a reliable tool to guide therapy, estimate prognosis, and evaluate patients for heart transplant.\textsuperscript{14} Quantification of the exercise response in heart failure is valuable because of its ability to determine prognosis and provide insight into the pathophysiological processes of the disease state.\textsuperscript{15,16} In healthy individuals, the ability to perform dynamic activities is largely determined by the heart's ability to appropriately increase cardiac output to provide adequate blood flow and oxygen to working muscles and organs.\textsuperscript{14} In heart failure, a reduced cardiac output along with pulmonary congestion and deconditioning lead to impairment in the ability to perform exercise\textsuperscript{17} therefore exercise intolerance is a hallmark symptom of heart failure along with pulmonary congestion. The relationship between exercise performance and heart failure severity has led to the use of exercise testing in the evaluation and management of heart failure patients.

Due to its ability to stratify risk and accurately measure exercise capacity, CPET is considered a core assessment of the heart failure patient.\textsuperscript{18} CPET variables have been shown to correlate with cardiac function, pulmonary hemodynamics, and neurohormonal status.\textsuperscript{18} Standard CPET variables assessed in heart failure include peak oxygen consumption, ventilatory anaerobic threshold, ventilatory efficiency slope, oxygen uptake efficiency slope, partial pressure of end-tidal carbon dioxide, presence of an exercise oscillatory breathing pattern, and respiratory exchange ratio.\textsuperscript{19}
The utility of CPET after MCS device implant is less well-established due to a scarcity of information on this unique patient population. Most of the available literature describing exercise in the MCS patient has been based upon 1st generation or pulsatile-flow left ventricular assist devices. There is, however, a distinct lack of studies examining the effects of exercise in MCS device patients particularly the newer continuous-flow LVAD devices. In regards to the exercise response of the TAH patient there is an even further paucity of information with very few studies available describing the functional status of the TAH patient. Therefore, the purpose of this study was to evaluate the cardiorespiratory responses to graded exercise in the TAH patient. Additionally, we sought to compare those responses to responses obtained from HeartMate II LVAD patients and non-MCS device patients with advanced heart failure who had been evaluated and accepted for heart transplantation. It is hypothesized that exercise capacity, specifically the peak oxygen uptake, will be significantly reduced in heart failure patients after TAH implant compared with HeartMate II LVAD patients and patients with advanced heart failure un-supported by MCS device. Additionally, it is hypothesized that an abnormally elevated ventilatory response to exercise exists in the TAH patient due to the early onset of acidosis. This will result in an increased ventilatory efficiency slope and a concomitant reduction in the oxygen uptake efficiency slope in the TAH patient compared with HeartMate II LVAD patients and patients with advanced heart failure un-supported by MCS device. The initial characterization of this exercise response along with comparisons to more common
patient populations will provide insight into the functional limitations of the TAH patient and possible mechanisms for their exercise intolerance.

This thesis document has been organized to include a relevant review of the literature in regards to heart failure and the use of CPET variables in HF evaluation & management. Furthermore, this includes an overview detailing the use of MCS in advanced HF management, the physiology and function of the MCS device, and lastly the exercise physiology of the MCS device patient. A manuscript titled “A Comparison of Maximal Exercise Responses among Patients with a Total Artificial Heart, a Left Ventricular Assist Device, or Advanced Heart Failure” is also included describing a cross-sectional retrospective analysis of symptom-limited CPET’s performed on the TAH patient which were compared with the HMII LVAD patient and non-MCS device patients with advanced heart failure. Additionally, within group comparisons were performed to elucidate contributors to the exercise intolerance of these patient populations.
Heart Failure

Heart failure is a clinical syndrome in which heart disease reduces cardiac output, increases venous pressures, and is accompanied by molecular and other abnormalities that cause progressive deterioration in cardiac function. The American College of Cardiology/American Heart Association Practice Guideline for the Diagnosis & Management of Heart Failure defines heart failure as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. It can be characterized as the result of various etiologies which damage the heart and cause impairment, disability and premature death. The cardinal signs/symptoms of heart failure are dyspnea, fatigue, exercise intolerance, and fluid retention which can lead to peripheral edema and/or pulmonary congestion. Because not all patients with heart failure exhibit fluid retention, the term “heart failure” is increasingly preferred over the historic term “congestive heart failure (CHF)”.

Incidence
In developed countries, heart failure has become epidemic. Based on recent American Heart Association (AHA) statistics, there are 5.7 million American adults living with a diagnosis of heart failure and 600,000 new cases of heart failure diagnosed annually. 2 The lifetime risk of developing heart failure is 1 in 5 individuals for both men and women. 4 However, this lifetime risk varies with the etiology of heart failure onset. At 40 years of age, the lifetime risk of heart failure occurring without a preceding MI is 1 in 9 for men and 1 in 6 for women. 4

Seventy-five percent of all heart failure cases are associated with a history of hypertension. 4 African-Americans appear to have the highest incidence of heart failure across the races. 5 They also appear to have the highest heart failure incidence without antecedent myocardial infarction. 5 The lifetime risk of developing heart failure for people with blood pressure >160/90 mmHg is double that of those with blood pressure <140/90 mmHg. 4

Heart failure incidence is known to increase with age. The incidence of heart failure approaches 10 per 1,000 people in those over the age of sixty-five years and rises to > 40 per 1,000 people in those aged 85 years or older. 4 This has important implications given the rising age of the U.S. population. The incidence of heart failure has been relatively stable over the past 30 years. However, the prevalence of heart failure is increasing, which is felt to be in part due to the aging of the population and the improved survival following myocardial infarction. While the overall mortality rate of acute myocardial infarction (AMI) has declined this improved
survival may be increasing the prevalence of heart failure as antecedent MI is a known risk factor for future development of heart failure. Lastly, with the growing prevalence of hypertension, and exponential increases in diabetes and obesity rates, which are both known heart failure risk factors, may explain the increased prevalence of heart failure.

**Burden**

Heart failure imposes both a significant health as well as financial burden. In terms of prognosis, approximately 50% of people diagnosed with heart failure will die within 5 years. In 2007, heart failure was associated with a mortality of 277,193 individuals (121,684 males and 155,509 females). Data from the Framingham Study suggested that of those with clinically-manifest heart failure, the median survival was only 1.7 years for men and 3.2 years for women, with only 25% of men and 38% of women surviving 5 years. This is a mortality rate 4 times that of the general population of the same age.

In terms of financial burden, heart failure is the most common hospital discharge diagnosis in adults over the age of sixty-five years in the United States. Heart failure is accountable for 1,000,000 hospitalizations per year and costs more than $25 billion. Heart failure is the most common Medicare hospital discharge diagnosis-related group, and more Medicare dollars are spent for the diagnosis and treatment of heart failure than for any other diagnosis.
Etiology

Heart failure (HF) can be caused by any type of condition that damages the heart. There are a host of known risk factors for heart failure including coronary heart disease, hypertension, cardiomyopathy, prior myocardial infarction, obesity, diabetes, lipid abnormalities, valvular heart disease, renal insufficiency, sleep-disordered breathing, and tachycardia. 1, 6

Coronary Heart Disease Based on National Health and Nutrition Examination Survey I (NHANES I) data, He and colleagues concluded that more than 60% of the heart failure that occurs in the general U.S. population might be attributable to coronary heart disease. 28

Hypertension Additionally, data from the Framingham study have shown that hypertension precedes heart failure in 91% of patients. 3 In contrast to the NHANES I data, the Framingham study credited hypertension with the highest population attributable risk (PAR) for heart failure, accounting for 39% of the risk in men and 59% of the risk in women. 7

Myocardial Infarction Prior myocardial infarction seems to account for 34% and 13% of heart failure risk in men and women, respectively. 7

Obesity In the Physicians Health Study, the risk of heart failure increased 11% for every 1-unit (kg/m²) increase in body mass index (BMI). Body weight status categorization revealed overweight participants have a 49% increased HF risk and obese individuals carry a 180% increased risk of heart failure compared with lean individuals (BMI <25). 29
Diabetes  Approximately 19% of those with heart failure have diabetes and it appears to account for 6 – 12% of HF incidence based on the Framingham study data. \(^7\) Poor glycemic control appears to have a positive relationship with HF risk. Iribarren and colleagues found that for every 1% increase in glycosylated hemoglobin (HgbA1c) the risk of heart failure increased by 8%. \(^30\)

Lipid Abnormalities  There appears to be a significant association between abnormal lipid profiles and incidence of heart failure. Sampietro et al. found a strong and independent association between low high-density lipoprotein (HDL) levels and the presence of dilated cardiomyopathy. \(^31\) They suggested low HDL levels may play a role in the endothelial-microvascular dysfunction seen in idiopathic dilated cardiomyopathy.

Valvular heart disease  Valvular heart diseases more than doubles the risk of HF but is present in only 5% of the population so that only 7% of HF can be attributed to this cause. \(^7\)

Impaired renal function  Renal insufficiency is related to a higher risk of new-onset heart failure even after adjusting for traditional risk factors. This risk also tends to increase based upon worsening of renal function. \(^32\)

Sleep disordered breathing  Sleep disordered breathing confers an increased risk of heart failure development. \(^33\) Javaheri et al. describes a prevalence of central sleep apnea (CSA) in 40% and obstructive sleep apnea (OSA) in 11% of heart failure patients. \(^34\) The reason for this increased risk seems to be multifactorial in regards to pathophysiology, but also persists after
accounting for associated risk factors. Sympathetic nervous system activity dependent upon sleep phases is disturbed by recurring episodes of apnea. In sleep apnea at the end of each apnea episode, sympathetic activation reaches a maximum level. Recurrent hypoxemic stress seems to increase endothelin secretion and induces vasoconstriction. Catecholamine levels are also elevated.

**Tachycardia** Tachycardia-induced cardiomyopathy also confers increased risk of heart failure. The Framingham Heart study demonstrated that for every 10-beat per minute increase in heart rate there was a >10% higher risk for heart failure.

Other traditional well-known modifiable coronary artery disease risk factors are associated with heart failure risk. Current cigarette smoking was found to be a major independent risk factor for development of heart failure in NHANES I. Smoking was associated with a relative risk of 1.45 and the relationship was independent of hypertension, body weight, and other heart failure risk factors. This indicates that the direct effects of smoking on heart failure are more than that attributed to its known coronary heart disease risk impact.

Lack of physical activity or physical inactivity has also been shown to be an important risk factor for heart failure development. Higher levels of physical activity are well-known to confer a reduced risk of antecedent heart failure risk factors such as CAD, hypertension, diabetes, and obesity. After adjusting for known antecedent HF risk factors, NHANES I found
that physical inactivity accounted for a population attributable risk for heart failure of approximately 9%. It is unclear, however, if a direct relationship exists between heart failure and physical activity levels. Lastly, depression has also been linked to heart failure incidence. Depressed elderly patients have been shown to have a two-fold higher likelihood of developing heart failure.

Pathophysiology

The signs/symptoms of heart failure are mainly the result of hemodynamic derangements. These derangements are influenced by neurohumeral abnormalities, cardiac remodeling, and cellular and molecular abnormalities.

The ability of the heart to pump blood is reduced in heart failure. Cardiac performance is influenced by heart rate, the volume of blood ejected with each heartbeat, and the pressure at which the blood is ejected. The volume of blood ejected with each heart beat is termed the stroke volume. Stroke volume is the result of end-diastolic volume (EDV) minus end-systolic volume (ESV). Cardiac output is the product of stroke volume x heart rate. It is the total amount of blood pumped by the heart per minute.

The pressure at which the blood is ejected is related to the filling properties and ejection capabilities of the ventricle. Ventricular filling is determined by venous return or pre-load, end-systolic volume from the previous heartbeat, and the ability of the ventricle to relax. The
ejection capabilities of the ventricle depend upon the arterial pressure (MAP) or after-load, end-diastolic volume prior to systole, and the contractility of the ventricle. 25

The reduced cardiac output seen in heart failure may be due to a derangement in the cardiac cycle (i.e. heart rate), failure of the ventricle to properly contract during systole, and/or failure of the ventricle to properly relax and fill during diastole. The systolic dysfunction seen in heart failure is characterized by abnormalities in the basic properties that determine stroke volume. 6 This includes contractility, myocardial mass, pre-load or EDV, and after-load or MAP.

Contractility is the ability of myocardial tissue to generate force. Ejection fraction, which is the percentage of the end-diastolic volume that is ejected during systole, is most commonly used to assess contractility or systolic function. However, ejection fraction is also influenced by pre-load, afterload, and myocardial mass. Ejection fraction is a known strong prognostic indicator in heart disease. 40 An ejection fraction of \( \leq 40\% \) is considered reduced or depressed and associated with poor outcomes. 41, 42

Myocardial mass is influenced by the degree of compensatory cardiac hypertrophy that takes place in heart failure. Left-ventricular hypertrophy is usually described as either concentric hypertrophy due to pressure overload and/or eccentric hypertrophy due to volume overload. Left-ventricular hypertrophy is an adaptive response wherein the myocardium compensates for increasing ventricular wall stress from either pressure and/or volume overload.
according to Laplace’s law. Laplace’s law states wall stress or tension is dependent upon LV pressure and/or LV size (radius) and is defined by the following equation: Wall stress = (pressure x radius)/ wall thickness. Concentric hypertrophy results in increased ventricular wall thickness without a change in ventricular chamber size. Eccentric hypertrophy results in increased ventricular chamber size without an accompanying change in wall thickness.

Pre-load is dependent upon venous return which affects end-diastolic volume which in turn affects myocardium sarcomere stretch. After-load is the force that myocardium must overcome in order to contract. As after-load increases contraction decreases leading to an increased end-systolic volume thus decreasing stroke volume.

The diastolic dysfunction seen in heart failure is a result of impaired ventricular relaxation and filling. Diastolic filling is driven by the left-atrial (LA) to left-ventricle (LV) pressure gradient. This pressure gradient is dependent upon myocardial relaxation, LV elastic properties, LV elastic recoil, LV contractile state, LA pressures, ventricular interaction, pericardial constraint, LA elastic properties, pulmonary veins, and mitral orifice. The failure of the ventricle to relax maybe in part due to enhanced sympathetic tone.

Although the key feature of heart failure is the inability of the heart to act as a pump, secondary adaptive responses to maintain short-term cardiac performance lead to maladaptation’s that contribute significantly to the long-term progression of heart failure.
These maladaptations due to the onset of heart failure occur in the peripheral circulation, the kidneys, skeletal muscle, and almost every other organ of the body. Neurohumeral Abnormalities

Neurohumeral abnormalities greatly influence the progression of heart failure. Early in heart failure, there may be a decrease in cardiac output, arterial pressure, and baroreceptor activity, leading to an adaptive increase in excessive neuroendocrine drive. The sympathetic nervous system is activated early, followed by activation of the renin–angiotensin–aldosterone system (RAAS). This leads to heightened levels of neurohumeral vasoconstrictors such as norepinephrine, angiotensin II, endothelin, vasopressin, neuropeptide Y which leads to increased systemic vascular resistance. Sodium and water retention also occur due to RAAS activation to maintain cardiac output and arterial blood pressure which comes at the expense of chronically elevated neuroendocrine activation. This leads to desensitization of sympathetic modulation and a decreased vagal tone. The reduction of parasympathetic control is a hallmark sign of how heart failure affects the central nervous system and is demonstrated by a loss of heart rate variability. Figure 1 illustrates the activation of the RAAS system.
**Cardiac Remodeling**

Maladaptive remodeling of cardiac myocyte size and shape begins long before clinical heart failure. \(^{47}\) Increased myocardial work from excess pressure-loading, volume-loading or ischemia causes alterations in cardiac myocyte proteins and architectural changes to ventricular myocardium. \(^{48,49}\) Cardiac myocyte hypertrophy occurs to compensate for the elevated ventricular wall stress. This causes structural change to the ventricular myocardium and leads to augmented ventricular mass, chamber size, and further deterioration of pump function. Collagen deposition in the cardiac interstitium is also a contributor to impaired ventricular function and structure. \(^{50}\) The neuroendocrine activated vasoconstrictors and RAAS system also facilitate this collagen deposition. \(^{51}\)

**Cellular and Molecular Abnormalities**

Skeletal muscle abnormalities in addition to myocardial abnormalities are well described in those with chronic heart failure. \(^{52,41}\) Heart failure alters skeletal muscle contraction at the level of the myosin-actin cross-bridge thereby...
adversely affecting muscular performance. This is felt to be one of the primary contributors to the exercise intolerance of the heart failure patient.

**Evaluation**

There is no single tool for the diagnosis of heart failure. Patient evaluation often includes: functional evaluation, cardiac structure evaluation, laboratory assessment, and symptomology. Most heart failure patients initially present to a healthcare provider in one of three ways: a syndrome of exercise intolerance, fluid retention disorder, or with signs or symptoms of another cardiac disorder. Identification of possible causes of the heart failure is first in the evaluation process and starts with the standard history & physical examination.

A staging system has been developed to classify patients with heart failure that takes into account both the development and progression of the disease. Patients are staged as A, B, C, or D as follows: heart failure risk (Stage A), structural changes to the heart although asymptomatic (Stage B), past or current heart failure symptoms accompanied by structural heart disease (Stage C), and those with refractory heart failure that do not respond to conventional treatment (Stage D) who may benefit from more advanced heart failure strategies. This strategy allows for more specific treatment depending upon stage to reduce mortality and morbidity.
Patients’ functional abilities are often characterized based on the New York Heart Association (NYHA) classification scale which is a subjective assessment of activity tolerance. The NYHA functional classification scale assigns patients to one of four classes based on presence of symptoms and limitations with varying levels of activity. It is, however, associated with a significant degree of inter-observer variability and does not reflect changes in exercise capacity. As a result, more objective indicators of functional status including the distance that a patient can walk in six-minutes (6MWD) and measurement of peak oxygen consumption with maximal exercise testing are utilized. Peak oxygen consumption with exercise testing is considered a key prognostic indicator in patients with heart failure. Evaluation of other exercise-related variables reflecting cardiac output, central nervous system function, and ventilation provide additional powerful prognostic information in the heart failure population.

Evaluation of cardiac structure allows for identification of mechanisms leading to heart failure. The most common and useful diagnostic test to assist in the evaluation of heart failure is the two-dimensional echocardiogram coupled with Doppler-flow to detect cardiac abnormalities. This allows evaluation of the myocardium, determination of ejection fraction, ventricular structure, valve-function, pericardium, and which chamber(s) are involved. Hemodynamic data such as atrial and ventricular filling pressures and stroke volume can also be estimated with the use of this modality.
Laboratory assessment can identify factors contributing to or exacerbating the progression of heart failure. Evaluation of patients with heart failure includes a complete blood count, urinalysis, serum electrolytes, glycosylated hemoglobin, lipid profile, tests of both renal and hepatic function, a chest radiograph, and a 12-lead electrocardiogram.\textsuperscript{1} Assessment of thyroid function and screening for human immunodeficiency virus is also recommended\textsuperscript{1}. Evaluation of the neurohormone brain-natriuretic peptide (BNP) is an accepted part of clinical practice in heart failure evaluation and is used to guide management.\textsuperscript{56} Elevated BNP is associated with elevated ventricular filling pressures, ischemia, and ventricular hypertrophy. Reduction of BNP is also associated with improved clinical outcomes.\textsuperscript{56}

Assessment of volume status is also critical in the heart failure evaluation. The presence of fluid retention is monitored through measurement of body weight, blood pressure, jugular venous distention, peripheral edema, and organ congestion. Volume status assessment helps determine the need for diuretic therapy and can be used to guide drug-therapies used to treat heart failure.\textsuperscript{1}

Identifying the presence and the extent of symptoms is part of the heart failure evaluation. Common signs and/or symptoms of heart failure include dyspnea, fatigue, orthopnea, nocturnal dyspnea, and exercise intolerance. Orthopnea is a difficulty in breathing that occurs while the patient is lying down. Nocturnal dyspnea is a shortness of breath that
occurs while sleeping which improves with sitting or standing upright. Complaints of chest discomfort also require evaluation as up to two-thirds of patients with heart failure are known to have coronary artery disease. \(^{57}\) It is noted, however, that up to one-third of patients with a non-ischemic cardiomyopathy also report chest discomfort symptoms. \(^{1}\) The type of symptoms present can influence patient management. \(^{58}\) Symptoms often attributed to heart failure can also be due to other contributing comorbid conditions such as obesity, deconditioning, anemia, and/or pulmonary disease. Cardiopulmonary exercise testing can assist in the determination of symptomology. \(^{14}\)

**Management**

The management of heart failure consists of trying to reverse the potential causes, ameliorate the symptoms, improve quality of life, and improve prognosis. \(^{6}\) A number of different evidence-based pharmacologic agents, nonpharmacologic therapies and/or electronic devices have demonstrated efficacy in heart failure management. \(^{1}\) Advanced heart failure therapies are available to those who are refractory to conventional management. \(^{1}\)

*Risk Factor Management*

Management of identified risk factors includes improving blood pressure control in hypertensives, lowering blood glucose in those with insulin resistance or diabetes, as well as improving the overall cardiovascular profile in those with CAD or substantial CAD risk.
Achievement of optimal blood pressure control can reduce risk of heart failure by 50%, this risk is decreased even further in those who improve blood pressure control following myocardial infarction. \(^{59}\) Individuals with hypercholesterolemia or CAD should similarly lower lipid levels. \(^{59}\) Removal of potential causes of myocardial injury (i.e. smoking, excess alcohol consumption, cocaine or stimulant use) is also recommended although this has not been shown to directly decrease heart failure risk. \(^{1}\)

**Pharmacologic Agents**

Diuretics are considered a cornerstone of heart failure therapy because most patients present with some form of organ congestion. \(^{13}\) Diuretics improve the signs and symptoms of heart failure despite little evidence to support their efficacy or impact on survival. \(^{13}\) They work primarily by removing excess salt and water thus lowering filling pressures and relieving congestion. Excess fluid restriction and reduction of sodium intake are also standard heart failure recommendations to achieve a similar outcome.

Digitalis glycosides which have been around for over 200 years also improve heart failure outcomes. They have been shown to improve quality of life, reduce symptoms, and increase exercise tolerance in individuals with heart failure in several placebo-controlled trials. \(^{60}\) Digitalis seems to act as both an inotropic agent as well as attenuating the RAAS system.
Because of the known effects of the RAAS system on heart failure, pharmacological agents targeting this system are an integral part of heart failure management. Specifically, inhibiting the conversion of angiotensin I to angiotensin II, and blocking the angiotensin and aldosterone receptors has been shown to alleviate symptoms, improve clinical status, and reduce risk of death and hospitalization in patients with heart failure. Angiotensin-converting enzyme inhibitors (ACE-Inhibitors) are the most widely studied of all heart failure agents and the recommended first choice RAAS inhibitors.

Increased sympathetic nervous system activation is one of the most important factors responsible for the progression of heart failure. It seems intuitive that agents which block sympathetic activity would improve heart failure prognosis. However, historically, it was thought that beta-adrenergic receptor antagonists (i.e. beta-blockers) would worsen heart failure due to their negative inotropic effects and in essence further compromise hemodynamic status. Results of large-scale clinical trials have clearly demonstrated the efficacy of beta-blockers in the treatment of heart failure. All-cause mortality risk is decreased on the order of approximately 35% in heart failure patients on beta-blockers.

Vasodilators such as isosorbide dinitrate and hydralazine also show efficacy in heart failure management in specific subgroups. Post-hoc analysis of the Vasodilator-Heart Failure
Study (V-HeFT) demonstrated African-American heart failure patients derived a significant benefit from these agents. 62

**Nonpharmacologic Therapies**

Cardiac resynchronization therapy (CRT) is yet another therapeutic option for persistently symptomatic heart failure patients. Dyssynchrony between the heart chambers is an important determinant of both systolic and diastolic function. Dyssynchrony is defined with a surface electrocardiogram wherein the QRS complex duration is greater than 120 milliseconds. The consequences of dyssynchrony include suboptimal ventricular filling, a reduction in the rise of ventricular contractile force or pressure, prolonged duration of mitral regurgitation, and paradoxical septal wall motion. 63 There is strong evidence to support the use of CRT in symptomatic heart failure patients to improve cardiac dyssynchrony. 1 CRT has been shown to improve quality of life, six-minute walk distance (6MWD), peak oxygen consumption (VO2), NYHA functional class, and ejection fraction. 64

Heart failure patients who have evidence of ventricular tachydysrhythmias or who are at risk of sudden cardiac death may also benefit from implantation of an automatic implantable cardioverter defibrillator (AICD). 1 AICD implantation is indicated in survivors of cardiac arrest. It is also indicated in NYHA Class II or III heart failure patients with an ejection fraction of ≤ 35% who have good functional status and a good 1-year prognosis. 65
Exercise training is recommended as an adjunct to pharmacotherapy for chronic stable heart failure patients.\textsuperscript{1} Historically, it was thought exercise training would accelerate the progression of ventricular dysfunction.\textsuperscript{66} This, however, is not the case with more recent evidence actually showing the reverse. Haykowsky et al. performed a meta-analysis of the effect of exercise-training on left ventricular remodeling and found aerobic exercise actually reverses LV remodeling.\textsuperscript{67} The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-Action) trial also demonstrated the efficacy as well as the safety of exercise-training in individuals with heart failure.\textsuperscript{68} This study found that exercise training was associated with modest, but significant, reductions in overall and cardiovascular mortality and hospitalization despite significant non-adherence to the exercise programs.

\textit{Advanced Heart Failure Therapies}

Advanced heart failure therapies are available for patients with end-stage disease who are refractory to conventional medical management. This comprises patients who are considered Stage D and symptomatic at rest (NYHA IV) and exhibit significant functional limitations. Therapies include continuous positive intravenous inotropic agents, mechanical circulatory support, and or heart transplantation.

Positive intravenous inotropic agents are often utilized to manage Stage D patients who are frequently hospitalized and require inotropic support to improve cardiac performance and
promote stability. This can help prevent deterioration of patients awaiting heart transplantation and/or allow these patients to be discharged for palliative care.

Heart transplantation remains the definitive therapy for those with refractory end-stage heart failure. Heart transplantation is indicated in those with a very-poor one year prognosis. The one year survival rate after heart transplant is approximately 88% with a median 50% survival rate approaching 11-years. Heart transplantation also improves quality of life with 75% of recipients reporting a healthy lifestyle or only a few disease symptoms within the first years after transplant. Unfortunately, the demand for heart transplants continues to significantly exceed the supply of donor hearts. The number of heart transplants being performed peaked in the mid-1990’s and has remained relatively stable in the current decade at around 4,000 per year world-wide and around 2,000 per year in the United States. The time spent waiting for a heart transplant as well as the severity of illness of the patient awaiting transplant has increased. This has led to the increasing use of mechanical circulatory support devices to keep patients alive until heart transplant.

Mechanical circulatory support (MCS) is increasingly being utilized as a bridge to heart transplant as well as a therapeutic option for patients with late or end-stage heart failure who does not respond to conventional medical management. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), a National Heart, Lung and Blood
Institute (NHLBI) sponsored collaborative database shows that 2,868 patients have received implantation of one or more durable MCS devices between June 2006 and September 2010. The number of MCS devices has increased from 100 total implants per year in 2006 to 668 total implants per year through June of 2010, a 568% increase. The majority of MCS devices implanted are left-ventricular assist devices (LVAD) which unload the native heart’s left ventricle and improve survival and quality of life. Current overall 1-year/2-year survival for LVAD patients is 79% & 66%, respectively. Due to the improving survival and acceptability of patients on MCS devices they are also being utilized as so-called “destination-therapy” for patients with refractory heart failure who are not candidates for heart transplantation, but desire prolonged survival and improved quality of life.

**Exercise Response in Heart Failure**

Exercise intolerance is a cardinal manifestation of heart failure. The exercise response is important because it is known that resting measures of cardiac function (i.e. ejection fraction, diastolic filling) do not correlate well with aerobic exercise capacity. Measurement of the exercise response is well-established in heart failure due to its use as a prognostic indicator and for the selection process of transplant recipients.
Use of the exercise response in Heart Failure Evaluation & Management

A number of exercise test variables have shown strong independent prognostic ability as well as the ability to assess therapeutic efficacy in the heart failure population. Due to its ability to stratify risk, exercise stress testing with ventilatory gas-analysis, commonly referred to as cardiopulmonary exercise testing (CPET) is considered a core assessment of the heart failure patient. CPET variables have been shown to correlate with cardiac function, pulmonary hemodynamics, and neurohormonal status. Common CPET variables assessed in heart failure include: peak oxygen consumption, ventilatory anaerobic threshold, ventilatory efficiency slope, oxygen uptake efficiency slope, partial pressure of end-tidal carbon dioxide, presence of oscillatory breathing pattern with exercise, and respiratory exchange ratio.

Important Exercise Variables Evaluated in Heart Failure

Peak Oxygen Uptake (Peak $\dot{V}O_2$)

Maximal oxygen uptake is the product of cardiac output (C.O.) and arteriovenous oxygen difference (a-$\dot{V}O_2$) at maximal physical exertion as shown through a rearrangement of the Fick equation wherein $\dot{V}O_2 = (\text{heart rate} \times \text{stroke volume}) \times a-\dot{V}O_2$. Maximal oxygen uptake is determined by measuring the volume and oxygen content of expired air. It is calculated using the following equation: $\dot{V}O_2 = V_e (F_iO_2 - F_eO_2)$ where $V_e$ = expired air, $F_eO_2$ = directly measured fraction oxygen in expired air, $F_iO_2$ = directly measured fraction oxygen in inspired
air. Additionally, \( \dot{V}O_2 \) is often expressed in metabolic equivalents (METs), with 1 MET representing the resting energy expenditure (\( \approx 3.5 \text{ mLO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)). Because the term \( \dot{V}O_2 \text{max} \) implies that a physiological limit or plateau has been reached, which is commonly not the case in clinical populations, the term peak \( \dot{V}O_2 \) is used clinically to define aerobic exercise capacity. \(^{75}\)

Peak \( \dot{V}O_2 \) is attractive clinically in heart failure because of its linear relationship with cardiac output. \(^{15}\) Peak \( \dot{V}O_2 \) has consistently shown to be a strong independent predictor of outcome in heart failure and is the most widely recognized exercise variable in the heart failure literature.\(^ {16}, \text{71} \)

A landmark study by Mancini and colleagues demonstrated the utility of peak \( \dot{V}O_2 \) to determine which patients benefit the most from heart transplantation. This study showed ambulatory heart failure patients with a peak \( \dot{V}O_2 \) of > 14 milliliters per kilogram of body weight per minute (\( \text{ml.kg}^{-1} \cdot \text{min}^{-1} \)) could safely defer heart transplantation. \(^ {76}\) Since the Mancini study, over 200 subsequent published studies have validated the use of cardiopulmonary exercise test variables to predict prognosis in heart failure. \(^ {71}\) A peak \( \dot{V}O_2 \) of < 14 \text{ml.kg}^{-1} \cdot \text{min}^{-1} \) is a recognized probable indication and < 10 \text{ml.kg}^{-1} \cdot \text{min}^{-1} \) a definite indication for heart transplant listing. \(^ {69}\)

More recently, the use of beta-blockade in heart failure which improves outcomes has led to the use of a peak \( \dot{V}O_2 < 12 \text{ml.kg}^{-1} \cdot \text{min}^{-1} \) as recommended criterion for heart transplant listing. \(^ {73}\)

Peak \( \dot{V}O_2 \) along with anaerobic threshold is also used to classify the severity of heart failure and
estimate cardiac reserve based upon the Weber functional classification system (Class A, B, C, and D). Table 1 is illustrates the Weber Functional classification.

<table>
<thead>
<tr>
<th>Class</th>
<th>Impairment</th>
<th>VO2 max</th>
<th>AT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>None to Mild</td>
<td>&gt; 20</td>
<td>&gt;14</td>
</tr>
<tr>
<td>B</td>
<td>Mild to Moderate</td>
<td>16 - 20</td>
<td>11 - 14</td>
</tr>
<tr>
<td>C</td>
<td>Moderate to Severe</td>
<td>10 - 16</td>
<td>8 - 11</td>
</tr>
<tr>
<td>D</td>
<td>Severe</td>
<td>&lt; 10</td>
<td>&lt; 8</td>
</tr>
</tbody>
</table>

**Ventilatory Anaerobic Threshold**

The ventilatory anaerobic threshold (VAT) is a submaximal indicator of cardiopulmonary function. This is based on the concept that at a given work rate, oxygen supply alone to the muscle does not meet the energy requirements. This imbalance increases the dependence on anaerobic glycolysis for energy output, with lactate as a final metabolic byproduct. Measurement of the VAT through ventilatory gas-analysis is based on the premise that specific changes in ventilation correlate with the progressive onset of lactate accumulation or the lactate threshold. The VAT is reduced in heart failure, correlates with disease severity, and
has been shown to strongly predict prognosis.\textsuperscript{78} An AT of $< 11 \text{ ml.kg}^{-1}\text{.min}^{-1}$ indicates increased risk in heart failure.\textsuperscript{78}

\textit{Ventilatory Efficiency Slope ($V_E/V_{CO_2}$ slope)}

The most widely used index of ventilatory efficiency is the $V_E/V_{CO_2}$ slope. It is expressed in units relative to the amount of minute ventilation in liters of air required to eliminate one liter of carbon dioxide. Optimally, it is assessed continuously from the start of exercise until peak exercise.\textsuperscript{16} A normal $V_E/V_{CO_2}$ slope is between 20 and 30, with values above 30 considered abnormal.\textsuperscript{79} An elevated $V_E/V_{CO_2}$ slope indicates worsening prognosis in heart failure.\textsuperscript{16} A $V_E/V_{CO_2}$ slope $> 35$ is considered an acceptable indication to list for heart transplant.\textsuperscript{73} The $V_E/V_{CO_2}$ slope is a reflection of the pathophysiology of an abnormal ventilatory response to exercise in heart failure. Ventilation during exercise in heart failure is inefficient due to ventilation-perfusion mismatching, early lactate accumulation, and deconditioning.\textsuperscript{71} The slope of the relationship between minute ventilation and carbon dioxide elimination ($V_E/V_{CO_2}$ slope) is superior to peak VO\textsubscript{2} in predicting heart failure outcomes.\textsuperscript{80} Arena et al. compared the prognostic ability of peak VO\textsubscript{2} with the $V_E/V_{CO_2}$ slope and found the $V_E/V_{CO_2}$ slope was better able to predict cardiac-related mortality in heart failure patients.\textsuperscript{80}

\textit{Oxygen Uptake Efficiency Slope (OUES)}
The oxygen uptake efficiency slope (OUES) is yet another marker of ventilatory efficiency shown to have prognostic significance in heart failure.\textsuperscript{19} It describes a non-linear ventilatory response to exercise and is the quotient of the logarithmic transformation of minute ventilation to oxygen uptake. It seems to be best defined as a regression slope ($y = mx + b$) and has usefulness as both a submaximal and maximal exercise test variable.\textsuperscript{81} The OUES is reduced in heart failure patients compared with normal individuals. Lower values are associated with worsening prognosis although it seems to be influenced by body mass index.\textsuperscript{82} In yet another study of ventilatory efficiency in heart failure, Arena and colleagues identified optimal prognostic threshold values for OUES that were dependent upon BMI. Cut-off values of $< 1.2$, $< 1.5$, and $< 1.7$ identified increased risk in normal weight, overweight, and obese heart failure patients, respectively.\textsuperscript{82}

*Partial pressure of end-tidal carbon dioxide (PetCO$_2$)*

Matsumoto and colleagues found the partial pressure of end-tidal carbon dioxide strongly correlated with cardiac output both at rest and during exercise in patients with heart failure. They found the sensitivity and specificity of PetCO$_2$ to predict an inadequate cardiac output response to exercise at the respiratory compensation point were 76.6\% and 75\%, respectively.\textsuperscript{83} Normal resting values are 36 – 42mmHg and usually increase by 3 – 8mmHg with moderate intensity exercise.\textsuperscript{79} Resting values $< 33$mmHg, exercise values at the
ventilatory anaerobic threshold < 36mmHg, and the inability to increase by at least 3mmHg with moderate level exercise indicates poor prognosis in heart failure. 84

Exercise Oscillatory Ventilation (EOV)

Approximately 30% of patients with heart failure exhibit an oscillatory breathing pattern to exercise. 85 Although its etiology is unclear, it seems to be related to abnormal CNS control of ventilation due to the pathophysiology of heart failure. 86 It is characterized by a periodic rise and fall in ventilation without apnea similar to Cheyne-Stokes respiration. 87 Corra et al defined exercise oscillatory ventilation (EOV) as cyclic fluctuations in minute ventilation at rest that persist into exercise lasting at least 60% of the total exercise duration, with an amplitude of ≥ 15% of the average resting value of minute ventilation. The presence of this abnormal breathing pattern portends a very poor prognosis in heart failure patients. 85 EOV has also shown to be strongly predictive of sudden cardiac death. 88

Respiratory Exchange Ratio (RER)

The respiratory exchange ratio is defined as the ratio of carbon dioxide production to oxygen consumption (VCO₂/VO₂) as measured with ventilatory gas analysis. It is a reflection of
substrate metabolism and is used in exercise testing to quantify subject effort. In the resting state, RER typically varies between 0.70 – 1.00 and increases with progressive exercise. A RER ≥ 1.0 is associated with energy release from anaerobic metabolism and exercise-induced metabolic acidosis with resulting increases in VCO₂. Healthy controls achieve a respiratory exchange ratio at peak exercise of between 1.10 and 1.20 or even higher, indicating that anaerobic metabolism is occurring. Such RER values are used to indicate maximal effort.

Assessment of maximal effort during exercise testing is important in heart failure, particularly if the results are used for prognostication or to determine the appropriateness of heart transplantation. A RER value equal to ≥ 1.0 is commonly used to describe adequate effort and motivation in the CHF population. The International Society of Heart and Lung Transplantation (ISHLT) define a maximal cardiopulmonary stress test as one with a RER > 1.05. It has also been described that a significant proportion, as many as 1 in 3 heart failure patients are unable to reach such a maximal effort defined by the RER. Furthermore, the prognostic ability of common CPET variables (i.e. peak VO₂, VE/VCO₂ slope) decreases when the RER is < 1.0.

Mechanical Circulatory Support (MCS) in Heart Failure
As previously mentioned, heart transplant remains the definitive therapy for those with end-stage heart failure, although the number of potential recipients significantly outnumbers the supply of donors.\textsuperscript{70} This has led to intense investigation of alternatives to heart transplant and/or ways to prolong survival while awaiting transplant.\textsuperscript{92} Since the inception of the artificial-heart program at the National Institutes of Health (NIH) in 1964, various circulatory-support devices have been developed for short-term use in patients with end-stage heart failure.\textsuperscript{93} To prevent the deaths of patients awaiting transplantation, many cardiac transplant centers have developed programs to bridge patients to transplantation by means of mechanical circulatory support devices.

Cooley and colleagues were the first to implant a total artificial heart (TAH) in a human who could not be weaned from cardiopulmonary bypass following heart surgery.\textsuperscript{94} The first permanent TAH implanted, the Jarvik-7 was performed by DeVries in 1982.\textsuperscript{94} In this well-publicized event, a patient by the name of Barney Clark was fully supported by the TAH for 112 days.\textsuperscript{94} The first successful bridge to cardiac transplantation with a mechanical device was performed by Reemtsma and colleagues in 1978, which successfully supported patients with intraaortic balloon pumps before transplantation.\textsuperscript{95} In 1984 and early 1985, Hill, Starnes, Copeland, and their associates performed successful bridging procedures using a pneumatic paracorporeal ventricular assist device (VAD), an implantable electrical left ventricular assist system, and a Symbion-Jarvik 7 pneumatic total artificial heart (TAH).\textsuperscript{96} Pennington and
colleagues were the first to demonstrate efficacy and improved long-term survival in transplant recipients who were bridged with mechanical assist devices compared with optimal medical therapy.96 The 28th annual Adult Heart Transplant report from the International Society of Heart and Lung Transplantation (ISHLT) reports the number of patients bridged to transplant with mechanical circulatory support devices exceeded 30% for the first time in 2009.70

The REMATCH trial demonstrated that the use of a left ventricular assist device in patients with advanced heart failure resulted in a clinically meaningful survival benefit and an improved quality of life.97 Patients supported by a left-ventricular assist device (LVAD) who were not heart transplant candidates demonstrated a 48% reduction in mortality compared with a medical-therapy only group.97

Current overall 1-year/2-year survival for LVAD patients is 79% & 66%, respectively.10 This improved survival rate is approaching that of heart transplantation and has led some to posit their utility on par with this current gold-standard for advanced heart failure.98

The INTERMACS database shows that 2,868 patients have received implantation of one or more durable MCS devices between June 2006 and September 2010.10 The number of MCS devices has increased from 100 total implants per year in 2006 to 668 total implants per year through June of 2010, a 568% increase.10 The use of MCS devices as an alternative to heart transplant for “destination-therapy” compromises 15% of all implants.10
Types of Mechanical Circulatory Support (MCS) Devices

A vast array of MCS devices exist that differ based upon location of device, ventricle(s) supported, indication of use, and type of blood flow. Intracorporeal MCS devices are those which are implanted within the body and indicated for longer-term support. Extracorporeal devices are located outside the body and are used in short-term situations for myocardial recovery or cardiogenic shock. 99

The most recent INTERMACS data reveals that 87% of all adult MCS devices implanted were left-ventricular assist devices, 10% biventricular assist devices, and 3% total artificial heart devices. 10 The left ventricle constitutes the majority of myocardial tissue thus the majority of ventricular dysfunction is seen in this region. All implantable LVADs consist of an inflow cannula connecting the left ventricle to the pump that then connects to an outflow cannula carrying augmented blood flow to the aorta. 100 Right ventricular dysfunction alone is rare although has been reported to be present following LVAD implant in up to 50% of instances. 101 Biventricular assist devices or BiVADs provide a parallel simultaneous mechanical circulatory support to the left and right ventricles, pumping blood to the systemic and pulmonary systems. 102 The total artificial heart (TAH) requires complete excision of the native ventricles and anastomosis of the prosthetic ventricles to the atrial cuffs. 103 All current implanted MCS
devices include a percutaneous exit for the driveline, a system controller, and an external power source.104

Applications

MCS devices also differ based upon their intended use. Mechanical circulatory support is utilized as a bridge to heart transplant, bridge to candidacy, destination therapy, and as bridge to recovery or rescue therapy.10 The most common indication is as a bridge to transplant in individuals accepted and listed for heart transplantation.10

Bridge to decision or candidacy represents a growing indication for use wherein patients receive a MCS device before a final decision has been rendered about heart transplantation. Destination therapy represents those implanted with devices that are not eligible for heart transplant because of advanced age or comorbidity. Advanced age (> 70 years), renal dysfunction, and high body mass index (BMI) are the leading three contraindications to transplant.10

Temporary or short-term use of mechanical circulatory support is indicated when recovery of native heart function is expected such as in acute myocarditis, postcardiotomy shock, or following myocardial infarction complicated by cardiogenic shock.100 105

MCS Flow-Type
Mechanical circulatory assist devices can be characterized into one of three categories based upon mechanism of action. First generation or volume-displacement pumps use pneumatic (air-driven) or electromagnetically actuated pusher plates to deform a membrane to deliver pulsatile flow. A volume displacement pump consists of a chamber that passively fills before a pusher plate compresses the chamber and ejects blood in pulsatile fashion through the outflow conduit. \(^{104}\) Pulsatile-flow pump LVAD’s were the first type of MCS device used for long-term ventricular support and were shown to improve survival. \(^{97}\) These devices however were fraught with complications such as pump-failure and very high risk of infection and thromboembolic events. \(^{97}\) This improved survival, but unacceptably high complication rate led to the development of second generation or axial-flow pumps.

Axial-flow pumps consist of an impeller (a rotor with helical blades) around a central shaft that propels blood by drawing it into the inflow cannula and out through the outflow tract along the axis of the impellar. \(^{104}\) These rotary pumps provide continuous-flow and are non-pulsatile. They are associated with a significantly reduced incidence of thromboembolic events, infection, smaller pump size, and significantly improved durability. \(^{106}\) The first 2\(^{nd}\) generation continuous-flow device approved for commercial use by the Food & Drug Administration (FDA) was the HeartMate II left-ventricular assist system© (Thoratec Corporation, Pleasanton, CA, USA). \(^{10}\) Continuous-flow pumps compromise > 98% of all adult LVAD implants in the most recent INTERMACS 6-month reporting period (January through June 2010). \(^{10}\) The HeartMate II
continuous-flow LVAD is the most commonly implanted MCS device on the market and the best-studied 2nd-generation LVAD to date. \textsuperscript{106}

Third generation LVAD devices consist of a rotary pump which uses electromagnetic or hydrodynamic forces to suspend an impeller within the housing to provide a contactless surface. \textsuperscript{104} It is anticipated that this type of pump will result in even further reduction of thromboembolic events and reduce power consumption allowing even further portability. However, there is limited information yet available on this generation of pumps although clinical trials are underway. \textsuperscript{104}

The total artificial heart (TAH) is a pulsatile-flow pump which uses a pneumatic driver to power both ventricles. Copeland and colleagues at the University of Arizona implanted the first TAH as a bridge to transplant in 1985. \textsuperscript{107} Currently, the SynCardia temporary TAH (formerly known as the Cardiowest TAH) is the most effective bridge to transplant for those with biventricular failure with a success rate of 79%. \textsuperscript{12}

**Eligibility/ Selection Criteria**

The selection criteria for use of a MCS device are similar to that of heart transplantation in those who are being bridged to transplant. The use of destination therapy, however, has expanded the number of those who qualify for MCS.
**Left-ventricular Assist Device (LVAD)**

The HeartMate XVE LVAS pulsatile-flow pump is intended for use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from non-reversible left ventricular failure. The HeartMate XVE is also indicated for use in patients with NYHA class IV end-stage left ventricular failure, who has received optimal medical therapy for at least 60 of the last 90 days, who have a life expectancy of less than two years, and who are not candidates for cardiac transplantation. It is intended for use both inside and outside the hospital. It is contraindicated for patients whose body surface area is less than $1.5m^2$.  

The HeartMate II continuous-flow axial pump is also intended for use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from non-reversible left ventricular failure. It is also indicated for use in patients with NYHA Class IIIb or IV end-stage left ventricular failure who have received optimal medical therapy for at least 45 of the last 60 days, and who are not candidates for cardiac transplantation. It is contraindicated in patients who cannot tolerate or are allergic to anticoagulation therapy.

**Total Artificial Heart**

The SynCardia Total Artificial Heart – temporary© (Syncardia, Tucson, AZ) is intended for use inside the hospital while patients await heart transplantation. The SynCardia total artificial heart (TAH) is indicated for use as a bridge to transplantation in cardiac transplant
candidates at risk of imminent risk of death from non-reversible biventricular failure.\textsuperscript{110} Other indications included those with acute or chronic allograft failure, restrictive cardiomyopathy, hypertrophic cardiomyopathy, extensive intracavitary thrombus and cardiomyopathy with aortic root aneurysm.\textsuperscript{24} The TAH system is also undergoing a clinical trial with a smaller portable driver system, aptly named the SynCardia Freedom Driver, for use as a bridge to transplantation in cardiac transplant candidates who are implanted with the TAH and are clinically stable. The portable driver will allow hospital discharge.\textsuperscript{111}

The TAH System is contraindicated for use in patients who: 1) are not cardiac transplant eligible, and 2) do not have sufficient space in the chest area vacated by the natural ventricles. Generally, this includes patients who have body surface areas $< 1.7 \text{m}^2$, or who have a distance between the sternum and the 10th anterior vertebral body measured by computed tomography imaging (CT scan) $< 10 \text{cm}$. Additionally, the TAH is contraindicated in patients who cannot be adequately anti-coagulated.\textsuperscript{110} The Freedom Driver System is contraindicated for use in TAH patients who are not clinically stable.\textsuperscript{111}

Physiology and Device Function of MCS

\textit{1st generation LVAD or pulsatile-flow pump systems}
Currently, the Thoratec HeartMate extended Lead Vented Electric Left Ventricular Assist System (XVE) is the only FDA-approved commercially available 1st generation ventricular assist device in the United States. It consists of an implanted blood pump, an external system controller, and external power supply components. The blood pump, or LVAD, is a pusher-plate type device that is capable of producing a stroke volume of 83ml, generating approximately 10 liters of blood flow per minute, and a pump rate up to 120 bpm. 108

The pump consists of a rigid titanium housing divided in half by a flexible diaphragm. One half functions as the blood chamber, while the opposite half serves as a chamber for the electric motor. This motor chamber is connected to the external control and power components via a percutaneous tube. Displacement of the diaphragm by rotation of the electric motor results in pumping of the blood. 108

The XVE System Controller is a microprocessor-based unit that initiates motor actuation, monitors and reports on system function, and serves as the primary interface with the system. The XVE System Controller provides two modes of operation, either Fixed Rate or Auto Rate. The Auto Rate is programmed with OptiFill™ Software, which varies in response to physiologic demand. LVAD function is adjusted by a switch panel located on the top of the system controller, or via a separate system monitor. The system controller’s audio and visual alarms alert users of potentially dangerous conditions. Alarms are sounded primarily if there are either low flow or low stroke conditions or if battery charge levels are low. 108

42
The XVE is routinely powered through the system controller by either a pair of wearable, rechargeable batteries, or via connection to a dedicated power supply device. Figure 2 provides an illustration of the HeartMate I XVE LVAD.

Figure 2: HeartMate I – XVE LVAD

2nd generation LVAD or continuous-flow systems

The Thoratec HeartMate II LVAD is currently the only commercially available FDA-approved ventricular assist device for bridge to transplant and destination therapy in the United States. It utilizes a rotary blood pump to generate flow and assist the left ventricle. It is an axially configured device where the path of the entering and exiting flow stream is parallel to
the pump’s axis. The device has only one moving part, the rotor assembly, which spins on bearings located at either end of the assembly. The pump is driven by an external power source via a percutaneous lead. Capable of generating blood flow up to 10 liters per minute, the LVAD operates in parallel with the heart, such that either can supply blood to the aorta. Blood enters the pump from the left ventricle via an inflow conduit. Blades on the spinning rotor move the blood through the pump to an outflow graft and ultimately to the native circulation. It may be surgically implanted beneath the diaphragm in either a preperitoneal or intra-abdominal location. An inflow conduit is inserted into the left ventricular apex of the heart. An outflow graft is attached to the ascending aorta. Figure 3 provides an illustration of the internal components and the blood-flow path within the HeartMate II LVAD.

![Figure 3: Internal workings of HMII LVAD](image)

A system controller controls the LVAD operation and serves as the primary user interface. This controls motor power and speed, monitors, interprets, and responds to the system, performs diagnostic monitoring, provides hazard and advisory alarms, records events in
memory, and transfers data to a system monitor.\textsuperscript{109} Device performance can be determined by monitoring the pump speed, power, flow, and pulsatility index.\textsuperscript{109}

The LVAD operates at a fixed speed determined by the physician during a speed ramp study. The fixed speed mode maintains the blood pump at a constant speed between 6,000 and 15,000 rpm. The fixed speed can be adjusted in increments of 200 rpm.\textsuperscript{109}

Pump power is a direct measurement of motor voltage and current. Changes in pump speed, flow, or physiological demand can affect pump power. Gradual power increases may signal a deposition or thrombus inside the pump. Depending on the speed, power values greater than 10 to 12 watts (W) may also indicate the presence of a thrombus.\textsuperscript{109}

The pump flow and power generally retain a linear relationship at a given speed. However, the power is directly measured by a system controller while the reported flow is estimated based on power. Since the displayed flow is a calculated value, it becomes imprecise at the low and high regions of the linear power-flow relationship.\textsuperscript{109}

The increase in ventricular pressure during contraction causes an increase in pump flow during cardiac systole. The magnitude of this flow pulse is measured and averaged over intervals of 15 seconds to produce a pulsatility index (PI). The PI calculation represents cardiac pulsatility, and values typically range from 1 to 10. In general, the magnitude of the PI value is related to the amount of assistance provided by the LVAD. Higher values indicate more ventricular filling and higher pulsatility (i.e. pump is providing less support to the left ventricle).
and lower values indicate less ventricular filling and lower pulsatility (i.e. pump is providing greater support, further unloading of the ventricle). PI values should be monitored and should not vary significantly during resting conditions. Under otherwise stable conditions, a significant drop in PI may indicate a decrease in circulating blood volume.  

Figure 4: Thoratec HeartMate II LVAD

**Total Artificial Heart (TAH)**

The implantable Syncardia TAH consists of two artificial ventricles, each made of a semi-rigid polyurethane housing with four flexible polyurethane diaphragms separating the blood
chamber from the air chamber. The diaphragms allow the artificial ventricle to fill and then eject blood when compressed by air from the external console. Mechanical valves, mounted in the inflow and outflow ports of each artificial ventricle, control the direction of blood flow. The TAH weighs 160 grams, is composed of two pneumatically driven pumps, and has the ability to deliver a cardiac output of up to 9.5 liters per minute at its maximal stroke volume of 70 ml.\textsuperscript{110}

The left artificial ventricle is connected via the left atrial inflow connector to the left atrium, and via the aortic outflow cannula to the aorta. The right artificial ventricle is connected via the right atrial inflow connector to the right atrium and via the pulmonary artery outflow cannula to the pulmonary artery. Each artificial ventricle’s driveline conduit is tunneled through the chest wall. The right and left artificial ventricle’s driveline conduits are attached to seven-foot pneumatic drivelines that connect to the back of the external console.\textsuperscript{110} Figure 5 provides a visual depiction of the TAH location in comparison to the native human heart.
The TAH has an external console (weighing 495 lbs. crated) aptly named “Big-Blue” with controllers permitting regulation of each of the ventricles. In addition to the controllers, the console consists of several components essential to the functioning of the device, including a vacuum pump, an alarm panel and two high-pressure air tanks. The console includes a
monitoring computer that provides noninvasive diagnostic and monitoring information to the user. Device pump rate, dynamic stroke volumes, and calculated cardiac outputs are displayed on a beat-to-beat basis. Drive pressure and flow waveforms, along with cardiac output trends are provided.\textsuperscript{110}

The basic parameters of the device console that modulate cardiac output include drive pressure, ejection rate, systolic ejection time and vacuum pressure during pump diastole. The drive pressure regulators control the pressure of the air entering the ventricles and can be set between 0 and 300 mmHg (with a typical range of 150 to 200 mmHg for the left ventricle and 55 to 90 mmHg for the right ventricle). The pump rate can be set between 25 and 199 beats per minute (bpm) (typical range 90 to 130 bpm). The systolic duration, or the percent of the cardiac cycle spent in systole, can be set at between 15% and 95% (typical range expected at approximately 50%, but can range from 45% to 65%). The TAH features a vacuum that can shorten ventricular filling time by drawing blood into the pumping chamber during pump diastole. This vacuum pressure can be set to between 0 and 60 mm Hg (typical range 5 to 12 mm Hg). The aforementioned parameters are adjusted to maintain full ejection during systole of both the right and left pump, and partial filling during diastole. The settings are adjustable and optimized to provide clinically appropriate cardiac output and systemic blood pressures.\textsuperscript{24, 110} Figure 6 provides an illustration of the TAH patient tethered to the “Big-blue” driver.
The TAH can also be powered by a portable console which is currently undergoing a clinical trial for FDA approval. This portable console, called the SynCardia Freedom Driver and weighs 14 lbs. is designed to improve patient portability and allow hospital discharge. All Freedom Driver console parameters are fixed except for the beat rate which can be adjusted manually by a physician. Figure 7 illustrates the TAH patient with the significantly smaller Freedom Driver console.
Exercise Physiology of MCS

In addition to prolonge\textsuperscript{d} survival, mechanical circulatory support offers heart failure patients the opportunity for enhanced quality of life by improving end organ function and activity tolerance. Advancements in device technology have led to increased portability, patient acceptance, and the ability to participate in further activities of daily living.\textsuperscript{10} Additionally, this allows the patient to undergo physical rehabilitation to further improve functional capacity. Patients who may have previously been bedridden are now able to participate in physical therapy and/or cardiac rehabilitation.\textsuperscript{20,112,113} To date most of the literature regarding exercise capacity or therapy in the MCS patient has been based upon 1\textsuperscript{st} generation or pulsatile-flow pump ventricular assist devices. In general, these studies support...
the safety and efficacy of exercise testing and intervention in the MCS patient. There is, however, a distinct lack of studies examining the effects of exercise in MCS device patients.

**1st generation LVAD or pulsatile-flow pump systems**

Although it is important to take into account native left ventricular function when considering exercise physiology in the LVAD patient, the LVAD device contributes most of the cardiac output. Early work by Jaski et al. and Branch et al. with 1st generation LVADs revealed that virtually all resting cardiac output was from LVAD support and its contribution to exercise was variable. LVAD contribution to exercise cardiac output ranged from 66% to 93% with the remainder due to function of the left ventricle. These studies were some of the first to show that the LVAD provides adequate cardiac output for most ADL level activities and exercise participation.

Morrone et al. described the largest exercise experience of patients with 1st generation LVAD’s. In a retrospective analysis of physical therapy intervention on patients surviving LVAD implantation (n = 34), they found treadmill exercise was tolerated by 82% of patients and could be initiated within 3 weeks of surgery. Exercise performance peaked at 6 to 8 weeks with patients able to perform 20 to 30 minutes at approximately 3.2 METs (estimated V\textsubscript{O}\textsubscript{2} 11.2 ml.kg\textsuperscript{-1}.min\textsuperscript{-1}. They reported maximal functional capacity was most influenced by medical complications, and the only exercise related complications were a transient decrease in pump
flow, which did not result in increased mortality/morbidity for the patients. These authors posited that a delay in heart transplantation until peak performance of functional ability may optimize post-operative recovery.

In the EVADE trial (Experience with left Ventricular Assist Device with Exercise trial), Jaski and colleagues found lower functional capacity determined by peak VO₂ in post-LVAD patients compared with post-heart transplant patients. Eighteen patients implanted with an intracoporeal LVAD underwent treadmill exercise testing with ventilatory gas analysis one to three months after LVAD and then again one to three months following heart transplant (HTx). Mean peak VO₂ was 14.5 ml.kg⁻¹.min⁻¹ post-LVAD and 17.5 ml.kg⁻¹.min⁻¹ post-HTx. The percentage of the predicted peak oxygen consumption based on gender, weight, and age was 39.5% post-LVAD and 47.7% post-HTx. The peak respiratory exchange ratio (RER) was similar post-LVAD and post-HTx at 1.15, consistent with a good effort in both groups. After LVAD implantation, peak total oxygen consumption correlated with peak LVAD rate and output.

In contrast, de Jonge observed that peak VO₂ 12 weeks after LVAD implant did not differ significantly from peak VO₂ 12 weeks after heart transplant (22.8 ml.kg⁻¹.min⁻¹ vs. 24.6 ml.kg⁻¹.min⁻¹ or 58% vs. 63% of predicted peak VO₂). They performed cardiopulmonary exercise testing (CPET) on 15 LVAD patients at 8 weeks and 12 weeks after LVAD implant and then again
12 weeks after heart transplant and once more at 1 year after heart transplant. All patients were started on an intensive post-operative rehabilitation regimen as soon as they were able to mobilize. Peak VO$_2$ improved from 8 weeks to 12 weeks post-LVAD and was commensurate with a Weber functional class A status. Twelve weeks after LVAD the anaerobic threshold (AT) was 14.4 ml.kg$^{-1}$.min$^{-1}$ and the VE/V$\text{CO}_2$ slope was 37.2. They emphasized the timing of exercise testing and the rehabilitation component as determinants of exercise capacity.  

In another study of exercise capacity in patients with a pulsatile-flow LVAD by Pruijsten and colleagues, peak VO$_2$ was 20.0 ml.kg$^{-1}$.min$^{-1}$ or 52% of predicted at a peak RER of 1.23, AT was 13.8 ml.kg$^{-1}$.min$^{-1}$, VE/V$\text{CO}_2 = 35.9$. Approximately 50% (44 out of 84) of the eligible patients underwent CPET at 12 weeks following LVAD implant. This exercise response was similar to the findings in the de Jonge study.  

Mancini et al. described the bicycle-ergometer exercise hemodynamic and metabolic response of pulsatile-flow LVAD patients (n=20) compared with ambulatory heart failure patients awaiting heart transplant. Peak VO$_2$ for the device patients was significantly greater than the heart failure patients (16 vs.12.1 ml.kg$^{-1}$.min$^{-1}$). The VE/V$\text{CO}_2$ at the anaerobic threshold (ratio of 39) was similar for both groups. Fatigue was the primary limiting factor in the LVAD group. Further peak exercise variables for the device patients were as follows: AT = 12.2 ml.kg$^{-1}$.min$^{-1}$, RER = 1.14, mean arterial pressure (MAP) = 96mmHg, peak heart rate (HR) = 148 bpm,
peak cardiac output (C.O.) = 11.2 liters, cardiac index (C.I.) = 5.8, lactate = 5.0 mmol/L, peak Borg RPE (0-10 scale) = 5.9, peak Borg RPD (i.e. perceived dyspnea) = 4.8 on a 0 – 10 scale.  

Simon and colleagues compared the exercise performance of patients with electric LVAD (n=18), pneumatic-driven LVAD (n=10), and pneumatic-driven BiVAD (n=10). They found percent predicted peak \( \dot{V}O_2 \) was significantly higher in the pneumatic-driven LVAD vs. electric LVAD (52.1% vs. 38.2%) with BiVAD having the lowest exercise tolerance (36.5%). This corresponded to oxygen consumption values of 15.7, 12.8, 11.8 ml.kg\(^{-1}.min\(^{-1}\)) respectively for pneumatic LVAD, electric LVAD, and pneumatic BiVAD. Peak METs were 3.4 to 4.4 and \( Ve/V_{CO2} \) slope values ranged from 41 – 43 between the groups. Peak mean arterial pressure (MAP) was 93 – 102 mmHg among the groups. Peak device outputs ranged from 6.5 to 7.9 liters per minute. Peak RER was 1.17 - 1.26.

It is notable that although pulsatile-flow LVAD and the heart function in parallel, native heart rate and pulsatile-flow LVAD pump rate are not simultaneous. Both increase in a linear fashion with exercise although independent of one another. The pulsatile-flow LVAD pump rate is fixed or based on physiologic demand wherein it operates in a fill-to-empty mode.

Laoutaris et al. looked at the benefits of physical training on exercise capacity, inspiratory muscle function, and quality of life in patients with a ventricular assist device long-term post-implantation. In this study, 15 patients, approximately 6.3 months after implant
underwent bicycle-ergometer CPET, 6MWT, and inspiratory muscle testing. This group consisted of a combination of intracorporeal continuous-flow rotary pump LVAD (n=2), extracorporeal pulsatile-flow LVAD (n=6), and extracorporeal pulsatile-flow BiVAD (n=7). Subjects were assigned to a training group or control in 2:1 fashion. The training group significantly increased peak VO₂ (16.8 to 19.3 ml.kg⁻¹.min⁻¹) at a mean RER of 1.13 - 1.2, increased VAT (12 to 15.2 ml.kg⁻¹.min⁻¹), increased 6MWD (462 to 527 meters), and lowered VE/VCO₂ slope (40 to 35.9).¹¹²

Alternatively, Humphrey et al. found that exercise-training in an LVAD group did not result in substantial increases in peak oxygen consumption as much as submaximal responses, such as the ventilatory anaerobic threshold.²⁰ This is, however, not surprising given that peak oxygen consumption via the Fick equation is largely determined by peak cardiac output which is mostly influenced by the LVAD device that has fixed upper limits.

In summary, a review of the above studies reveals that exercise capacity is generally improved with ventricular assist device support compared with medically managed end-stage heart failure patients. However, it is generally lower compared with post-heart transplant patients. Exercise capacity in the MCS patient ranges from 14 to 24 ml.kg⁻¹.min⁻¹ (4 – 6.9 METs) for peak VO₂ although remains at about 40-60% of predicted compared with normal. The observed anaerobic threshold values seem to range from 12 to 14 ml.kg⁻¹.min⁻¹ or 3.4 – 4.0
METs. It also appears the $V_{E}/V_{CO2}$ slope remains high and above normal after device implant with values ranging from 36 to 43 units. The high RER values (i.e. $>1.1$) from these studies also support that sufficient effort was put forth during testing indicative of a maximal effort. It is also noted that overall the sample size of available exercise studies is small (i.e. $\sim 10 - 34$ patients). As expected, exercise training also seems to influence the exercise response. Currently, there do not appear to be any studies in the literature describing the OUES, EOV, or PetCO$_2$ response to exercise in MCS device patients.

*2nd generation LVAD or continuous-flow systems*

Haft et al. demonstrated exercise performance was similar in those with a continuous-flow pump LVAD compared with pulsatile-flow pump devices. 122 Thirty-four patients with a volume-displacement HeartMate XVE (n=16) or HeartMate II (HMII) continuous-flow rotary pump (n=18) underwent right-heart catheterization, echocardiography, and CPET 3-months post-operatively. Exercise capacity was similar ($\bar{VO}_2$ for XVE = 47% of predicted vs. 49% for HMII) between the groups. The results indicated both types of LVAD pumps provided equivalent degrees of hemodynamic support and exercise capacity. Additional peak exercise response variables compared between the groups were as follows: Peak $\bar{VO}_2$ -XVE = 15.4 vs. HMII = 15.6 ml.kg$^{-1}$.min$^{-1}$, METs-XVE = 4.4 vs. HMII = 4.3, RER-XVE = 1.13 vs. HMII = 1.11, peak HR-XVE = 131 bpm vs. HMII = 124 bpm. 122
This similar finding of exercise capacity is important as previous studies have suggested axial-flow rotary pumps provide similar degrees of pressure unloading but less volume unloading of the left-ventricle (LV) as compared with pulsatile-flow pumps. Thus axial-flow rotary pumps at a fixed rotor speed may not appropriately adjust to the increased LV preload during exercise leading to impaired exercise performance. The Haft study did show a major difference in the degree of LV volume unloading between device types although equivalent exercise performance.

Important considerations when interpreting the exercise response of the continuous or pulseless-flow LVAD are the measurement of cardiac output and arterial blood pressure. Cardiac output in the pulseless-flow LVAD is only an estimation of pump flow based upon power consumption. Lack of a direct assessment of cardiac output during exercise does not allow determination of the contribution of native ventricular function. Jaski et al. demonstrated, albeit with a pulsatile-flow LVAD, that resting cardiac output was almost solely due to LVAD support, but during exercise aortic ejection was apparent and total systemic cardiac output exceeded the LVAD support.

Brassard and colleagues performed a study wherein they invasively determined cardiac output, leg blood flow, cerebral perfusion and whether an increase in LVAD pump speed with work rate would increase organ blood flow. Eight patients with a HeartMate II continuous-
flow LVAD underwent incremental cycle ergometer exercise testing with a progressive protocol of 30-watt stages of 2-minutes using a modified semi-supine ergometer at a pace of 60 rpm. Exercise time was approximately 12 minutes and subjects were able to reach peak workloads of 150 – 180 watts. They found significant increases in cardiac output to maximal exercise at both a constant pump speed of 9775 rpm (7.0 to 13.6 L/min) and an increasing pump speed of 400 rpm per stage (6.0 to 12.1 L/min). Both groups exhibited poor cerebral blood flow although this was augmented with increasing pump speed. 125

Unfortunately, this group did not report on ventilatory gas-analysis measurements (i.e. peak VO₂) and only very limited information regarding the LVAD device estimated function from the system controller. Measurement of peak VO₂ and device estimated function would have allowed determination of device and native LV contribution to exercise cardiac output. Additionally, this could have led to potential correlations between device flow estimates and exercise capacity.

The major hemodynamic effects of a continuous-flow LVAD are increases in diastolic pressure and flow. Because these devices pump continuously throughout the entire cardiac cycle, aortic flow is also present during diastole when normal pulsatile flow is absent. When the pump speed of a continuous-flow LVAD is increased, the diastolic pressure rises, the systolic pressure remains fairly constant, and the pulse pressure (systolic pressure minus diastolic
pressure) is greatly reduced. Owing to the reduced pulse pressure during continuous-flow LVAD support, it is often difficult to palpate a pulse and measure blood pressure accurately by the usual auscultatory or automated methods. When listening with a manual blood pressure cuff, the start of the Korotkoff sound is a pressure value that is estimated to be in the range of the systolic and diastolic pressures. The arterial blood pressure is most reliably assessed using Doppler and a sphygmomanometer. Pressure values obtained using the Doppler method may be measured at any point during the cardiac cycle and should not necessarily be considered the actual systolic, diastolic, or mean pressure values.

**Total Artificial Heart (TAH)**

The effectiveness of the TAH as a bridge to transplant has made it a viable option for those with end-stage biventricular heart failure. The demonstrated improvement in mortality and its increasing usage necessitates a shift in focus to quality of life in the TAH patient including functional ability. The assessment of functional ability is further called for considering a current FDA-trial investigating the efficacy of a portable TAH device allowing reintegration into the community. As seen with other MCS devices, functional ability is largely influenced by the limits of the device. This is certainly the case in the TAH patient wherein there is no native heart to contribute cardiac output during exercise.
In 1989 Everett described the effect of graded exercise on cardiac output of the Jarvik-7-70 total artificial heart in a human. The Jarvik-7-70 TAH was an earlier version of the current SynCardia TAH. Using a cycle ergometer with 18-watts (est. METs ~2.7) resistance the TAH patient could exercise with an auto-regulated cardiac output and no deleterious effects. Exercise was started on the 35th post-operative day and performed without adjusting fixed device parameters. Increasing the work of exercise produced an increased cardiac output through an augmented exercise stroke volume facilitated by changes in venous return.

Later, Copeland and colleagues described the early functional status in a series of SynCardia TAH patients awaiting heart transplant. They reported 75% of patients were out of bed within one week of implant and were walking greater than 100 feet within two weeks.

Nicholson et al. describe a detailed physical therapy intervention in the TAH patient. This was a single-patient case study during which they chronicled a 12-week progressive exercise regimen wherein the patient safely progressed to tolerating 46 minutes of treadmill ambulation at 1.4 mph/0% grade or approximately 2.1 metabolic equivalents (METs). Physical therapy was initiated on the 7th post-operative day and treadmill training was initiated on the 42nd post-operative day (i.e. 6-weeks). The patient was successfully transplanted after 83 days on the artificial heart. This single patient case study was the first to demonstrate the safety of a progressive exercise regimen in the TAH patient.
Bellotto et al. utilized the fixed central component in the TAH patient to examine the peripheral adaptations to exercise training. They reported the case of a single TAH patient who underwent a comprehensive exercise training program and was evaluated by repeated cardiopulmonary exercise tests. The TAH patient experienced a 24% increase in peak \( \dot{V}O_2 \) and an improvement in recovery kinetics during the training period of 29 months. The patient, a 53-year-old male (BMI = 25 kg/m\(^2\), Hemoglobin = 10.1 g/dL) underwent 4 repeated CPET’s approximately 6 months apart using a cycle-ergometer and a progressive work rate protocol of 5-watts per minute. Peak \( \dot{V}O_2 \) improved from a baseline of 13.9 ml.kg\(^{-1}\).min\(^{-1}\) to a highest value of 17.3 ml.kg\(^{-1}\).min\(^{-1}\). The AT improved from 9.8 to 10.6 ml.kg\(^{-1}\).min\(^{-1}\). Average resting blood pressure was 116/83 mmHg and changed to 121/79 mmHg at peak exercise. Average RER and \( V_e/VCO_2 \) slope was 1.2 and 27.8, respectively. The cardiac output response to exercise was approximately 1.7 liters per minute. Comparison of the CPET results shows the peak \( \dot{V}O_2 \) significantly increased despite similar device flow, hemoglobin, and carbon dioxide output. This suggests a greater extraction of oxygen from the blood perfusing the muscles reflecting a peripheral adaptation. This appears to be the only study in the literature describing ventilatory gas-analysis variables during exercise in the TAH patient.

Most recently, Kohli and colleagues retrospectively reviewed the exercise performance of TAH patients (n=37) undergoing inpatient rehabilitation and compared blood pressure response and submaximal exercise capacity with a HeartMate II LVAD group. Physical
therapy was initiated at a median 5\textsuperscript{th} post-operative day and treadmill exercise was initiated on the 19\textsuperscript{th} post-operative day. TAH patients were able to safely tolerate progressive aerobic exercise training over time. Over eight weeks, patients were able to significantly improve exercise duration (up to 26 ± 15 minutes) and intensity (up to 2.3 ± 0.5 METs). Compared with LVADs, TAH patients demonstrated a blunted blood pressure response to exercise.\textsuperscript{24} To date this is the most comprehensive series evaluating the exercise response in the TAH patient.

**Summary/ Conclusions**

A diagnosis of heart failure carries with it an ominous prognosis. A number of pharmacologic and therapeutic regimens have proven efficacious at ameliorating its pathological process. For patients with advanced heart failure, heart transplantation remains the most effective treatment. Unfortunately, there is a long-term trend wherein the number of eligible recipients significantly outweighs the number of available donors. Mechanical circulatory support devices have proven to be an effective short and long-term option to reduce mortality in those who await heart transplant. These devices also confer improvements in quality of life, reduce symptoms, and improve functional status in patients with end-stage heart failure leading to their additional use as destination-therapy in individuals who do not qualify for heart transplant.
For patients with severe biventricular heart failure the total artificial heart (TAH) has become a viable option to bridge patients until transplant becomes available. Its abrupt restoration of blood flow allows rehabilitation and organ recovery to take place promoting optimization of the candidate before transplant. The demonstrated safety, increased usage, growing transplant wait-list times, and an ongoing clinical trial with a portable-driver necessitate further study of the TAH response to physical activity. This will allow determination of device safety, elucidate the role of exercise training, potentially provide advice on optimization of device settings, and provide guidelines on the functional limits of the device. Presently, there is a dearth of information available in the literature on the exercise response of the MCS device patient particularly the TAH patient. What is available demonstrates a significantly reduced but functional exercise capacity. No studies to date have analyzed the prognostic potential of the exercise response in this population. The goal of this study will be to advance the knowledge base of the exercise response in this growing patient population.
A Comparison of Maximal Exercise Responses among Patients with a Total Artificial Heart, a Left Ventricular Assist Device, or Advanced Heart Failure

ABSTRACT

Objectives. The purpose of this study was to evaluate graded exercise responses to treadmill exercise in patients with a total artificial heart (TAH). Additionally, this study sought to compare the exercise response in TAH patients to both advanced heart failure (HF) patients on medical management only and HeartMate II (HMII) LVAD patients. Background. For patients with biventricular heart failure the total artificial heart (TAH) is a viable option to bridge patients until transplant becomes available. Its demonstrated improvement in mortality and increasing usage necessitates a shift in focus to quality of life in the TAH patient including functional ability. The evaluation of cardiorespiratory responses to graded exercise provides an objective measure of functional ability. There is very limited information in the literature on the exercise response of the mechanical circulatory support (MCS) device patient, particularly the TAH patient. Methods. A study was conducted on previously gathered data of MCS patients who underwent symptom-limited cardiopulmonary exercise testing (CPET) following device implant of either TAH or HMII. ANOVA was performed to compare differences between the two device groups and HF patients listed for heart transplant. Results. Fourteen TAH patients underwent CPET (9 male, 5 female) with peak oxygen consumption (VO₂) of 0.926 ± .168 L-min, 36 ± 8% % predicted, 11.0 ± 2.3 ml.kg.min or 3.1 ± 0.7 METs. Ventilatory anaerobic threshold (VAT) was 0.706 ± .181 L-min. Peak VO₂ % pred. VO₂ and VAT were significantly lower in the TAH compared with HMII and advanced HF (p = 0.0012, p = 0.0106, p = 0.0009, respectively). Peak RER was significantly higher (p = <.0001) and OUES was significantly lower (p = 0.0004) in the TAH. Conclusion. Exercise capacity is significantly reduced in the TAH patient below that observed in HMII LVAD and advanced HF patients. This provides a baseline for expected functional status and has implications on the ADL tolerance of these individuals. The next step is to develop strategies to ameliorate this continued exercise intolerance.
Abbreviations

MCS = Mechanical circulatory support
M = Male
F = Female
C = Caucasian
AA = African-American
O = Other

CPET = Cardiopulmonary exercise test
ARB = Angiotensin II receptor blocker
CCB = Calcium channel blocker
HDZN/ISDN = Hydralazine/Isosorbide dinitrate
VO2 = oxygen uptake

M = Male
F = Female

VE = Minute ventilation

CCB = Calcium channel blocker

C = Caucasian

VCO2 = Carbon dioxide output

NICM = Non-ischemic cardiomyopathy
ICM = Ischemic cardiomyopathy
CHD = Congenital heart disease
BMI = Body mass index
Hgb = Hemoglobin

LVEF = Left-ventricular ejection fraction

BTT = Bridge to transplant
BTD = Bridge to decision
DT = Destination therapy
DM = Diabetes
PVD = Peripheral vascular disease

VO2 = oxygen uptake

LVAD = Left-ventricular ejection fraction

AOE = Oxygen uptake efficiency slope

VE = Minute ventilation

BMI = Body mass index
LVEF = Left-ventricular ejection fraction

Hgb = Hemoglobin

CHD = Congenital heart disease

RHR = Resting heart rate

Afib = Atrial fibrillation
AICD = Automatic internal cardioverter defibrillator

B-blocker = beta-blocker
ACE-I = ACE Inhibitor

Introduction

Heart failure, which is a syndrome that includes circulatory congestion and/or inadequate tissue perfusion, can be caused by any type of condition that damages the heart and typically leads to debilitating symptoms of dyspnea, fatigue, and exercise intolerance. It
carries attributable risks, increasing incidence, an ominous prognosis, complex
pathophysiology, and can be a challenge to manage. The American Heart Association
estimates that there are 5.7 million Americans living with heart failure and 600,000 new cases
are diagnosed annually. Lifetime risk of heart failure development is 1 in 5 for both men and
women, and hypertension is associated with 75% of all heart failure cases. Furthermore, the
incidence is highest among African-Americans and it increases with advancing age. Risk
factors for the development of heart failure include coronary artery disease, hypertension,
cardiomyopathy, myocardial infarction (MI), obesity, diabetes, dyslipidemia, valvular heart
disease, renal insufficiency, sleep-disordered breathing, and tachycardia. Antecedent MI and
hypertension are the most attributable risk factors. Approximately 50% of those diagnosed
with heart failure will die within 5 years and it carries a mortality risk that is four times that of
the general population of like age. Lastly, heart failure is the most common hospital
discharge diagnosis and consumes more Medicare dollars than any other diagnosis.

Advanced heart failure therapies are available for patients with end-stage disease who
are refractory to conventional medical management. This includes the use of inotropic agents,
heart transplantation, and mechanical circulatory support (MCS) devices. Heart
transplantation remains the definitive therapy for those with refractory end-stage heart
failure. Unfortunately, the demand for heart transplants continues to significantly exceed the
supply of donor hearts. This has led to the increasing use of mechanical circulatory support
devices to keep patients alive until heart transplant. To date, the majority of MCS devices implanted are left-ventricular assist devices (LVAD) which unload the native heart’s left ventricle and improve survival and quality of life. However, there is a subset of patients with advanced heart failure that are not appropriate candidates for LVAD therapy due to right-sided heart failure or biventricular failure. For these patients, the SynCardia Total Artificial Heart (TAH) is the most effective treatment therapy as a bridge to heart transplant. The TAH consists of two pneumatically driven pumps that orthotopically replace the failing hearts native ventricles.

Typically, clinical evaluation of the heart failure patient includes identification of causes, description of symptoms, evaluation of cardiac structure, and quantification of functional status. Patients are stratified according to heart failure risk, presence of cardiac structural changes, functional status, and presence of symptoms. This allows determination of prognosis and guides management. In heart failure, cardiopulmonary exercise testing (CPET) has proven to be a reliable tool to guide therapy, estimate prognosis, and evaluate patients for heart transplant. Quantification of the exercise response in heart failure is valuable because of its ability to determine prognosis and provide insight into the pathophysiological processes of the disease state. In healthy individuals, the ability to perform dynamic activities is largely determined by the hearts ability to appropriately increase cardiac output to provide adequate blood flow and oxygen to working muscles and organs. In heart failure, a reduced
cardiac output along with pulmonary congestion and deconditioning lead to impairment in the ability to perform exercise\textsuperscript{17} therefore exercise intolerance is a hallmark symptom of heart failure along with pulmonary congestion. The relationship between exercise performance and heart failure severity has led to the use of exercise testing in the evaluation and management of heart failure patients.

Due to its ability to stratify risk and accurately measure exercise capacity, CPET is considered a core assessment of the heart failure patient.\textsuperscript{18} CPET variables have been shown to correlate with cardiac function, pulmonary hemodynamics, and neurohormonal status.\textsuperscript{18} Standard CPET variables assessed in heart failure include peak oxygen consumption, ventilatory anaerobic threshold, ventilatory efficiency slope, oxygen uptake efficiency slope, partial pressure of end-tidal carbon dioxide, presence of an exercise oscillatory breathing pattern, and respiratory exchange ratio.\textsuperscript{19}

Most of the available literature describing exercise in the MCS patient has been based upon 1\textsuperscript{st} generation or pulsatile-flow left ventricular assist devices. There is, however, a distinct lack of studies examining the effects of exercise in MCS device patients\textsuperscript{20} particularly the newer continuous-flow LVAD devices. In regards to the exercise response of the TAH patient there is an even further paucity of information with very few studies available describing the functional status of the TAH patient.\textsuperscript{12,21,22-24} Therefore, the purpose of this study was to evaluate the
cardiorespiratory responses to graded exercise in the TAH patient. Additionally, we sought to compare those responses to responses obtained from HeartMate II LVAD patients and non-MCS device patients with advanced heart failure who had been evaluated and accepted for heart transplantation. We hypothesized that exercise capacity, specifically the peak oxygen uptake, will be significantly reduced in heart failure patients after TAH implant compared with HeartMate II LVAD patients and patients with advanced heart failure un-supported by MCS device. Additionally, we hypothesized that an abnormally elevated ventilatory response to exercise exists in the TAH patient due to the early onset of acidosis. This will result in an increased ventilatory efficiency slope and a concomitant reduction in the oxygen uptake efficiency slope in the TAH patient compared with HeartMate II LVAD patients and patients with advanced heart failure un-supported by MCS device. The initial characterization of this exercise response along with comparisons to other HF populations will provide insight into the functional limitations of the TAH patient and possible mechanisms for their exercise intolerance.

**Methodology**

This study was conducted on previously gathered data of cardiopulmonary exercise tests (CPET) that were performed on patients who received a mechanical circulatory support (MCS) device at Virginia Commonwealth University Medical Center (VCUMC) from June 2010 through
December 2011. Additionally, the CPET results of patients with MCS devices were compared with advanced heart failure (ESHF) patients without a MCS device who underwent evaluation and subsequent listing for heart transplant within the VCU Medical Center Advanced Heart Failure program during the same time period. Institutional review board approval was granted prior to data analysis. All patient information was de-identified to maintain privacy and confidentiality. All exercise tests were clinically-mandated by an attending cardiologist within the VCU Medical Center Advanced Heart Failure program. Rationale for testing was to determine exercise capacity, to develop a cardiac rehabilitation exercise prescription, to establish activity guidelines, to stratify risk, and to assess device function during exercise. All patients were informed of the exercise test rationale, protocol, and associated risks prior to consent being obtained.

Patient Population

The study was comprised of patients with an established diagnosis of heart failure who were being followed by the VCU Medical Center Advanced Heart Failure program. Patients were separated into 3 groups: 1) Thoratec© HeartMate II continuous-flow left-ventricular assist device (HMII), 2) SynCardia© total artificial heart (TAH), and 3) advanced heart failure (ESHF) without an MCS device who were listed for heart transplant.
Twenty-two patients underwent TAH implant during June 2010 through December 2011. Out of the TAH group 14 patients (64%) were able to undergo CPET. The remaining 8 patients did not undergo post-operative CPET for the following reasons: 4 patients underwent heart transplant before CPET, 3 patients were medically unstable, and 1 patient expired.

Thirty-four patients underwent HeartMate II LVAD implant from June 2010 through June 2011. Nineteen of 34 HMII patients (56%) underwent post-operative CPET. Reasons for not completing CPET for the remaining 15 patients included: 8 were not medically stable or a physician deemed the patient too debilitated to tolerate treadmill exercise testing, 4 were lost to follow-up, and 3 expired. Five of the original nineteen HMII CPET’s were performed with a different testing modality (i.e. bicycle ergometry) and were not comparable to the other groups thus were excluded from the final analysis. Fourteen HMII patients who underwent treadmill CPET were included in the final analysis.

The advanced heart failure (ESHF) patients were a convenience sample of those who underwent treadmill CPET as part of their heart transplant evaluation and were subsequently listed for heart transplant during the same time period at VCU Medical Center. Seventeen patients with advanced heart failure who underwent symptom-limited treadmill CPET and listed for heart transplant by the VCUMC Heart Transplant committee were included in the final analysis.
The following clinical characteristics were examined in all groups to describe the sample: 1) Age (years), 2) Gender (Male or Female), 3) Race (Caucasian, African-American, Other), 4) HF etiology (Non-ischemic cardiomyopathy (NICM), Ischemic cardiomyopathy (ICM), Congenital Heart disease (CHD)), 5) Body mass index (BMI) in kg/m², 6) Hemoglobin concentration (Hgb) expressed as milligrams per deciliter (mg/dL). Additionally, left-ventricular ejection fraction (LVEF %) was obtained in the ESHF and HMII groups. Indication for MCS device was determined in the TAH and HMII groups as either: 1) Bridge to transplant (BTT), 2) Destination therapy (DT), 3) Bridge to decision (BTD). Post-operative day of CPET was also obtained in the MCS device groups and was defined as the number of days between device implant and date of CPET.

Presence of comorbidities that might affect the exercise response was examined across the three groups. Comorbidities of interest included diabetes (DM), peripheral vascular disease (PVD), smoking status within last 6 months, chronic obstructive lung disease (COPD), electronic cardiac pacemaker at the time of CPET, presence of atrial fibrillation at the time of CPET, and sedentary lifestyle defined as not meeting American College of Sports Medicine physical activity guidelines for adults at the time of CPET.

Standard heart failure therapies were also examined including automatic internal cardioverter defibrillator (AICD) use and pharmacological therapies of Beta-blocker, ACE inhibitor (ACE-I), Angiotensin II receptor antagonist (ARB), Aldosterone antagonist, Calcium
channel blockers (CCB), Hydralazine/ Isosorbide dinitrate (HDZN/ISDN), other cardiovascular vasoreactive medications.

Testing Protocol

Contraindications to exercise testing were based on established American College of Cardiology/ American Heart Association Guidelines for exercise testing.\textsuperscript{25} MCS device patients were considered appropriate for CPET once they were deemed medically stable by the attending physician and felt to be sufficiently ambulatory per cardiopulmonary rehabilitation staff. Sufficient ambulatory status was arbitrarily defined as able to tolerate motorized treadmill walking of at least 1.0 mph for at least 5 minutes duration without a rest break. All tests were symptom-limited in nature and physician supervised. Testing was administered by a qualified clinical exercise physiologist.

The treadmill protocol utilized was a conservative incremental ramping protocol wherein the speed and grade increased by approximately 0.6 estimated metabolic equivalents (est. $\text{VO}_2 \sim 2 \text{ ml.kg}^{-1}\text{.min}^{-1}$) every 30 seconds. This treadmill protocol has been previously described and utilized in a heart failure population.\textsuperscript{26} Ventilatory gas-analysis was performed using a VMax Encore metabolic cart (Carefusion, Yorba Linda, CA) with a standard mouthpiece and nose clip. The metabolic cart was calibrated for volume and gas-concentration prior to every test. Testing was not performed without successful calibration. Ventilatory gas-analysis
measurements were obtained for at least 3 minutes in the seated position before the start of exercise, continuously throughout exercise and 2 minutes into the recovery period. Blood pressure was monitored with a Tango+ exercise blood pressure system (Suntech Medical, Morrisville, NC) in the ESHF and TAH groups. HMII patient blood pressure was monitored via aneroid sphygmomanometer and Huntleigh - 8MegaHertz Doppler probe (Arjohuntleigh, USA). Blood pressure obtained with this method was a single reading and defined as the mean arterial pressure (MAP). Sphygmomanometer blood pressure cuff and Doppler probe is the recommended way to monitor blood pressure in this patient population. Blood pressure measurements were monitored during seated rest, standing, every 2 minutes during exercise, and every minute following exercise up to 6 minutes into recovery and/or until the patient was stable. Twelve-lead electrocardiography was performed continuously in the ESHF and HMII patients with standard Mason-Likar exercise lead placement.

The TAH hospital driver (“Big-blue”) function was assessed through a CPU monitor attached to the pneumatic driver displaying calculations of left and right fill volume and cardiac output. The CPU monitor also displays waveforms indicating ejection pressure and chamber filling with each cardiac cycle. The TAH Freedom Driver system console displays calculations of left fill volume and left cardiac output in addition to the set device pump rate. Device parameters were recorded pre, during exercise every two minutes and during the recovery period. All device settings remained fixed throughout testing.
HMII function was assessed through a display console that reported estimated device flow, speed, pulsatility index, and pump power. The HMII speed was left unchanged during testing. Device parameters were recorded pre, during exercise every two minutes, and during the recovery period.

Exercise Variables Assessed

The following CPET exercise variables were compared between the three groups: peak oxygen consumption (peak \( \dot{V}O_2 \)), anaerobic threshold (VAT), peak respiratory exchange ratio (RER), ventilatory efficiency slope (VE/VCO\(_2\) slope), oxygen uptake efficiency slope (OUES), presence of exercise oscillatory breathing pattern (EOV), and partial pressure end-tidal CO\(_2\) (PetCO\(_2\)) at rest, VAT, and peak exercise.

- Peak oxygen consumption (peak \( \dot{V}O_2 \)) is considered the gold-standard measurement of exercise capacity. It is also the most frequently described exercise variable in the heart failure literature.\(^{28}\) Moreover, there is a high test-retest reliability and reproducibility of this measurement in heart failure patients.\(^{29,30}\) In normal healthy individuals exercise capacity (i.e. aerobic exercise capacity) can be determined from work rate due to the close linear relationship between work rate and oxygen consumption.\(^{31}\) However, in HF oxygen uptake kinetics with exercise are altered.\(^{32}\) Therefore, direct measurement of exercise capacity is recommended over estimates based upon exercise time or workload.
in this population. Peak $\dot{V}O_2$ was defined as the highest 30 second interval average obtained from breath by breath measurements of $\dot{V}O_2$ during peak exercise. It was expressed and analyzed with both absolute (Liters·minute) and relative to bodyweight ($mLO_2·kg^{-1}·min^{-1}$). Additionally, it was expressed and analyzed by percent of predicted (% predicted) normal values using the reference values of Wasserman et al.\textsuperscript{33}

- The ventilatory anaerobic threshold (VAT) is a submaximal indicator of exercise capacity. In normal healthy individuals it is highly reproducible and identifiable.\textsuperscript{31} This measure has also been found to be reproducible in HF patients.\textsuperscript{30} In heart failure, VAT is often more difficult to ascertain partly due to the abnormal ventilatory pattern often observed in this population.\textsuperscript{34} Anaerobic threshold was defined using the ventilatory equivalents method.\textsuperscript{35} This consists of using the $\dot{V}O_2$ value observed when the minute ventilation (VE) to oxygen consumption (VE/$\dot{V}O_2$) ratio reaches its nadir and starts to subsequently increase without a simultaneous increase in the minute ventilation to carbon dioxide output (VE/VCO$_2$) ratio. It was expressed and analyzed as both absolute (Liters·minute) and relative to bodyweight ($mLO_2·kg^{-1}·min^{-1}$). Additionally, it was expressed and analyzed by percent of predicted (% predicted) normal peak $\dot{V}O_2$ values using the reference values of Wasserman et al.\textsuperscript{33}
• The peak respiratory exchange ratio (RER) is defined as the ratio of $\text{VCO}_2/\text{VO}_2$ corresponding to the peak $\dot{\text{VO}}_2$ at the end of exercise. This is used to quantify subject effort during exercise testing. A peak RER of 1.10 or greater is considered a universal indicator of maximal exercise effort independent of patient characteristics such as age, sex, fitness, and disease state.\(^{36}\) Peak RER was defined as the highest 30 second interval average obtained during exercise.

• The slope of the relationship between VE and VCO\(_2\) describes the ventilatory efficiency during effort, showing the amount of air that must be ventilated to eliminate 1 liter of carbon dioxide. The VE/VCO\(_2\) slope is defined as the linear regression value ($y = mx + b$ where $m =$ slope) of the relationship between minute ventilation and carbon dioxide production during exercise. Data analysis was based upon 10-second interval averages for minute ventilation and carbon dioxide production throughout the entire exercise period.

• The oxygen uptake efficiency slope (OUES) represents the rate of increase of $\dot{\text{VO}}_2$ in response to a given VE during incremental exercise, indicating how effectively oxygen is extracted and utilized. It is a reliable and reproducible measure of exercise ventilatory efficiency and highly correlates to peak $\dot{\text{VO}}_2$.\(^{37,\,38}\) The OUES is determined from the linear relation of $\dot{\text{VO}}_2$ (y-axis) versus the logarithm transformation of VE (x-axis) during
exercise, that is, $\dot{V}O_2 = a \log_{10} VE + b$, where ‘a’ is the OUES and ‘b’ is the intercept. Data analysis was based upon 10-second interval averages for minute ventilation (Liters·minute) and absolute oxygen uptake (Liters·minute) throughout the entire exercise period.

- Exercise oscillatory ventilation (EOV) was identified based upon the definition used by Corra et al.\textsuperscript{39} Presence of EOV is indicated by cyclic fluctuations in pulmonary minute ventilation at rest that persist during effort lasting $\geq 60\%$ of the exercise duration, with an amplitude $\geq 15\%$ of the average resting value.

- Partial pressure of end-tidal carbon dioxide (PetCO$\textsubscript{2}$) is the measurement of carbon dioxide present in exhaled air and is expressed in mmHg. It is a reliable and noninvasive estimate of the partial pressure of arterial carbon dioxide (PaCO$\textsubscript{2}$).\textsuperscript{40} It correlates well with peak $\dot{V}O_2$, VE/VCO$\textsubscript{2}$, cardiac output, and pulmonary function.\textsuperscript{33, 40, 41} Lower values at rest and during exercise are observed in heart failure compared with normal individuals and measurements of PetCO$\textsubscript{2}$ correlate with cardiac output and severity of disease.\textsuperscript{41, 42} Resting measurements were based on the average value of at least two minutes of pre-exercise resting data. Exercise measurements were expressed as the PetCO$\textsubscript{2}$ observed at the anaerobic threshold or the highest value obtained if anaerobic threshold is undetectable.\textsuperscript{19, 42, 33}
Statistical Analysis

All exercise variables were described using measures of central tendency and dispersion. Normally distributed data was described using mean ± standard deviation. Abnormally distributed data was described via median and interquartile range (IQR). Categorical variables were assessed using Chi-square analysis. A one-way analysis of variance (ANOVA) equal variance F-test was employed to assess for differences between the three HF groups for the following variables: peak \( \dot{V}O_2 \), VAT, peak RER, VE/VCO\(_2\) slope, OUES, EOV, and PetCO\(_2\) values at rest, during exercise at the VAT and peak exercise. Tukey’s HSD test for multiple comparisons was used to determine wherein the difference lies when a significant difference was detected. Additionally, within group correlation was performed to assess for potential associations between peak \( \dot{V}O_2 \) and the described clinical characteristics and the remaining common clinical CPET variables. A post-hoc analysis of covariance (ANCOVA) was also performed to determine if there were significant main effects for peak \( \dot{V}O_2 \) and if there was a significant interaction between hemoglobin and peak \( \dot{V}O_2 \) between the heart failure groups. A p-value of < .05 was used for significance. JMPv9® statistical software (SAS Institute Inc., Cary, NC) was utilized for statistical analysis.

Results
The clinical characteristics of the three HF groups are displayed in Table 1. There was a significant difference in BMI between the groups (F (2, 42) = 3.3, p-value = 0.0463). Specifically, the TAH group BMI was 6.1 units lower than the HMII group (p-value = 0.0471, SE = 2.47, 95% CI’s (0.07 – 12.08). BMI was similar between the ESHF and HMII groups although it is noted they both would be classified as obese. Hemoglobin (Hgb) concentration was also significantly different between the groups (F (2, 42) = 52.4, p-value = <0.0001). Hemoglobin was significantly lower in both MCS device groups compared with the ESHF group. TAH hemoglobin was 5.8 mg/dL lower than ESHF (p-value = <0.0001, SE = 0.59, 95% CI’s (4.4 – 7.3), whereas HMII hemoglobin was 4.1 mg/dL lower than ESHF (p-value = <0.0001, SE = 0.59, 95% CI’s (2.7 – 5.6). Additionally, TAH Hgb was significantly lower than HMII (Mean Diff. = 1.7 mg/dL, p-value = 0.0234, SE = 0.62, 95% CI’s (0.2 – 3.2). Beta-blocker usage was also different between the groups as this medication is not part of the pharmacologic regimen in the TAH patient. No significant difference was observed in beta-blocker usage between the other two groups. Aldosterone antagonist usage was significantly different between the groups due to less TAH patient usage (Chi-square = 6.3, df = 2, p-value = 0.0427). Alternatively, calcium channel blocker use was higher in the TAH patients (Chi-square = 11.8, df = 2, p-value = 0.0027).
<table>
<thead>
<tr>
<th></th>
<th>TAH (n = 14)</th>
<th>HMII (n = 14)</th>
<th>ESHF (n = 17)</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43 (38 - 53)</td>
<td>53 (37 - 59)</td>
<td>59 (41 - 65)</td>
<td>0.4421</td>
</tr>
<tr>
<td>Gender (M,F)</td>
<td>9,5</td>
<td>9,5</td>
<td>15,2</td>
<td>0.1846</td>
</tr>
<tr>
<td>Race (C,AA,O)</td>
<td>9,4,1</td>
<td>7,7,0</td>
<td>10,7,0</td>
<td>0.4887</td>
</tr>
<tr>
<td>HF Etiology</td>
<td></td>
<td></td>
<td></td>
<td>0.1749</td>
</tr>
<tr>
<td>NICM</td>
<td>13</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>ICM</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>$27.5 \pm 5.5^a$</td>
<td>$33.6 \pm 8.0$</td>
<td>$32.1 \pm 5.9$</td>
<td>*0.0463</td>
</tr>
<tr>
<td>Hgb (mg/dL)</td>
<td>$7.9 \pm 1.4^a$</td>
<td>$9.6 \pm 1.5^b$</td>
<td>$13.7 \pm 2.0$</td>
<td>*&lt;.0001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>$21 \pm 10$</td>
<td>$16 \pm 8$</td>
<td></td>
<td>0.1583</td>
</tr>
<tr>
<td>Indication for MCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BTT</td>
<td>14 (100%)</td>
<td>8 (52%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DT</td>
<td>4 (29%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BTD</td>
<td>2 (14%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-op day of CPET (#)</td>
<td>46 (35 - 100)</td>
<td>61 (49 - 95)</td>
<td></td>
<td>0.9876</td>
</tr>
<tr>
<td>Comorbidities (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>3 (21%)</td>
<td>5 (36%)</td>
<td>5 (29%)</td>
<td>0.7014</td>
</tr>
<tr>
<td>PVD</td>
<td>1 (7%)</td>
<td>3 (21%)</td>
<td>3 (18%)</td>
<td>0.5212</td>
</tr>
<tr>
<td>Smoker</td>
<td>2 (14%)</td>
<td>1 (7%)</td>
<td>0</td>
<td>0.1868</td>
</tr>
<tr>
<td>COPD</td>
<td>0</td>
<td>2 (14%)</td>
<td>0</td>
<td>0.0871</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>0</td>
<td>5 (36%)</td>
<td>6 (35%)</td>
<td>0.9806</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 (21%)</td>
<td>7 (41%)</td>
<td></td>
<td>0.2363</td>
</tr>
<tr>
<td>Sedentary</td>
<td>14 (100%)</td>
<td>14 (100%)</td>
<td>15 (82%)</td>
<td>0.1321</td>
</tr>
<tr>
<td>Therapies (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AICD</td>
<td>0</td>
<td>13 (93%)</td>
<td>17 (100%)</td>
<td></td>
</tr>
<tr>
<td>B-blocker</td>
<td>0$^a$</td>
<td>11 (79%)</td>
<td>15 (88%)</td>
<td>*&lt;0.001</td>
</tr>
<tr>
<td>ACE-I</td>
<td>6 (43%)</td>
<td>8 (57%)</td>
<td>9 (53%)</td>
<td>0.7371</td>
</tr>
<tr>
<td>ARB</td>
<td>0</td>
<td>1 (7%)</td>
<td>4 (24%)</td>
<td>0.0596</td>
</tr>
<tr>
<td>Anti-Aldosterone</td>
<td>3 (21%)$^a$</td>
<td>8 (57%)</td>
<td>11 (65%)</td>
<td>*0.0427</td>
</tr>
<tr>
<td>CCB</td>
<td>6 (43%)$^a$</td>
<td>1 (7%)</td>
<td>0</td>
<td>*0.0027</td>
</tr>
<tr>
<td>HDZN/ISDN</td>
<td>2 (14%)</td>
<td>0</td>
<td>0</td>
<td>0.0871</td>
</tr>
<tr>
<td>Other*</td>
<td>1 (7%)</td>
<td>1 (7%)</td>
<td>0</td>
<td>0.3764</td>
</tr>
</tbody>
</table>

* Nesiritide *Sildenafil
$^a$ = significant difference between HMII and ESHF(p <.05), $^b$ = sig. difference between ESHF (p <.05)
Table 2 lists MCS device specific parameters at the time of CPET. These parameters were set prior to CPET by the attending cardiologist/cardiothoracic surgeon to optimize clinical condition. TAH driver was the type of driver utilized at time of CPET. Right and left-drive pressure is the amount of air entering the respective artificial ventricles for ejection. % systole is the percent of the cardiac cycle spent in systole. Beat rate is the pump rate or heart rate of the device. In the HMII, pump speed is the set speed in revolutions per minute (rpm) of the rotor assembly housed within the pump.

**Table 2: MCS Device Specific Variables**

<table>
<thead>
<tr>
<th>TAH</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TAH driver (n, %)</td>
<td></td>
</tr>
<tr>
<td>Big-Blue Driver</td>
<td>10 (71%)</td>
</tr>
<tr>
<td>Freedom Driver</td>
<td>4 (29%)</td>
</tr>
<tr>
<td>RDP (mmHg)</td>
<td>83 (74 - 110)</td>
</tr>
<tr>
<td>LDP (mmHg)</td>
<td>205 (199 - 210)</td>
</tr>
<tr>
<td>% Systole (%)</td>
<td>53 (50 - 60)</td>
</tr>
<tr>
<td>Beat rate (bpm)</td>
<td>130 (120 - 138)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HMII</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pump speed (rpm)</td>
<td>9671 ± 487</td>
</tr>
</tbody>
</table>

Abbreviations: RDP= Right drive pressure, LDP=Left drive pressure
Table 3 shows the mean ± SD by HF group for standard exercise test variables. All of the exercise tests were symptom-limited in nature and were terminated by patient request to stop. No adverse events occurred with any of the CPET’s performed in this very high-risk patient population. Reasons for test termination are provided with (n, %) for primary symptomology within each group. There was a significant difference noted in peak exercise mean arterial pressure (MAP) (F (2, 42) = 6.1, p-value = 0.0048) and peak Borg rating of perceived exertion (RPE) 6 – 20 scale (F (2, 42) = 4.6, p-value = 0.0151). Specifically, the HMII peak MAP was 15mmHg higher than the TAH group (p-value = 0.04, SE = 6.2, 95% CI’s (0.6 – 31) and 20mmHg higher than the ESHF (p-value = 0.0045, SE = 5.9, 95% CI’s (5.5 – 34) and peak Borg RPE was significantly higher (1.5 units) in the ESHF group compared with TAH patients (p-value = 0.022, SE = 0.5, 95% CI’s (0.2 – 2.8).
Table 3: Standard Exercise Test Variables

<table>
<thead>
<tr>
<th></th>
<th>TAH</th>
<th>HMII</th>
<th>ESHF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise Time (min)</td>
<td>5.6 ± 1.2</td>
<td>5.3 ± 2.2</td>
<td>6.7 ± 2.7</td>
<td>0.1765</td>
</tr>
<tr>
<td>RHR (bpm)</td>
<td>128 ± 6a</td>
<td>82 ± 12</td>
<td>78 ± 19</td>
<td>*&lt;0.0001</td>
</tr>
<tr>
<td>Peak HR (bpm)</td>
<td>128 ± 6</td>
<td>117 ± 20</td>
<td>120 ± 21</td>
<td>0.2241</td>
</tr>
<tr>
<td>Resting MAP (mmHg)</td>
<td>89 ± 11</td>
<td>86 ± 10</td>
<td>81 ± 14</td>
<td>0.1743</td>
</tr>
<tr>
<td>Peak MAP (mmHg)</td>
<td>87 ± 14</td>
<td>102 ± 15b</td>
<td>82 ± 19</td>
<td>*0.0048</td>
</tr>
<tr>
<td>Peak RPE (6 - 20)</td>
<td>14.5 ± 0.7</td>
<td>14.7 ± 1.7</td>
<td>16.0 ± 1.8</td>
<td>*0.0151</td>
</tr>
<tr>
<td>Peak RPD (0 - 10)</td>
<td>4.4 ± 1.8</td>
<td>3.9 ± 2.0</td>
<td>5.6 ± 2.1</td>
<td>0.0711</td>
</tr>
</tbody>
</table>

Test Termination

<table>
<thead>
<tr>
<th></th>
<th>DOE</th>
<th>General Fatigue</th>
<th>LE Fatigue</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 (29%)</td>
<td>2 (14%)</td>
<td>6 (43%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td></td>
<td>7 (50%)</td>
<td>4 (29%)</td>
<td>2 (14%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td></td>
<td>7 (41%)</td>
<td>4 (24%)</td>
<td>4 (24%)</td>
<td>2 (11%)</td>
</tr>
</tbody>
</table>

\( ^a = \) sig. between HMII and ESHF (p<.05), \( ^b = \) sig. difference between TAH and ESHF, \( ^c = \) sig. difference between TAH

CPET Variables

Table 4 describes the mean ± SD values for the variables obtained from CPET in the different groups. A significant difference was noted between groups for peak oxygen consumption (L·min) \( F (2, 42) = 7.9, \) p-value = 0.0012) and percentage of predicted peak oxygen consumption \( F (2, 42) = 5.1, \) p-value = 0.0106) when expressed in absolute terms, but
not relative to bodyweight (mL·kg\(^{-1}\)·min\(^{-1}\)) (p-value = 0.08). Similarly, there was a significant difference in ventilatory anaerobic threshold values \((F(2, 33) = 8.7, p\text{-}value = 0.0009)\) and VAT percent of predicted peak \(\dot{V}O_2\) \((F(2, 33) = 5.0, p\text{-}value = 0.0125)\) between the three groups for absolute values, but not for relative values \((p\text{-}value = 0.056)\) although there was a trend towards lower relative peak \(\dot{V}O_2\) values in the TAH group. Specifically, the TAH group had significantly lower absolute peak oxygen consumption, percentage of predicted peak oxygen consumption, absolute ventilatory anaerobic threshold, and VAT percent of predicted peak \(\dot{V}O_2\) compared with the other two groups. Additionally, the TAH group had a significantly higher peak RER \((F(2, 42) = 14.1, p\text{-}value = <0.0001)\), and a lower oxygen uptake efficiency slope \((F(2, 42) = 9.3, p\text{-}value = 0.0004)\). No significant difference was found between the HMII and ESHF groups for peak \(\dot{V}O_2\), % predicted peak \(\dot{V}O_2\), VAT, VAT % predicted of peak \(\dot{V}O_2\), RER, and OUES. The ESHF group did have a significantly higher presence of EOV \((\text{Chi-square} = 7.73, \ df = 2, p\text{-}value = 0.0228)\) than either MCS device group. No significant difference was noted in the VE/VCO\(_2\) slope between groups although the TAH group trended towards a higher value. No significant difference was noted in PetCO\(_2\) values at rest, VAT, or peak exercise between the groups. However, it is noted that a flat PetCO\(_2\) response to exercise was observed in all three groups.
Table 4: Descriptive CPET Variables

<table>
<thead>
<tr>
<th></th>
<th>TAH</th>
<th>HMII</th>
<th>ESHF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO₂ (L·min)</td>
<td>0.926 ± 0.168&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.270 ± 0.364</td>
<td>1.340 ± 0.331</td>
<td>*0.0012</td>
</tr>
<tr>
<td>% Pred. VO₂</td>
<td>36 ± 8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>49 ± 12</td>
<td>50 ± 17</td>
<td>*0.0106</td>
</tr>
<tr>
<td>Peak VO₂ (ml.kg.min)</td>
<td>11.0 ± 2.3</td>
<td>12.6 ± 2.8</td>
<td>13.9 ± 4.7</td>
<td>0.0800</td>
</tr>
<tr>
<td>% Pred. VO₂</td>
<td>33 ± 7</td>
<td>40 ± 14</td>
<td>44 ± 16</td>
<td>0.1051</td>
</tr>
<tr>
<td>Peak METs</td>
<td>3.1 ± 0.7</td>
<td>3.6 ± 0.8</td>
<td>4.0 ± 1.3</td>
<td>0.0777</td>
</tr>
<tr>
<td>VAT (L·min)</td>
<td>0.706 ± 0.181&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.008 ± 0.252</td>
<td>0.996 ± 0.201</td>
<td>*0.0009</td>
</tr>
<tr>
<td>% Pred. peak VO₂</td>
<td>27 ± 7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>37 ± 10</td>
<td>38 ± 12</td>
<td>*0.0125</td>
</tr>
<tr>
<td>VAT (ml.kg.min)</td>
<td>8.4 ± 2.5</td>
<td>10.0 ± 2.1</td>
<td>10.6 ± 2.2</td>
<td>0.0566</td>
</tr>
<tr>
<td>% Pred. peak VO₂</td>
<td>25 ± 7</td>
<td>30 ± 15</td>
<td>33 ± 10</td>
<td>0.1997</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.30 ± 0.09&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.12 ± 0.14</td>
<td>1.1 ± 0.11</td>
<td>*&lt;.0001</td>
</tr>
<tr>
<td>OUES</td>
<td>0.96 ± 0.25&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.69 ± 0.52</td>
<td>1.58 ± 0.59</td>
<td>*0.0004</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>39.8 ± 8.0</td>
<td>34.1 ± 6.6</td>
<td>34.9 ± 7.6</td>
<td>0.0968</td>
</tr>
<tr>
<td>Presence of EOV</td>
<td>4 (29%)</td>
<td>4 (29%)</td>
<td>12 (71%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>*0.0228</td>
</tr>
<tr>
<td>PetCO₂ @ Rest (mmHg)</td>
<td>33.6 ± 3.2</td>
<td>34.3 ± 3.5</td>
<td>34.2 ± 3.9</td>
<td>0.8804</td>
</tr>
<tr>
<td>PetCO₂ @ VAT (mmHg)</td>
<td>32.5 ± 3.0</td>
<td>33.9 ± 3.9</td>
<td>34.8 ± 4.8</td>
<td>0.3084</td>
</tr>
<tr>
<td>PetCO₂ @ Peak (mmHg)</td>
<td>29.1 ± 4.2</td>
<td>32.2 ± 4.3</td>
<td>31.2 ± 5.8</td>
<td>0.2315</td>
</tr>
</tbody>
</table>

<sup>a</sup> = sig. difference between HMII and ESHF (p < .05), <sup>b</sup> = sig. difference between TAH and HMII
Figure 1 provides a visual depiction of the difference in peak oxygen consumption between the three groups. The mean diamonds show the respective mean and 95% CI’s. The hash marks represent the standard deviations.

Figure 1: Peak VO₂ by Heart Failure Group
Table 5 is a contingency table based on the objective risk stratification classification systems commonly employed to stratify heart failure severity and guide clinical management.

No significant difference was noted between the groups although TAH patients tended to fall into lower Weber functional classes and higher ventilatory classes.

**Table 5: Weber Functional & Ventilatory Class Schema**

<table>
<thead>
<tr>
<th>Weber Class</th>
<th>TAH</th>
<th>HMII</th>
<th>ESHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>0</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>4 (29%)</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>C</td>
<td>9 (64%)</td>
<td>7 (50%)</td>
<td>8 (47%)</td>
</tr>
<tr>
<td>D</td>
<td>5 (36%)</td>
<td>3 (21%)</td>
<td>3 (18%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ventilatory Class</th>
<th>TAH</th>
<th>HMII</th>
<th>ESHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>4 (29%)</td>
<td>5 (29%)</td>
</tr>
<tr>
<td>II</td>
<td>6 (43%)</td>
<td>5 (36%)</td>
<td>6 (35%)</td>
</tr>
<tr>
<td>III</td>
<td>4 (28.5%)</td>
<td>4 (21%)</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>IV</td>
<td>4 (28.5%)</td>
<td>1 (7%)</td>
<td>3 (18%)</td>
</tr>
</tbody>
</table>

Correlation analysis demonstrated there was a significant positive association between the clinical characteristics of body mass index ($r = 0.36$, df = 43, p-value = 0.0159) and hemoglobin concentration ($r = 0.62$, df = 43, p-value = <0.0001) with absolute peak oxygen
uptake. After controlling for HF group assignment, HMII was the only group which retained a significant association between BMI and peak \( \dot{V}O_2 \). Similarly, there was a significant association observed between gender and peak \( \dot{V}O_2 \) in the HMII group only (\( t = 2.28, df = 12, p\text{-value} = 0.0419 \)) with females having a peak \( \dot{V}O_2 \) of 0.402 L\cdot min less than the males (\( p\text{-value} = 0.0419, SE = 0.18, 95\% \text{ CI's (0.02 - 0.79)} \)). Hemoglobin concentration had a significant positive association within all three HF groups: TAH (\( r = 0.57, df = 12, p\text{-value} = 0.0347 \)), HMII (\( r = 0.66, df = 12, p\text{-value} = 0.0102 \)), ESHF (\( r = 0.70, df=15, p\text{-value} = 0.0018 \)). OUES also showed a significant positive correlation with peak oxygen uptake (\( r = 0.71, df = 43, p\text{-value} = <0.0001 \)).

An ANCOVA model indicated there were significant main effects for peak \( \dot{V}O_2 \) due to HF group and hemoglobin concentration (\( F(5,39) = 7.66, p\text{-value} = <0.0001 \)). However, there was not a significant interaction effect found between peak \( \dot{V}O_2 \) and hemoglobin between the heart failure groups.

**Discussion**

Exercise capacity is indeed reduced in TAH patients. Peak exercise oxygen consumption, percentage of predicted peak \( \dot{V}O_2 \), and oxygen consumption at the ventilatory anaerobic threshold is reduced in TAH patients compared with HMII LVAD patients as well as those with advanced heart failure on medical-management only awaiting heart transplant. This is accompanied by a significant elevation in peak exercise RER values and a significant reduction in
Additionally, there was a significantly blunted peak exercise mean arterial pressure for the TAH group compared to the HMII group. Not surprisingly, hemoglobin status at the time of CPET appears to significantly affect exercise capacity in all HF groups.

In this study all three groups exhibited very low peak $\dot{V}O_2$ values consistent with significant advanced heart failure which is similar to that previously reported in non-MCS patients. Although it must be noted the peak oxygen consumption and ventilatory anaerobic threshold values observed in the MCS device groups (TAH, HMII) were both somewhat lower than that previously cited by others particularly when referenced to bodyweight. This may be somewhat misleading in the HMII group due to the excessive BMI values (BMI = 33.6 ± 8) observed in this cohort compared with that reported by others. For example, de Jonge and colleagues reported peak $\dot{V}O_2$ values of 22.8 ml.kg$^{-1}$.min$^{-1}$ in LVAD patients 3 months after implant with a mean BMI of 22. Haft et al. observed a peak $\dot{V}O_2$ of 15.6 ± 4.7 ml.kg$^{-1}$.min$^{-1}$ in a group of HMII LVAD recipients with a BMI of 27 ± 6.

In comparison to the only other study evaluating CPET variables in the TAH patient by Bellotto et al., the absolute peak $\dot{V}O_2$ and $\dot{V}O_2$ at the ventilatory anaerobic threshold of TAH patients in our study was similar to that observed in the first CPET (0.945 L.min, 0.666 L.min, respectively) performed by their subject at approximately 3 months following TAH implant. Of note, the single subject in the Bellotto study was normal weight evidenced by BMI status (BMI =
22) and had a hemoglobin 2.2 g/dL higher than the average observed in the present study.23 During this same test an elevated peak RER was also observed (RER = 1.32) along with a flat blood pressure response consistent with that noted in this study. Conversely, the Bellotto subject displayed normal VE/VCO₂ slope values (26.51 – 29.09) across all four sequential CPET’s although the present investigation observed an elevated VE/VCO₂ slope consistent with a Ventilatory Class III rating indicative of a poor prognosis in HF patients.16

The blunted blood pressure response noted in the TAH group is similar to that previously reported by Kohli and colleagues.24 The present study differs in that the MAP values were obtained with maximal exercise testing versus a submaximal assessment during an exercise session. This confirms that the blood pressure response observed is potentially related to the limitations of the TAH device and not exercise intensity. Interestingly, the average exercise training intensity noted in the Kohli study (2.3 ± 0.5 METs) is similar to the mean MET level (2.4 METs) at the VAT observed in the present study. This may indicate the average exercise workloads observed by Kohli might represent the highest sustainable exercise intensity capable in this population.

The Fick equation (\(\dot{V}O_2 = \text{Cardiac Output} \times (a-V\dot{O}_2 \text{ difference})\)) demonstrates that \(\dot{V}O_2\) is largely dependent upon increases in cardiac output. It is universally accepted that maximal cardiac output is the major determinant of maximal oxygen uptake during exercise.49 Factors
that determine oxygen uptake with exercise include: 1) pulmonary diffusing capacity, 2) maximal cardiac output, 3) oxygen carrying capacity of the blood, and 4) skeletal muscle characteristics (i.e. O₂ extraction capabilities of muscle).\textsuperscript{49} Previous work in MCS patients has shown that the device is responsible for the majority of the cardiac output increase seen during exercise.\textsuperscript{50,51} The TAH patient has a fixed pump rate (i.e. heart rate) with exercise thus has a fairly fixed cardiac output response to exercise. The only augmentation of cardiac output is derived via enhanced venous return by the skeletal muscle blood pump during exercise and compensatory venoconstriction.\textsuperscript{21,52} Bellotto observed a limited cardiac output response in the TAH patient on the order of a 1.6 to 2.9 L/min increase with peak exercise.\textsuperscript{23}

The TAH patient peak oxygen uptake values noted in the present study approximate a three-fold increase above resting metabolism (METS = 3.1 ± 0.7). When cardiac output is unchanged oxygen uptake can only increase approximately three-fold due to the limits of maximal oxygen extraction with exercise.\textsuperscript{33} As the ability to increase cardiac output decreases, the a-VO₂ diff. has a greater influence on the VO₂ response to exercise. In healthy individuals, a-VO₂ diff. is approximately 5ml/100mL blood at rest and can increase to approximately 15 ml/100mL blood at maximum exercise. This, however, is also dependent upon hemoglobin status and hemoconcentration with exercise. Anemia is known to be common in heart failure and associated with poor outcome and reduced exercise capacity.\textsuperscript{53} Agostoni and colleagues evaluated the relationship between hemoglobin and peak VO₂ in heart failure patients.\textsuperscript{54} They
found anemic patients had lower peak $\dot{V}O_2$, $\dot{V}O_2$ at the anaerobic threshold, and a higher VE/VCO$_2$ slope than non-anemic HF patients. Their linear regression slope demonstrated that each gram of hemoglobin accounted for a 109 ml.min change in $\dot{V}O_2$ (0.97 ml.kg.min). Using the assumption of Agostoni, and all other things being equal, the TAH group in the present study could potentially improve peak $\dot{V}O_2 > 0.5$ L-min if hemoglobin was treated to a level exhibited in the ESHF group.

Another observation from this study was the continued presence of an oscillatory breathing pattern with exercise in both MCS device groups. The frequency is similar to that observed in other studies of chronic heart failure patients. The prognostic significance of this finding is unclear in the MCS device population, but underscores the multifactorial pathophysiology of this phenomenon.

Obvious limitations of this study were the low number of participants affecting validity although it is noted the number of MCS device patients in this study is similar to others in the literature in this novel population. A significant proportion of the original MCS cohort was not available for CPET (36% TAH, 44% HMII) due to medical status, low functional status, or unavailability (i.e. underwent heart transplant, lost-to follow up) which may have affected the representativeness of the sample population. This was only a cross-sectional study examining the exercise capacity of MCS patients relatively early after device implant. The postoperative
date (POD#) of CPET was smaller than that recommended for optimal functional results in the post-MCS patient.\textsuperscript{45} The mean POD# for TAH and HMII was 46 days (\~6.7 weeks) and 61 days (\~8.7 weeks) where as deJonge and others have observed optimal timing for CPET was at least 12 weeks post-implant.\textsuperscript{45,47}

\textit{Implications/ Recommendations}

The persistently low exercise capacity following MCS device implant, particularly the TAH device necessitates the need for strategies to further improve functional status in these individuals. This low functional status needs to be considered when examining the exertional symptoms or ADL tolerance of these patients. Furthermore, the presence of CPET variables with strong prognostic significance in the heart failure population (i.e. low peak VO\textsubscript{2}, low VAT, high VE/VCO\textsubscript{2} slope, low OUES, blunted PetCO\textsubscript{2} response to exercise, low peak blood pressure, presence of EOV) persist in the short-term following MCS device implantation although their clinical importance in this population is unknown.

Efforts to improve the persistent significant anemia seen in the TAH patient will help to improve oxygen extraction and utilization during exercise thus augmenting oxygen consumption and functional status. Aerobic exercise training will also likely improve exercise capacity via a peripheral adaptation (i.e. increased a-VO\textsubscript{2} difference). Future studies should examine the correlation between the auto-regulated cardiac output and fill-volumes (stroke
volume) derived from the TAH and oxygen consumption. This may shed light on optimal device settings with exercise. Furthermore, the effects of up-titrating the TAH beat rate during exercise to augment cardiac output similar to the normal intrinsic heart rate increase with exercise requires further study.

Summary/Conclusions

This is the first study to directly measure the maximal exercise capacity in a group of advanced heart failure patients supported with total artificial heart. Additionally, this study compared the responses to graded exercise in TAH patients with both a group of patients implanted with a HMII left ventricular assist device and a group of patients with advanced heart failure being assessed for transplant. Based on these findings, symptom-limited exercise testing can be safely performed in the TAH patient. The exercise capacity of the TAH patient is reduced compared with other MCS devices and in those with advanced heart failure. We now have a baseline for expected functional ability and exercise responses in this unique patient population. This may facilitate formulation of appropriate functional goals and exercise prescription guidelines in the rehabilitation setting. It will help inform discussions of activity guidelines for those entering the community in light of a current FDA trial using a portable driver. It may also provide an objective reference for future technology improvements.
Manuscript Bibliography


Appendix 1
Thesis Bibliography


89. Ingle L, Witte KK, Cleland JGJF, Clark AL. The prognostic value of cardiopulmonary exercise testing with a peak respiratory exchange ratio of < 1.0 in patients with chronic heart failure. *Int J Cardiol.* 2008;127:88-92.


### Table 1: Significant Differences of CPET Variables between HF groups

#### Peak VO\textsubscript{2} (L•min)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference</th>
<th>SE</th>
<th>Lower CL</th>
<th>Upper CL</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESHF - TAH</td>
<td>0.415</td>
<td>0.1092</td>
<td>0.149</td>
<td>0.680</td>
<td>0.0013</td>
</tr>
<tr>
<td>HMII - TAH</td>
<td>0.345</td>
<td>0.1144</td>
<td>0.067</td>
<td>0.623</td>
<td>0.0119</td>
</tr>
<tr>
<td>ESHF - HMII</td>
<td>0.070</td>
<td>0.1092</td>
<td>-0.196</td>
<td>0.335</td>
<td>0.7995</td>
</tr>
</tbody>
</table>

#### % predicted Peak VO\textsubscript{2} (L•min)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference</th>
<th>SE</th>
<th>Lower CL</th>
<th>Upper CL</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESHF - TAH</td>
<td>14.0</td>
<td>4.70</td>
<td>2.5</td>
<td>25.4</td>
<td>0.0133</td>
</tr>
<tr>
<td>HMII - TAH</td>
<td>12.5</td>
<td>4.92</td>
<td>0.5</td>
<td>24.5</td>
<td>0.0388</td>
</tr>
<tr>
<td>ESHF - HMII</td>
<td>1.5</td>
<td>4.70</td>
<td>-10.0</td>
<td>12.9</td>
<td>0.9481</td>
</tr>
</tbody>
</table>

#### VAT (L•min)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference</th>
<th>SE</th>
<th>Lower CL</th>
<th>Upper CL</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMII - TAH</td>
<td>0.302</td>
<td>0.0886</td>
<td>0.085</td>
<td>0.519</td>
<td>0.0048</td>
</tr>
<tr>
<td>ESHF - TAH</td>
<td>0.291</td>
<td>0.0799</td>
<td>0.095</td>
<td>0.487</td>
<td>0.0026</td>
</tr>
<tr>
<td>HMII - ESHF</td>
<td>0.011</td>
<td>0.0899</td>
<td>-0.209</td>
<td>0.232</td>
<td>0.9911</td>
</tr>
</tbody>
</table>

#### VAT (% predicted Peak VO\textsubscript{2} (L•min))

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference</th>
<th>SE</th>
<th>Lower CL</th>
<th>Upper CL</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESHF - TAH</td>
<td>10.8</td>
<td>3.69</td>
<td>1.7</td>
<td>19.9</td>
<td>0.0165</td>
</tr>
<tr>
<td>HMII - TAH</td>
<td>9.7</td>
<td>4.09</td>
<td>-0.4</td>
<td>19.7</td>
<td>0.0606</td>
</tr>
<tr>
<td>ESHF - HMII</td>
<td>1.1</td>
<td>4.15</td>
<td>-9.1</td>
<td>11.3</td>
<td>0.9608</td>
</tr>
</tbody>
</table>

#### Peak RER

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference</th>
<th>SE</th>
<th>Lower CL</th>
<th>Upper CL</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAH - ESHF</td>
<td>0.205</td>
<td>0.0412</td>
<td>0.104</td>
<td>0.305</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>TAH - HMII</td>
<td>0.181</td>
<td>0.0432</td>
<td>0.076</td>
<td>0.286</td>
<td>0.0004</td>
</tr>
<tr>
<td>HMII - ESHF</td>
<td>0.023</td>
<td>0.0412</td>
<td>-0.077</td>
<td>0.123</td>
<td>0.8407</td>
</tr>
</tbody>
</table>

#### OUES

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference</th>
<th>SE</th>
<th>Lower CL</th>
<th>Upper CL</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMII - TAH</td>
<td>0.731</td>
<td>0.1830</td>
<td>0.286</td>
<td>1.175</td>
<td>0.0007</td>
</tr>
<tr>
<td>ESHF - TAH</td>
<td>0.612</td>
<td>0.1748</td>
<td>0.187</td>
<td>1.036</td>
<td>0.0031</td>
</tr>
<tr>
<td>HMII - ESHF</td>
<td>0.119</td>
<td>0.1748</td>
<td>-0.306</td>
<td>0.544</td>
<td>0.7759</td>
</tr>
</tbody>
</table>

#### Presence of EOV

Likelihood ratio chi-square = 7.73, df = 2, p-Value = 0.021
Appendix 3

Institutional Review Board Approval

VCU Memo
Virginia Commonwealth University

DATE: February 17, 2012

TO: Keyur B. Shah, MD
    Internal Medicine
    Box 980204

FROM: Lloyd H. Byrd, MS
       Vice-Chairperson, VCU IRB Panel B
       Box 980568

RE: VCU IRB #: HM14197
    Title: Maximal Exercise Response of the TAH (Total Artificial Heart) Patient Compared with LVAD (Left-Ventricular Assist Device) and Chronic Heart Failure Patients

On February 14, 2012 the following research study qualified for exemption according to 45 CFR 46.101(b) Category 4. This determination includes the following items reviewed by this Panel:

RESEARCH APPLICATION/PROPOSAL: NONE

PROTOCOL: Maximal Exercise Response of the TAH (Total Artificial Heart) Patient Compared with LVAD (Left-Ventricular Assist Device) and Chronic Heart Failure Patients, version 1-1/18/12, received 1/30/12

HIPAA PROCESS:
The following pathways for accessing and/or using PHI have been approved:
- De-identified Data

ADDITIONAL DOCUMENTS:
- None

The Primary Reviewer assigned to your research study is Gwendolyn Parker, MS, FNP-C. If you have any questions, please contact Ms. Parker at gwparker@vcu.edu and 828-5090; or you may contact Donna Gross, IRB Coordinator, VCU Office of Research Subjects Protection, at dngross@vcu.edu or 827-2261.

Attachment – Conditions of Approval (PLEASE NOTE RECENT CHANGES TO #3)


Conditions of Approval:

In order to comply with federal regulations, industry standards, and the terms of this approval, the investigator must (as applicable):

1. Conduct the research as described in and required by the Protocol.

2. Provide non-English speaking patients with a translation of the approved Consent Form in the research participant’s first language. The Panel must approve the translation.

3. The following changes to the protocol must be submitted to the IRB panel for review and approval before the changes are instituted. Changes that do not meet these criteria do not have to be submitted to the IRB. If there is a question about whether a change must be sent to the IRB please call the ORSP for clarification.

THESE CHANGES MUST BE SUBMITTED:

   a) Change in principal investigator
   b) Any change that increases the risk to the participant
   c) Addition of children, wards of the state, or prisoner participants
   d) Changes in survey or interview questions (addition or deletion of questions or wording) that change the level of risk or add questions related to sexual activity, abuse, past or present illicit drug use, illegal activities, questions reasonably expected to provoke psychological anxiety, or would make participants vulnerable, or subject them to financial, psychological or medical risk
   e) Changes that change the category of exemption or add additional exemption categories
   f) Changes that add procedures or activities not covered by the exempt category(ies) under which the study was originally determined to be exempt
   g) Changes requiring additional participant identifiers that could impact the exempt category or determination
   h) Change in inclusion dates for retrospective record reviews if the new date is after the original approval date for the exempt study. (ex: The approval date for the study is 9/24/10 and the original inclusion dates were 01/01/08 to 09/24/10. This could be changed to 01/01/06 to 09/24/10 but not to end on 09/25/10 or later.)
   i) Addition of a new recruitment strategy
   j) Increase in the planned compensation to participants

4. Monitor all problems (anticipated and unanticipated) associated with risk to research participants or others.

5. Report Unanticipated Problems (UPs), following the VCU IRB requirements and timelines detailed in VCU IRB WPP.VIII.7.

6. Promptly report and/or respond to all inquiries by the VCU IRB concerning the conduct of the approved research when so requested.

7. The VCU IRBs operate under the regulatory authorities as described within:
   a) U.S. Department of Health and Human Services Title 45 CFR 46, Subparts A, B, C, and D (for all research, regardless of source of funding) and related guidance documents.
   b) U.S. Food and Drug Administration Chapter 1 of Title 21 CFR 50 and 56 (for FDA regulated research only) and related guidance documents.
   c) Commonwealth of Virginia Code of Virginia 32.1 Chapter 5.1 Human Research (for all research).