ASSESSMENT OF EXERCISE CAPACITY IN AN INDIVIDUAL WITH LVAD EXPLANTATION WITHOUT HEART TRANSPLANTATION

A Thesis by

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I have examined the final copy of this thesis for form and content, and recommend that it be accepted in partial fulfillment of the requirement for the degree of Master of Education in Physical Education with a major in Exercise Science.

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ABSTRACT

BACKGROUND: Left Ventricular Assist Device's (LVAD) have become a viable treatment alternative to heart transplantation. While under LVAD support, some have shown significant recovery of native heart function allowing for the removal of the device.

METHODOLOGY: The patient in this study was diagnosed with idiopathic dilated cardiomyopathy and demonstrated worsening heart failure over a five year period with a maximum left ventricular end diastolic diameter of 8.99 cm and an ejection fraction between 20-25%. Upon implantation of a LVAD, the patient's central hemodynamic function returned to near normal and the device was removed. Four months post explantation a cycle ergometry graded exercise peak VO_2 test was performed. Exercise began at 0 Watts and increased 25 Watts per 3 minute stage. 12 lead EKG was used to determine heart function.

RESULTS: The patient showed improvement in peak aerobic capacity when compared to pre LVAD cardiopulmonary stress tests. VO_2 increased from pre LVAD measures of 11.8 ml·kg^{-1}·min^{-1} to 17.0 ml·kg^{-1}·min^{-1}. Time to maximal exertion increased from 5 minutes 27 seconds to 15 minutes.

CONCLUSION: The results from this case study indicate that significant improvements in native heart function is possible with a period of mechanical unloading through LVAD support.

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DEFINITIONS

ACE inhibitor: A serum protease inhibitor that prevents the conversion of angiotensin I to angiotensin II. This class of drug also decreases the deregulation of bradykinin.

Afterload: Pressure against which the left ventricle must eject its volume against during systole.

Angina: Chest pain.

Angiography: Visualization of the heart and arteries via x-ray after the injection of a radioactive medium.

Aortic valve: Heart valve separating the left ventricle from the aorta, preventing the backflow of blood from the aorta into the ventricle.

Apnea: Absence of spontaneous respiration.

Atrophy: Wasting of tissues, organs, or the entire body due to inadequate nourishment.

Baroreceptors: A pressure sensitive nerve ending located in the atrial wall, aortic arch, and carotid sinus.

Beta-blockers: A class of drugs that block neurohormonal activation of the sympathetic nervous system.

Bradycardia: A heart rate of less than 60 beats per minute.

Cachexia: Generalized ill health and malnutrition.

Cannulation: Insertion of a cannula.

Cardiac Output: Amount of blood in liters, expelled by the ventricles per minute. Calculated as a product of stroke volume and heart rate.

Chronotropic Incompetence: Inadequate heart response to increased metabolic demand.

Coronary Artery Disease: Any abnormal condition of the arteries that prevents or reduces the flow of oxygen and nutrients to the myocardium.

Diaphoretic: excessive production of sweat.

Diastole: The relaxation phase of the cardiac cycle.

Distensibility: The ability to become stretched, dilated, or enlarged.

Diuretics: A class of drug that promotes the excretion of urine.

Dyspnea: The sensation of uncomfortable breathing.

Echocardiography: A diagnostic procedure used to determine the structure and motion of the heart.

Edema: Accumulation of fluid in the interstitial spaces of tissues.

Ejection Fraction: Percentage of blood ejected from the ventricle with each contraction compared to the maximum volume of the ventricle.

Embolism: A foreign body that has become lodged in a blood vessel.

Heart Catheterization: The introduction of a catheter into the heart.

Fatigue: A state of exhaustion, loss of strength or endurance.

Heart Failure: Inability of the heart to adequately pump enough blood to meet metabolic demand.

Heart Transplant: Surgical procedure where a heart is removed from a donor and implanted into a recipient.

Hemoptysis: The coughing up of blood from the lungs.

Hyperlipidemia: Elevated level of cholesterol.

Hypertension: Persistent elevation blood pressure over 140/90.

Hypertrophy: An increase in tissue size.

Hypokalemia: Potassium deficiency.

Hypokinesis: Diminished or abnormally slow movement.

Idiopathic Dilated Cardiomyopathy: Ventricular dilation of undetermined cause.

Ischemia: Insufficient supply of oxygenated blood to a tissue or organ.

Left Ventricular Assist Device: A device that assists the left ventricle by mechanically circulating blood flow.

MET: Metabolic equivalent equal to 3.5 ml·kg^{-1}·min^{-1}.

Mitral Valve: A bicuspid valve that prevents the backflow of blood from the left ventricle into the left atrium.

Myocarditis: An inflammation of the myocardial tissues.

Muscular Endurance: The ability to perform work over a period of time.

Muscular Power: The capacity to quickly generate muscular force.

Muscular Strength: The capacity to generate force.

Nausea: A sensation of the urge to vomit.

Orthopnea: A condition where a person must sit up or stand in order to breathe comfortably.

Paroxysmal Nocturnal Cough: A severe attack of coughing at night.

Preload: Maximal end diastolic stretch on the myocardium.

Pulmonary Semilunar Valve: Valve preventing the backflow of blood from the pulmonary artery into the right atrium.

Respiratory Exchange Ratio: A ratio of carbon dioxide produced to oxygen uptake.

Sinoatrial Node: Modified heart tissue that produces the electrical impulse responsible for contraction of the heart chambers.

Stenosis: The narrowing of an opening or passageway.

Stroke Volume: The volume of blood ejected from the ventricle with each contraction.

Systole: The contraction phase of the cardiac cycle.

Tachycardia: A heart rate of over 100 beats per minute.

Tachypnea: An abnormally high respiration rate, usually over 20 breaths per minute.

Thrombus: An accumulation of clotting factors attached to the interior wall of an artery or vessel.

Tricuspid Valve: A valve preventing the backflow of blood from the right ventricle into the right atrium.

LIST OF ABBREVIATIONS

AHA: American Heart Association

ATP: Adenosine Tri-phospate

CHF: Chronic Heart Failure

cm: Centimeter

EF: Ejection fraction

HF: Heart failure

HTx: Heart transplant

kg: Kilogram

LVAD: Left Ventricular Assist Device

LVAS: Left Ventricular Assist System

min: Minute

ml: Milliliter

mm: Millimeter

mmHg: Millimeters of mercury

NYHA: New York Heart Association

Q: Cardiac output

VO$_2$: Symbol for oxygen uptake

CHAPTER 1

INTRODUCTION

Cardiovascular disease is a growing problem in the United States. Over time this condition can lead to heart failure (HF). The American Heart Association (AHA) (2006) reports that there are approximately 5 million Americans diagnosed with HF and an additional 550,000 new cases diagnosed each year. In all, this accounts for more than 12 million hospital visits per year, costing between $10 to $40 billion annually (Rose et al., 2001). Due to an annual mortality of 250,000 and a five year mortality rate of 70% (Jessup, 2001), heart transplantation (HTx) has become the final treatment option for the majority of those living with severe HF (DeRose et al., 1997). In recent years, inclusion criteria have become more lax. This is due to advancements in pharmacological suppression of the immune system, transplant techniques, and organ procurement (Sapirstein et al., 1995). Pre-transplant disease management has also become more effective, leading to decreased early mortality. With a diseased population living longer, and more of those individuals being eligible for HTx, there is an increased demand for donor hearts. However, the number of available hearts suitable for transplantation is severely limited. In 2005 there were approximately 2,125 successful heart transplants performed in the United States, and 2,016 performed in 2006 (AHA, 2007). Due to the combination of better disease management and a lack of available heart donors, more patients are requiring long term mechanical circulatory assistance using left ventricular assist devices (LVAD) (Mettauer et al., 2001).

LVAD's were originally used as a bridge to transplantation. Patients that were eligible candidates for HTx underwent implantation of the device, which allowed for a longer wait period for a donor heart to become available. LVAD use in those awaiting HTx has been shown to improve hemodynamics and organ function while also improving quality of life. The use of these

devices also allows for the patient to return home, thus decreasing overall hospital costs (Rose et al., 2001). Recently LVAD's were approved by the Food and Drug Administration for use as destination therapy, allowing advanced treatment options for those who do not meet the necessary qualifications for HTx (Long et al., 2005).

It has been well established that HF patients have an impaired vasodilatory response, oxygen uptake, endothelial function, and peripheral blood flow (Linke et al. 2001). Recently researchers have shown that exercise training is safe and can improve deficiencies resulting from heat failure (Mettauer et al. 2001). Adaptations resulting from exercise work to increase the amount of oxygen that is delivered to the working tissues, resulting in improved exercise capacity and functional ability (McKelvie et al. 2002). Many of these same physiological improvements and safety results have been reported in studies that used participants with LVAD as well (Jaski et al., 1997 and 1999). Results demonstrated improved aerobic capacity, peripheral blood flow, and exercise tolerance. In addition, there have been some reports of patients undergoing LVAD implantation and then demonstrating reverse remodeling of the heart, where normal heart function returns and the LVAD can be explanted without HTx. However, little is known about the effects of exercise on patients who have undergone LVAD explantation without HTx (Burkhoff et al., 2006). The purpose of this study is to examine the physiological response to exercise for a patient who was supported with LVAD for 9 months, demonstrated a return to normal heart function and had the LVAD removed.

CHAPTER 2

LITERATURE REVIEW

2.1 Normal Heart Function

Before understanding HF and the processes that lead to the need for a LVAD, it is necessary to understand normal heart function. During normal heart function, the four chambers of the heart demonstrate periods of contraction (systole) and relaxation (diastole). This series of contraction and relaxation phases is the cardiac cycle, and is defined as the period of time from the beginning of the systolic phase of one heartbeat to the initiation of the systolic phase of the next heartbeat (McKinley and O'Loughlin, 2006). Atrial systole marks the beginning of the cardiac cycle. Initiated by the sinoatrial node, this is a simultaneous contraction of both the right and left atria in which blood is pushed out of the atria and into the ventricles. This phase accounts for the final 30% of ventricular filling (McKinley and O'Loughlin, 2006). Once atrial systole is complete, atrial diastole begins. During this phase, deoxygenated blood is delivered to the right atrium via the superior and inferior vena cava, which are responsible for venous return from systemic structures, and the coronary sinus, which is responsible for venous return from coronary arteries, while oxygenated blood is delivered to the left atrium via the pulmonary vein (Malhotra et al., 2003).

Concurrent with the beginning of atrial diastole is ventricular systole. During ventricular systole, the ventricles contract and pressure increases, forcing the tricuspid and mitral valves to close. This prevents blood from regurgitating into the atrial chambers. Once ventricular pressure has surpassed that of the pulmonary artery on the right side of the heart and the aorta on the left side, the pulmonary semilunar valve and aortic valve open, allowing the flow of blood to exit the heart and continue into the vasculature. When ventricular systole has concluded and diastole

begins, pressure within the ventricles begins to fall. Once ventricular pressure falls below the pressure within the aorta and pulmonary artery, the aortic valve and pulmonary semilunar valves close, preventing the backflow of blood into the ventricles. As ventricular pressure falls below that of the atria, the tricuspid and mitral valves open, allowing for the passive flow of blood into the ventricles, which accounts for the initial 70% of ventricular filling. Passive flow continues until atrial systole begins again and the cardiac cycle repeats (McKinley and O'Loughlin, 2006).

During diastole the ventricles fill to approximately 110-120 ml. This volume is the end diastolic volume (Guyton, 1991). The amount of blood that is ejected from the ventricles during systole is the stroke volume and ranges from 70-75 ml. The remaining blood in the ventricle at the end of systole is the end systolic volume and is normally 40-50 ml (Guyton, 1991). Stroke volume is determined by subtracting end systolic volume from end diastolic volume. Stroke volume is used to determine the overall ejection fraction as well as cardiac output (Q) (Malhotra et al., 2003). Ejection fraction is the percentage of end diastolic volume ejected from the ventricles during systole. Values typically fall within a range of 55-75%. Cardiac output is the volume of blood ejected from the heart per minute and is the product of stroke volume and heart rate (Malhotra et al., 2003). This is dependent upon the activation of the sympathetic nervous system, specifically the vagus nerve, which innervates the heart. While at rest, cardiac output is approximately 5.25 liters per minute (McKinley and O'Loughlin, 2006), however, with increased physical activity this value can increase considerably depending upon exercise intensity (Squires, 1998).

2.1.1 The Frank-Starling Mechanism

The volume of blood ejected from or remaining in the ventricles following each contraction is regulated by a principle referred to as the Frank-Starling mechanism. When a large

volume of blood enters the ventricles (i.e., increased venous return), the myocytes are put under a greater stretch than previously. This causes a greater contraction with increased force due to increased actin-myosin overlapping. The increased contractile force automatically ejects the increased volume of blood, noted as increased stroke volume (Guyton, 1991).

In individuals that have HF, the Frank-Starling mechanism is the first compensatory mechanism that attempts to maintain a balance between stroke volume, cardiac output, and ejection fraction as well as end diastolic and end systolic pressures. Impaired ventricular function leads to a decreased stroke volume at a given preload when compared to normal, which causes diminished ejection fraction. With a greater volume of blood remaining in the ventricle during diastolic filling, the muscle fibers of the heart stretch beyond that which they normally would. The increased stretch on the myofibers invokes the Frank-Starling mechanism, which will cause them to contract with greater force during the next contraction. The increased contractile force of the heart causes an increase in stroke volume which empties the ventricle and increases cardiac output (Dyer and Fifer, 2003). This mechanism is able to maintain cardiac output for awhile, however as vascular volume increases via neurohormonal adaptations and the ventricular wall becomes more stiff and less compliant (Schlant et al., 1998), the ventricle becomes ineffective at filling and ejecting blood.

2.2 Pathophysiology of Heart Failure

HF is a complex and complicated syndrome that is difficult to define. This is due to a lack of standardized criteria, varying terminology and underlying causes of the disease (Clegg et al., 2005). It is a disease that can result from any condition that decreases the ability of the heart to adequately pump blood and can present as an acute or chronic condition. HF is defined as the inability or a decline in the ability of the heart to adequately pump blood at a rate that meets the

body's metabolic demand at normal filling pressures (Clegg et al., 2005). Acute HF can result from sudden and severe damage to the myocytes of the heart attenuating the ability to fully contract, causing reduced pumping ability. Acute HF can be characterized when the patient demonstrates severe difficulty breathing, tachycardia, and edema, especially in the lungs and lower extremities. Chronic HF (CHF) typically results from external demands that exceed the ability of the heart to maintain normal function. CHF demonstrates a more gradual onset. It is characterized by the presence of left ventricular dysfunction as well as physiological changes in the peripheral vasculature such as impaired vasodilation and altered organ function such as renal insufficiency causing sodium and water retention (Clegg et al., 2005, Dyer and Fifer, 2003, Schlant et al, 1998). Regardless of the length of onset, those with HF present decreased cardiac output and peripheral vascular resistance (Schlant et al., 1998).

Historically, HF was identified as forward failure or backward failure. Forward failure is described as the inability of the heart to pump blood forward throughout the vasculature at a rate that adequately perfuses the tissues of the body, and can result form aortic stenosis or myocarditis secondary to a large myocardial infarction (Schlant et al., 1998). Backward failure is the ability of the heart to pump enough blood to adequately perfuse the tissues only if filling pressures are abnormally high (Dyer and Fifer, 2003).

The classification of HF as forward or backward failure has proven to be of little use. This is because forward failure and backward failure coexist (Schlant et al., 1998). If the heart is unable to pump sufficient blood forward, there is an increased end diastolic volume which prevents normal filling upon the subsequent diastole (backward failure). Without normal filling, stroke volume decreases which reduces tissue perfusion (forward failure) (Schlant et al., 1998). A more appropriate and useful distinction is made between systolic and diastolic dysfunction.

Diastolic dysfunction results from impaired ventricular relaxation or from obstructed or impaired ventricular filling. Impaired ventricular relaxation can be due to left ventricular hypertrophy, hypertrophic or restrictive cardiomyopathy, or transient myocardial ischemia, whereas impaired ventricular filling can result from mitral stenosis or pericardial constriction (Dyer and Fifer, 2003). Typically diastolic dysfunction demonstrates a thick walled or hypertrophied ventricle and a normal to small ventricular cavity (Schlant et al., 1998). Approximately 66% of those diagnosed with HF suffer systolic dysfunction. Systolic dysfunction results from an increase in afterload or from impaired contractility. An increase in afterload can be caused by aortic stenosis or from hypertension, whereas impaired contractility results from myocardial infarction, myocardial ischemia, dilated cardiomyopathy, or chronic volume overload resulting from mitral or aortic regurgitation (Dyer and Fifer, 2003). Systolic dysfunction is primarily characterized by an elevated end diastolic volume with a decreased stroke volume which results in a diminished ejection fraction (Schlant et al., 1998).

2.2.1 Left Heart Failure

In the United States, the majority of HF cases result from left ventricular dysfunction and are characterized by a decreased ejection fraction below 40% and a dilated left ventricle (Keteyian, 1997). Most incidents are due to hypertension, coronary artery disease, or idiopathic dilated cardiomyopathy (Clark and Sherman, 1998). As a result of a lower ejection fraction and decreased efficiency of the left ventricle, cardiac output also decreases. These changes in central hemodynamics leads to neurohormonal dysfunction, including alterations in skeletal muscle metabolism, vasomotor tone, and impaired peripheral perfusion (Linke et al., 2001). When this takes place, a number of compensatory measures occur to help stabilize left ventricular function.

These include the Frank-Starling mechanism, myocardial hypertrophy and ventricular remodeling, and alterations in neurohormonal activation.

As stroke volume decreases, by impaired contractility or increased afterload, end diastolic volume increases resulting in an increased preload. The increased preload causes abnormal myocardial fiber length at the end of the diastolic phase. The lengthened muscle fibers result in greater systolic contractility which improves stroke volume (via the Frank-Starling mechanism). With a continually elevated preload, in an effort to restore cardiac output, the ventricles become dilated. Over time, the heart undergoes remodeling of the ventricles causing the myocytes to permanently become longer and thicker (Schlant et al., 1998). This results in increased stiffness of the ventricular wall (Dyer and Fifer, 2003). The elevated pressure within the ventricles during diastole is eventually passed on into the left atria and pulmonary vasculature. Once the capillary pressure exceeds 20 mm Hg, pulmonary congestion occurs secondary to fluid accumulating within the pulmonary interstitium (Dyer and Fifer, 2003). Normally, peripheral capillary pressure is approximately 40 mm Hg (McKinley and O'Loughlin, 2006), however as elevated diastolic pressure progresses through the vasculature into the capillaries the increased pressure causes fluid to back up, resulting in peripheral edema.

Decreased cardiac output initiates a number of neurohormonal adaptations including stimulation of the sympathetic nervous system, suppression of the parasympathetic nervous system, activation of the renin-angiotensin-aldosterone system, and the secretion of antidiuretic hormone (Dyer and Fifer, 2003). Baroreceptors interpret reduced cardiac output as decreased perfusion pressure. This deactivates the parasympathetic nervous system while activating the sympathetic system via the release of norepinephrine. Norepinephrine causes increased heart rate and greater ventricular contractility, which directly affects cardiac output (Radaelli et al., 1996).

The release of renin acts upon angiotensinogen which is produced by the liver to form angiotensin I (Keteyian, 1997). This is then converted to angiotensin II which initiates vasoconstriction, resulting in increased stroke volume as well as blood volume (Schlant et al., 1998). The activation of baroreceptors along with increased levels of angiotensin II initiates the release of antidiuretic hormone. Antidiuretic hormone assists in increasing intravascular volume via water retention (Dyer and Fifer, 2003). While these mechanisms are intended to increase and maintain cardiac output, consequently they also increase vascular resistance, placing greater load on the heart (Keteyian, 1997).

Vascular tone is also influenced by endothelial dysfunction. Endothelial cells regulate vasodilation through the release of nitric oxide, which is mediated by acetylcholine, L-arginine, and the stimulus of sheer stress (Linke et al., 2001). However, in an effort to maintain cardiac output, activation of the sympathetic nervous system and the renin-angiotensin system causes vasoconstriction, thus reducing vasodilatory capacity (Hornig et al., 1996). Prolonged vasoconstriction damages the vascular endothelium resulting in a delayed response to acetylcholine (Link et al., 2001) which affects the ability to release nitric oxide, therefore inhibiting vasodilation. Inadequate dilation has been shown to impede blood flow in large vessels as well as reducing peripheral perfusion (Hornig et al., 1996).

2.2.2 Right Heart Failure

The right ventricle accepts blood from the right atrium within a range of low pressures and ejects blood into the pulmonary artery against low vascular resistance (Dyer and Fifer, 2003). Due to the low pressures and decreased resistance that the right ventricle works against, the chamber walls are much thinner and are less durable than that of the left ventricle. This also allows the right ventricle to be very compliant, accepting and ejecting volumes of blood that may

vary widely. Although able to function within a wide range of acceptable pressures and volumes, the right ventricle is very susceptible to failure (Dyer and Fifer, 2003).

Right side heart failure typically results from left side failure (Schlant et al., 1998). This is due to excessive afterload caused by increased pressure within the pulmonary vasculature secondary to left ventricular dysfunction. As the ventricle fails, increased diastolic pressures are transmitted to the right atrium through the tricuspid valve (Dyer and Fifer, 2003). The increased diastolic volume in the right atrium results in decreased filling volume causing increased congestion within the peripheral vasculature. This causes an increase in peripheral pressures and can result in edema. Decreased compliance of the right ventricle also affects the left ventricle (Schlant et al., 1998). As pressure within the right ventricle increases, the interventricular septum can become displaced (Baker et al., 1984). At high pressures, this can cause altered geometry and distensibility of the left ventricle, resulting in greater left ventricular dysfunction (Weber et al., 1981). Further, left ventricular dysfunction results from a reduction in blood output from the right ventricle. This results in decreased left ventricular preload, which can cause the stroke volume to decrease (Dyer and Fifer, 2003).

2.3 Signs and Symptoms

The signs and symptoms of HF are vast, however many of those suffering from the disease remain asymptomatic for an extended period of time (Dyer and Fifer, 2003). This is because impairment during the early phases of HF is minimal due to mechanical, neurohormonal, and structural adaptations such as altered contractility, vasoconstriction, increased heart rate, and increased vascular volume are compensating for any dysfunction present (Dyer and Fifer, 2003). Most often, clinical signs and symptoms of the disease only present once compensatory mechanisms fail and heart function becomes unbalanced. This

typically results from increased metabolic demand such as illness or infection, increased preload, increased afterload, contractile dysfunction, cessation of medication, as well as excessive bradycardia (Dyer and Fifer, 2003).

The clinical signs and symptoms are dependent upon the severity of the disease as well as the side of the heart that is failing. Common symptoms include bloating, abdominal pain, and nausea, as well as persistent cough and edema (Schlant et al., 1998). More severe patients may demonstrate cachexia and appear to be diaphoretic. Rapid breathing is also a common symptom. Those with end stage HF may also demonstrate a Cheyne-Stokes respiration pattern which is characterized as alternating periods of tachypnea and apnea (Dyer and Fifer, 2003). The hallmark symptoms of HF are fatigue and dyspnea, especially upon exertion (Dziekan et al., 1998, Beniaminovitz et al., 2002). Currently, there is controversy surrounding the cause of dyspnea and fatigue. Conflicting arguments state that these symptoms can manifest due to reduced cardiac output resulting in inadequate perfusion, or due to pulmonary congestion causing an inability of efficient gas exchange secondary to increased interstitial fluid (Schlant et al., 1998). However, more recent evidence suggests that the cause of dyspnea and fatigue are not related to hemodynamics, but to structural and metabolic changes that occur within the skeletal muscle (Karlsdottir, 2002). These changes are similar to those seen in deconditioning (McKelvie, 2002) and include skeletal muscle myopathy which is characterized by slow oxidative fiber atrophy. Other changes include reduced enzyme capacity, and reduced mitochondrial density. These changes result in decreased muscular strength, power and endurance (Pu, 2001).

Impaired central hemodynamic and vascular congestion do cause the manifestation of other primary symptoms of HF though. Increased pulmonary interstitial fluid results in persistent cough, paroxysmal nocturnal cough, and orthopnea, as well as increased exertion during

respiration (Schlant et al., 1998). These symptoms are due to excess pressure placed upon the alveoli, causing greater energy demand of breathing and may cause hemoptysis (Dyer and Fifer, 2003). Edema in the lower extremities occurs due to a similar process observed in pulmonary congestion. Due to increased afterload and increased vascular volume, blood pressure increases within the peripheral vasculature. When capillary pressure exceeds approximately 40 mm Hg, fluid begins to back up and leak into the interstitial spaces of the lower extremities causing swelling (Schlant et al., 1998). These common symptoms of HF generally result from decrease cardiac output and and/or pulmonary and peripheral congestion (Dyer and Fifer, 2003). However, many of these symptoms only present once the patient has been in HF for a period of time long enough for compensatory actions to fail (Schlant et al., 1998).

While skeletal muscle abnormalities may be the primary cause of exercise intolerance as opposed to pulmonary congestion and abnormal central hemodynamics directly, there is an interaction between them. Typically those who suffer from HF are deconditioned. When symptoms resulting from pulmonary congestion, reduced cardiac output, and decreased peripheral tissue perfusion begin to present, sufferers are likely to reduce their level of physical activity even more. This leads to further deconditioning and reduced ability to perform work.

2.4 Diagnosis and Classification

HF is an increasing cause of death and disability in the United States (Keteyian et al., 1997). Unfortunately, HF is difficult to diagnose and estimates are that the prevalence of the disease will continue to increase in the United States. This is attributed to improved survival rates of those with the underlying causes of HF, increasing average lifespan, and improved pharmacological therapies (Pu et al., 2001). The difficulty in diagnosing HF is due to the non-specific nature of symptoms (Davis et al., 2002). In the past, HF was described according to the

features, compensatory mechanisms, and symptoms that present with each individual case. These include acute or chronic, systolic or diastolic, congestive or non-congestive, or any combination of the above (Clegg, et al., 2005). Due to the wide variation in disease characteristics, a number of systems have been devised to classify the diagnosis based on symptom severity and patient quality of life (Clegg et al., 2005).

Diagnosis can be made through various means. Diagnostic tests include the presence of classic signs and symptoms such as fatigue, dyspnea, and edema in the lower extremities, direct measurement and indirect estimation of VO_2, heart catheterization with angiography, and echocardiography (Ross, 1998). Direct measurement of VO_2 requires the use of an incremental treadmill or cycle ergometry graded exercise test and the ability to measure peak oxygen consumption. This method is used regularly because it allows for the determination of disease severity, thus identifying which patients are in need of aggressive treatment (Keteyian, 2003). Tests are conducted at steady state and typically use protocols such as Bruce, Modified Bruce, Naughton and Modified Naughton (Keteyian, 1997).

Indirect estimation of VO_2 can be determined by the workload that the patient performed, expressed in METS. This method gives an evaluation of overall work capacity and implication of symptoms, however it does not allow for a determination of cardiac or hemodynamic abnormalities (Ross, 1998). Heart catheterization with angiography is an effective tool for the diagnosis of HF, however this is an expensive and invasive technique that should only be performed when exact diagnostic measures are necessary and other non-invasive methods are contraindicated. The most effective method for the diagnosis of HF is echocardiography. This method makes use of ultrasound to view the heart and measure ejection fraction. While this method gives accurate measures of cardiac function, it does not give information regarding

symptom severity and tolerance to physical activity (Keteyian, 2003). The appropriateness of which techniques to use depends on the patient's symptoms and underlying pathophysiological cause of disease. Ultimately, a person is considered to have HF if their ejection fraction is below 40% (Keteyian, 2003). While these techniques are sufficient to diagnose HF, to determine the extent of disease and the effects that the disease has had on both the cardiac and peripheral tissues, preload, afterload, and end diastolic pressures must be determined at rest as well as during exercise (Ross, 1998). The values collected from diagnostic tests determine the patient's disease classification.

The most common classification system is the New York Heart Association (NYHA) Classification of Heart Failure. This system is comprised of four stages with I being the least severe, to IV being the most severe and considered end stage HF (Clegg et al., 2005). NYHA Stage I HF is characterized by the presence of disease without the manifestation of symptoms. These patients are able to perform all activities of daily living without limitation or resulting fatigue, dyspnea, nausea, or angina. A patient diagnosed with NYHA Stage II HF suffers from some limitations of physical activity. These patients are typically comfortable at rest and with low levels of physical activities. However, symptoms of fatigue, dyspnea, or angina do present upon ordinary levels of activity. Those described as being NYHA Stage III HF demonstrate noticeable limitations with increased physical activity. These patients are comfortable at rest but are not able to perform any physical activities without symptoms such as fatigue, dyspnea, or angina. The final classification of HF by the NYHA is Stage IV HF. These patients are the most severe and are considered to be in end stage HF. They are unable to perform any form of physical activity without extreme discomfort and many demonstrate symptoms of fatigue, dyspnea, nausea, angina, and severe cardiac insufficiency. So long as those in this group do not

have any lifestyle, disease, or other co-morbidities that would prevent candidacy, these patients are candidates for HTx, bridge to transplantation LVAD, or destination LVAD therapy.

The American Heart Association Task Force on Practice Guidelines has also developed a classification system for HF. This is a four stage system, A through D, which is to be used in conjunction with the NYHA classification system. Those in AHA class A are at risk for developing HF. Patients do not yet demonstrate any cardiac dysfunction but do suffer from cardiovascular disease that predisposes HF such as hypertension, coronary artery disease, and/or family history of any cardiomyopathy. AHA class B is characterized by the manifestation of structural dysfunction secondary to heart disease. However these patients do not demonstrate any symptoms characteristic of HF. AHA class C is for those who have a current diagnosis of HF, or who have previously been diagnosed with HF. These patients demonstrate structural dysfunction of the heart characterized by symptoms of fatigue and dyspnea. Finally, AHA class D patients demonstrate obvious signs and symptoms of HF. Similar to those with a NYHA stage IV classification, these patients are considered to be in end stage HF and require interventions such as HTx or mechanical circulatory support (Hunt et al., 2002). The severity of disease will ultimately determine the treatment course.

One of the primary methods for determining the severity of HF is direct measurement of peak ventilatory oxygen uptake (VO_2 peak). VO_2 peak is the maximum amount of oxygen that is able to be extracted from inspired air during a bout of exercise. This value represents the functional limits of ones cardiovascular, metabolic, and respiratory systems and is measured in $ml·kg^{-1}·min^{-1}$ (Bonzheim and Skelding, 2003). This method is used because of the marked reduction in aerobic capacity secondary to compensatory measures and the resulting symptoms that occur in those with HF. The more symptomatic a patient is the lower aerobic capacity will

generally be (Liang et al., 1992). However, NYHA classification poorly predicts exercise capacity (Smith et al., 1993). Smith and associates (1993) showed that VO_2 varied widely when compared to NYHA classification. Of those studied with a VO_2 below 10 ml·kg-1·min-1, 27% were classified as stage II HF and 72% as stage III-IV. Of those with a VO_2 between 10 and less than 15 ml·kg-1·min-1, 4% were classified as stage I, 54% were classified as stage II, and the remaining 42% stage III-IV. For those with 15 ml·kg-1·min-1 or greater, 11% were stage I, 56% stage II, and 34% stage III-IV (Smith et al., 1993). Another problem with the NYHA classification system is that it is not a quantitative index of HF severity. The assessment of presenting symptoms is subjective and can vary from patient to patient and clinician to clinician. This in turn, can lead to patients being placed in a class inappropriate for the actual severity of HF (Keteyian, 2003).

Due to the disparity between VO_2 and NYHA classification and its subjective nature, Weber and colleagues (1988) devised a classification system that considers stroke volume and cardiac output, which may be more applicable for describing the severity of disease. They found that during maximal exercise, increases in stroke volume and cardiac output were closely related to VO_2 (Weber et al., 1988). This allowed for a patient to be classified based on presenting symptoms as well as an accurate determination of VO_2. Because VO_2 is a direct and quantifiable measurement, use of the Weber classification system can reduce variability in patient placement seen within the NYHA system (Squires, 1998).

The Weber classification index consists of four classes ranging from A to D where patients are placed according to impairment and VO_2. Class A consists of those who have a VO_2 above 20 ml·kg^{-1}·min^{-1}and demonstrate little or no physical impairment. Class B consists of those with a VO_2 ranging from 16-20 ml·kg^{-1}·min^{-1}and show mild to moderate impairment. Class C

guidelines include moderate to severe physical impairment with a VO_2 ranging from 10-16 ml·kg^{-1}·min^{-1}, while class D is severe impairment and a VO_2 below 10 ml·kg^{-1}·min^{-1} (Squires, 1998).

2.5 Treatment

HF is a disease resulting from any condition causing decreased ability of the heart to pump blood. Due to the complex and complicated nature of the syndrome, disease management is complex and complicated as well. Disease management and treatment is further complicated by the lack of symptoms early in the disease state (LeJemtel et al., 1998). Treatment includes identifying and treating the underlying cause of HF, treating the compensatory mechanism responsible for presenting symptoms, correction of neurohormonal changes, and management of the current symptoms including pulmonary, vascular, and cardiac (Dyer and Fifer, 2003). This is accomplished through a number of therapies including pharmacological, lifestyle changes, and exercise.

One of the primary symptoms of HF is edema. This can occur in the lower extremities as well as in the lungs. Both peripheral and pulmonary edema result from increased vascular volume (Schlant et al., 1998). To reduce edema, patients are urged to limit sodium and fluid intake, as well as to modify their diet and reduce body weight. However this can be difficult because many of those suffering from HF, especially severe HF, also suffer from malnutrition (Ankers et al., 1997). When unable to control peripheral and pulmonary edema through other means, pharmacologic therapy is indicated. Diuretics are prescribed to decrease the amount sodium and water through renal excretion. This reduces vascular volume by preventing the buildup of fluid within the pulmonary extra cellular matrix thus relieving congestion. Decreased vascular volume also reduces hypertension which decreases preload and afterload within the

heart muscle itself (Ndumele et al., 2003). The most common types of diuretics prescribed are grouped by the part of the kidney affected by the drug and include thiazides, loop diuretics, and potassium-sparing diuretics.

Vasodilators are commonly prescribed to HF patients. The most widely used vasodilators for the treatment of HF are angiotensin-converting enzyme (ACE) inhibitors (Dyer and Fifer, 2003). This class of drug works on neurohormonal changes associated with the renin-angiotensin system. The conversion of angiotensin I to angiotensin II causes vasoconstriction and ACE inhibitors work by preventing this conversion (Love and McMurray et al., 1996). The primary effects of ACE inhibitors in HF include decreased afterload via decreased vascular resistance, decreased preload, and increased cardiac output. These changes can also help to prevent the progression of ventricular remodeling that typically occurs secondary to abnormal central hemodynamics (Keteyian, 1997; Cohn, 1992). Blocking the conversion of angiotensin I to angiotensin II also prevents the metabolism of bradykinin, which is a naturally occurring vasodilator (Ndumele et al., 2003).

Other common vasodilators include those that affect the venous and/or arteriole systems. Vasodilators that only dilate the venous circulatory system are nitrates. These drugs increase venous capacity while decreasing venous return to the heart, which results in decreased preload (Dyer and Fifer, 2003). Due to reduced preload, diastolic ventricular pressure decreases and pulmonary congestion improves. Despite these improvements, some patients cannot take nitrates due to an undesirable drop in cardiac output (LeJemtel et al., 1998). Arteriolar vasodilators work to dilate the arteries. Arteriolar vasodilation reduces vascular resistance which decreases afterload resulting in improved Frank-Starling response and increased stroke volume. Due to

decreased vascular resistance and increased stroke volume, cardiac output also increases in an effort maintain blood pressure (Ndumele et al., 2003).

Inotropic drugs are prescribed to increase the contractile force of the myocardium. This is accomplished by increasing the amount of calcium available to produce contractility. As a result the Frank-Starling mechanism is modified which increases stroke volume and cardiac output (Dyer and Fifer, 2003). The most common inotropic drug is digitalis. As well as increasing stroke volume and cardiac output, digitalis also improves ejection fraction, reduces ventricular hypertrophy, and increases the sensitivity of baroreceptors. By increasing baroreceptor sensitivity, the sympathetic response to increased pressure is reduced which decreases afterload. Digitalis can also be prescribed to reverse chronotropic incompetence by regulating the refractory period of the atrioventricular node (Ndumele et al., 2003). A side effect of this drug is that the sympathetic nervous system may not be adequately stimulated with increased physical activity, which is due to decreased ability to detect and respond to vasodilation causing a sudden drop in blood pressure (Sullivan et al., 1989).

When inotropic drugs are contraindicated, beta-blockers are prescribed. These drugs are known for their negative inotropic effects. Previously, beta-blockers were contraindicated for use in HF however, more recent studies have shown that patients have long term benefits that result from the ability of the drugs to reduce neurohormonal activation. Benefits include improved mortality, improved hemodynamics, and decreased deterioration of the left ventricle (Foody et al., 2002). This is accomplished by decreasing heart rate, conduction velocity through the myocardium, contractility, and reducing hypertension (Ndumele et al., 2003; Bell, 2003).

Non-pharmacological therapies for HF include lifestyle modification and exercise, and in severe cases surgery such as HTx and/or LVAD implantation. Lifestyle modifications include

diet, smoking cessation, and elimination of caffeine. Dietary changes that should occur include decreased sodium consumption, typically less than 3 grams per day for most HF patients and less than 2 grams per day for those with severe pulmonary congestion or peripheral edema (Karon, 1995). Sodium restriction can also postpone the need for diuretic medications (LeJemtel et al., 1998). Alcohol should also be avoided, especially for those on inotropic medications. This is because alcohol has negative inotropic effects, which could cause a negative interaction with the drug. Most patients suffering from HF are also overweight. This should be corrected with a low fat and low cholesterol diet that promotes weight loss. A reduction in adiposity decreases the amount of tissue requiring perfusion, therefore reducing metabolic demand, which can decrease the stress on the heart.

Smoking should be discouraged for all, healthy and diseased, due to its vast negative effects on health. HF patients in particular should not smoke because smoking decreases the amount of oxygen that is able to attach to hemoglobin. Nicotine also causes vasoconstriction which can exacerbate HF symptoms (Soler-Soler and Permanyer-Miralda, 1994). Patients who smoke or have a recent history of smoking are often ineligible for sometimes necessary HTx surgery.

2.5.1 Heart Failure and Exercise

Decreased work capacity with increased dyspnea and fatigue are major causes of mortality in HF patients, especially in those who limit physical activity in an effort to avoid these symptoms (Piepoli et al., 1996). Historically, exercise was contraindicated for this population (Clark and Sherman, 1998). This is because the physiological changes that occur within the cardiovascular, respiratory, muscular, and nervous systems, which are the primary factors limiting exercise (McKelvie et al., 2002), were thought to be exacerbated with physical activity

(Delagardelle et al., 1998). It is now believed that excessive bed rest increases disability and that a proper exercise prescription is not only safe, but is also effective at improving survival and quality of life (Pu et al., 2001, Kavanagh et al., 1996) as well as the patient's overall prognosis (Delagardelle et al., 1998).

When compared to normal subjects, HF patients demonstrate 45% lower peak power output, approximately 40% lower cardiac output and VO2, approximately 50% lower stroke volume, and approximately 20% lower heart rate. During sub-maximal exercise, HF patients demonstrate higher heart rate, decreased stroke volume, delayed increase in cardiac output, as well as greater oxygen extraction from circulating blood when compared to those without HF (Keteyian et al., 1997). Evidence suggests that HF patients also demonstrate decreased skeletal muscle function and abnormalities within the skeletal muscle (Katz, 1997). Abnormalities include atrophy and loss of type I fibers, decreased oxidative enzyme capacity, premature activation of glycolysis, decreased perfusion, and decreased vasodilation. Evidence also suggests that immune activation within the muscle may also be involved in decreased exercise tolerance (Adamopoulos, 2002). These changes in skeletal muscle histology, metabolism, and vasodilatory response result in decreased muscular power, endurance, strength, and exercise tolerance (Pu et al., 2001).

The lack of vasodilation within the muscles in response to increased activity results from endothelial dysfunction (Hambrecht et al. 1998). An inability to dilate leads to increased vascular resistance which limits peripheral perfusion. Insufficient oxygen delivery to the metabolizing tissues causes a shift from oxidative phosphorylation to glycolytic metabolism and acidosis, which in turn causes a diminished ability to perform work for a sustained period of time

(Beniaminovitz et al. 2002). Only 30-40% of patients cease physical activity due to dyspnea, the remaining stop due to leg secondary to decreased circulation resulting in inadequate tissue perfusion (Keteyian et al., 1997).

Exercise has been shown to reverse the effects of endothelial dysfunction, which in turn improves vasodilation which then decreases systemic vascular resistance (Katz et al., 1997). Improved peripheral hemodynamics allows for increased blood flow as well as increased blood flow velocity to the metabolizing muscles. This allows more oxygen to the working muscles preventing a premature shift to glycolysis for ATP production (Beniaminovitz et al. 2002). Studies have shown that other important improvements occur with physical activity as well, however improvements attributed to increased physical activity in this population are mostly peripheral in nature and do not include central hemodynamics (Kostis et al., 1994). Some of the improvements noted include decreased heart rate variability, improved minute ventilation and peak ventilation, improved peripheral hemodynamics (Keteyian et al., 1997), and increased time to maximal exertion (McKelvie et al., 2002). It has also been shown that exercise for patients in NYHA class II and class III is safe and results in improved time to maximal exertion, anaerobic threshold, as well as improved quality of life (Wielenga et al., 1999). Hambrecht and colleagues (Hambrecht et al., 2000) reported that aerobic exercise training significantly improves central hemodynamics. They showed that six months of strenuous cycle ergometry of 20 minutes or more per day increased maximum ventilation as well as improved time to maximal exertion and exercise capacity. Subjects showed decreased resting heart rate and increased stroke volume while at rest. The researchers also noted that improved resting stroke volume correlated well with increased cardiac output during exercise (Hambrecht et al., 2000).

Early studies in HF were limited to aerobic exercise as it was thought that the isometric component of resistance training would result in cardiac pressure overload causing a significant decrease in stroke volume, ejection fraction, and cardiac output (Selig et al., 2004). However, a number of recent studies have demonstrated that resistance training is safe improves peripheral muscle function resulting in greater improvements in functional capacity (Selig et al., 2004, Keteyian, 2001, Dubach et al., 2001, Pollock et al., 2000). While no significant changes in resting heart rate, blood pressure, and respiratory exchange ratio were noted, combined aerobic and resistance exercise does improve VO_2, increase the duration of exercise, and improve vasodilation (Maiorana et al., 2000, Delagardelle et al., 1999). Further studies have shown that strength training alone significantly improves submaximal walking distance (Ades et al., 1996). Other improvements that have been noted include decreased sympathetic activation, increased muscular power and endurance, and improved peripheral circulation (Selig et al., 2004).

2.5.2 Left Ventricular Assist Devices

The standard treatment regimen for those with class I through class III HF includes pharmacological therapy, lifestyle modification, diet, and exercise. For those with severe HF, or end stage HF, more aggressive treatment methods are necessary. Previously the only treatment that provides substantial benefit is HTx. However the number of suitable hearts available for transplantation is severely limited, estimated at fewer than 3000 donor hearts worldwide (Rose, et al., 2001). This is further complicated by an increasing number of diseased individuals who meet transplant criteria and are eligible for HTx. Due to the disparity between those eligible for donor hearts and the number of available organs, transplant waiting lists and waiting times have become longer (Kasirajan, 2000). Those suffering from end stage HF have little chance of receiving a donor heart with a one year mortality rate of over fifty percent. Given that the need

for treatment is so great, the left ventricular assist device (LVAD) has become a widely available and viable alternative for both bridge to HTx as well as destination therapy (Milano et al., 2006).

A number of different LVAD models exist and these are divided into two groups according to type of flow, pulsatile or axial flow (i.e., constant flow). First generation LVAD's, which were developed in the early 1990's, are the most widely used. Pumps in these systems draw blood in from the ventricle and then eject it into either the aorta or arterial system via an electrically or pneumatically driven mechanism. The pumps method of ejecting blood imitates that of the native heart while the ventricle is unloaded (Clegg et al., 2005). Axial LVAD's provide circulatory support through non-pulsatile continuous means. However, Bourque and colleagues (2006) have demonstrated that they can operate in a pulsatile fashion. These devices are much smaller than pulsatile versions and, excluding battery packs, are fully implantable. They operate via a rotor and impeller blades that are driven by an electromagnetic mechanism. The impeller blades are the only moving parts in these systems, eliminating the need for directional valves, which in turn eliminates the need for anticoagulation medication and heparin (Clegg et al., 2005).

Implantable LVAD's are attached to the native heart at the apex of the left ventricle and inserted into the apex of the ascending aorta (Shinn, 2005). During surgery the apex of the ventricle is cannulated, allowing for the drainage of blood into the device. A battery usually worn on a holster and carried by the patient, powers the artificial pump located outside the heart which draws blood in and pumps it through an outflow graft anastomosed directly into the aorta (Figure 2.5.2). During support, the native ventricle contracts normally, but little to no blood passes through the aortic valve (Humphrey, 1997). The use of mechanical circulatory support has been shown to improve both central and peripheral hemodynamics by unloading the heart, which

decreases the amount of work that it must perform (Goldstein et al., 1998). Indications for LVAD implantation include those who are candidates for HTx but have developed acute disease (Helman et al., 1999). Hemodynamic indications include a cardiac output of less than 2 L • min^{-1} and a capillary wedge pressure greater than 20 mmHg (Kasirajan, 2000).

Improvements seen in patients after LVAD implantation include improved hemodynamics, decreased diameter of the left ventricle at end diastole, decreased levels of b-type natriuretic peptide, decreased collagen within the extracellular matrix, as well as decreased myocyte size (Nishimura et al., 1999, Xydas et al., 2006, Kasirajan et al., 2000). Improved hemodynamics are observed secondary to decreased vascular resistance resulting from decreased vasoconstriction (Nishimura et al., 1999), which in turn improves tissue perfusion (Sezai et al., 1999). Increased perfusion allows patients to increase their levels of physical activity, which contributes to an improved quality of life. A decrease in collagen deposits within the cardiac extra cellular matrix combined with decreased myocyte size result in decreased diameter of the left ventricle. This allows the heart to function more normally, improving central hemodynamics (Xydas et al., 2006, Bruggink et al., 2006). James and colleagues (2005) showed that neurohormonal activation also decreases with LVAD. This is due to decreased peripheral resistance and improved central hemodynamics, resulting in decreased sympathetic stimulation. Kidney and liver function, as well as other organ function, has also been shown to improve or return to normal (Kasirajan et al., 2000). In rare cases, the unloaded ventricle may recover from HF through the process of reverse remodeling (Kasirajan et al., 2000).

Despite the benefits of LVAD implantation for those with severe HF, it involves major surgery and many other risks. A primary risk is infection (Chinn et al., 2005). The REMATCH trial reported a mortality rate of 41% in the LVAD group which was directly attributed to
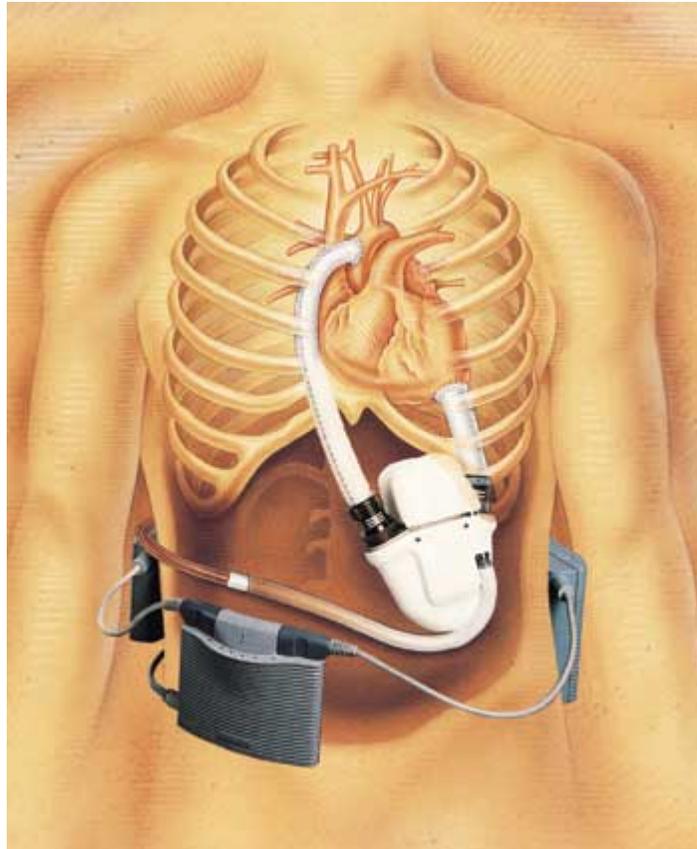
infection (Rose et al., 2001). Other risks include excessive bleeding secondary to anticoagulant medications and liver dysfunction (Salzberg et al., 2003). This occurs in 20-40% of LVAD recipients (Kasirajan et al., 2000). Due to the presence of an artificial device in the body and decreased anticoagulation medications, LVAD patients risk the formation of a thrombus which could lead to an embolism. Other risks include device failure such as mechanical and electrical problems, valve insufficiency, and air entering the blood stream through the inflow graft (McCarthy et al., 1998).

2.6 Reverse Remodeling with LVAD

The effects of HF and disease-associated compensatory mechanisms were believed to cause severe irreversible damage to the myocardium (Burkhoff et al., 2006). However new research is showing that mechanical circulatory support can reverse the remodeling undergone by the heart (Burkhoff et al., 2006). Reverse remodeling is characterized by decreased left ventricular size and mass secondary to a restored collagen network resulting from a decrease in the volume of the extracellular matrix, and decreased size of cardiac myocytes (Bruggink et al., 2006, Heerdt et al., 2006, Akgul et al., 2005). This leads to improved pumping function, pressure loads, and volume within the heart (Heerdt et al., 2006). Decrease in cardiac hypertrophy and myocyte size also lead to improved contractility and inotropic response (Brukner et al., 2004). The exact mechanisms that allow for reverse remodeling to occur are still unknown and under investigation. Current research indicates that mast cell populations (Akgul et al., 2006) calcium cycling and SERCA2a upregulation, as well as age, sex, and pharmacological therapy may play an important roll (Heerdt et al., 2006). However, little is known regarding how

FIGURE 2.5.2

PICTURE OF NOVACOR® LEFT VENTRICULAR ASSIST SYSTEM

Notes: Picture obtained 4-25-2007 from

http://journals.iranscience.net:800/www.memagazine.org/www.m
emagazine.org/contents/current/features/telltale/telltale.ht
ml

these changes reverse neurohormonal, structural, and hemodynamic dearrangements. What is known is that in those who undergo extensive recovery with a LVAD, explantation without HTx is possible (Entwistle III, 2003).

2.7 Exercise with a Left Ventricular Assist Device

Implantation of LVAD's has been shown to improve central and peripheral hemodynamics, secondary organ dysfunction, and neurohormonal activation, all of which improve functional capacity and quality of life (Kasirajan et al., 2000, Xydas et al., 2006, and Bruggink et al., 2006). Although the operating parameters of the LVAD may limit oxygen consumption and therefore limit activity (Humphrey, 1997), Jaski and colleagues (1997) showed that exercise with a LVAD is safe and improvements to be adequate for activities of daily living and comparable to values seen in those who undergo HTx.

Jaski and colleagues (1997) used in *vivo* methods to measure hemodynamics and Doppler echocardiography to determine cardiac function. Patients participating in treadmill walking demonstrated increased heart rate and LVAD flow rate as well as increased VO_2 up to 14.1 ± 2.9 $ml \cdot kg^{-1} \cdot min^{-1}$ and an improved respiratory exchange ratio. However, there was no significant increase in blood pressure or LVAD stroke volume (Jaski et al., 1997). Further study by Jaski comparing response to exercise with LVAD to the response to exercise with HTx showed that patients with LVAD have lower peak VO_2 and lower time to maximal exertion when compared to HTx patients during the first 1-3 months following implantation (Jaski et al., 1999). However, these finding could be attributed to an inability of the LVAD to increase output in response to increased metabolic demand. Similar results to exercise in LVAD patients were reported by de Jonge and colleagues (2001), who showed comparable VO_2 values in LVAD and HTx patients.

Research data are limited regarding the effects of exercise with LVAD support and bridging to recovery through reverse remodeling. A limited number of studies have investigated the response to exercise in patients currently under LVAD support however, the number of subjects in these studies are limited (Perme et al., 2006; Humphrey 1997; Mettauer et al., 2001; Arena, Humphrey, and McCall, 1999; Foray et al., 1996; Nishimura et al., 1996; Jaski et al., 1997 and 1999; de Jong et al., 2001). Data regarding bridging to recovery through reverse remodeling is even more limited. Due to a small number of LVAD patients who recover sufficient cardiac function to undergo LVAD explantation, the concept of bridging to recovery is quite new.

CHAPTER 3

METHODOLOGY

3.1 Significant Medical History

The patient is a 47 year old white male. His significant cardiac history begins in June 2002 when he was diagnosed with idiopathic dilated cardiomyopathy, NYHA functional class IV, and had previously been hospitalized with decompensated HF. The patient also suffered from a previous diagnosis of ventricular tachycardia resulting in the implantation of an Automatic Implantable Cardioverter-Defibrillator placement with a single ventricular lead. Evaluation on September 15, 2005 revealed severe left ventricle dilation and reduced ejection fraction. Further diagnosis included morbid obesity with a body mass index (BMI) of 35.7, sleep apnea, chronic renal insufficiency due to reduced cardiac output, hypertension, hyperlipidemia, and delayed interventricular conduction. The patient was treated with optimum pharmacotherapy and underwent multiple cardio-pulmonary stress tests and cardiac catheterization. All tests documented worsening HF leading up to candidacy for LVAD implantation and are described further in Chapter 4.

The patient underwent implantation of a Novacor® Left Ventricular Assist System on January 12, 2006 (Figure 2.5.2). This device consists of a pump/drive unit and its percutaneous lead, the inflow and outflow conduits, and two valve conduits, all of which are implanted. External components include the system controller and rechargeable batteries or an external monitor plugged into the wall. The patient was under mechanical circulatory support for 9 months with documented improvement in heart function via echocardiography. The patient was subsequently hospitalized August 31, 2006 with an infection of the outflow graft. Due to

improvement in central hemodynamics along with increased risk of recurrent infection of the outflow graft, the Novacor® LVAS device was explanted in October 2006.

3.2 Exercise Testing

At four months post-LVAD explantation the patient underwent a maximal graded exercise test to assess exercise response and peak oxygen consumption (VO_{2peak}). A VO_{2peak} test was conducted under medical supervision. After written, informed consent was obtained; the patient began exercising on a cycle ergometer. Peak oxygen consumption (VO_{2peak}) was determined during a symptom-limited graded exercise test on an electronically-braked cycle ergometer (Ergomed, Siemens, Erlangen, Germany), commencing at zero Watts and increasing by 25 Watts every 3 minutes. 25 Watt increments were selected due to limitations of the cycle ergometer. The test continued until the patient reached complete physical failure or stopped at volitional request. The PhysioDyne Instrument metabolic cart with a Max II oxygen analyzer (# Pm1111E), and a carbon dioxide analyzer (# 1r1507) were used. Heart rate and ECG were measured by 12-lead electrocardiographic (Marquette, USA) monitoring throughout exercise and recovery. Blood pressure was measured and recorded by a physician using a mercury sphygmomanometer before exercise, during exercise (every three minutes), at maximum exertion, and several times throughout recovery. Expired air was collected and analyzed for ventilation, oxygen intake, carbon dioxide output, and gas exchange ratio (RER) using a large two-way non-rebreathing valve (Hans Rudolph) leading to a mixing chamber (RFU 1975). The gas analyzer and flow meter were calibrated according to the manufacturer's recommendations before and immediately after the test. The gas meters were calibrated against gases of known concentrations before the test. Oxygen uptake (VO_2) and carbon dioxide output (VCO_2) were

determined from the measurement of oxygen and carbon dioxide concentration in the inspired and expired air. Cycling continued until the patient was no longer able to maintain at least 50 rev/min, or cardiovascular signs or symptoms intervened.

TABLE 3.1

DESCRIPTIVE CHARACTERISTICS OF THE PATIENT

		Characteristics
Age (years)	at Diagnosis of HF	43
	at LVAD Implantation	46
	at LVAD Explantation	47
Sex		Male
Height (meters)		1.75
Weight (kg)	at peak VO_2 Test	109.1
BMI	Pre LVAD	35.7
	at LVAD Explantation	32.14
	at peak VO_2 Test	32.1
HF Diagnosis		Idiopathic Dilated Cardiomyopathy

CHAPTER 4

RESULTS

After three years of worsening idiopathic dilated cardiomyopathy, the patient consulted with a cardiologist on September 15, 2005 to determine the optimum course of treatment. Resulting diagnosis includes decreased ejection fraction (15-20%), NYHA functional class IV, morbid obesity with a BMI of 35.7, sleep apnea, chronic renal insufficiency secondary to decreased cardiac output, left ventricle dilated to 8.0 cm compared to normal measures of 3.5-5.7 cm, interventricular conduction relay with QRS duration of 118 milliseconds, and mild edema in the lower extremities. At the time of consultation the patient was on optimal HF pharmacotherapy which included digoxin, ACE inhibitor, non-selective beta-blocker, and diuretics. A complete list of medications and dosage can be found in Table 4.1. Subjective findings include decreased ability to perform physical activity, shortness of breath at rest, PND and orthopnea at 45° as well as the patient reporting decreased energy level.

On September 16, 2005 the patient received left heart catheterization, selective left and right coronary angiography, and right heart catheterization with and without Nipride infusion. Selective left and right coronary angiography determined the left main to be normal. The left anterior descending artery and the ramus intermediate were free of significant disease. Results from right heart catheterization with and without Nipride infusion can be found in Table 4.2. Subsequent to the heart catheterization procedure the patient participated in a cardio-pulmonary stress test. The patient exercised on a cycle ergometer free wheel for two minutes, then ramped at 10 watts per minute for a duration of 9 minutes 50 seconds. As shown in Table 4.3, maximum workload achieved was 79 Watts. The test concluded secondary to overall fatigue and dyspnea.

TABLE 4.1

PRESCRIBED PHARMACOTHERAPY AT INITIAL CONSULTATION

Medication	Dose	Frequency
Aldactone	25 mg	Once Daily
Altace	2.5 mb	Once Daily
Ativan		As Needed
Coreg	12.5 mg	Twice Daily
Digoxin	0.125 mg	Once Daily
Dopamine	2 mcg·kg·min^{-1}	
Remeron	30 mg	Once Daily
Restoril	15 mg	As Needed

Notes: List of medications prescribed to patient
before 9-15-2005 consultation

TABLE 4.2

LEFT HEART CATHETERIZATION, SELECTIVE LEFT AND RIGHT CORONARY
ANGIOGRAPHY, AND RIGHT HEART CATHETERIZATION WITH AND WITHOUT
NIPRIDE INFUSION

	Pre-Nipride Infusion	Post Nipride Infusion
RA pressure	31/26, mean 26	18/15, mean 15
RV Pressure	77/27, mean 33	48/14, mean 18
PA Pressure	75/49, mean 63	47/32, mean 38
PCW Pressure	43/52, mean 43	28/27, mean 23
Cardiac Output (L/min)	3.5	4.82
Cardiac Index (L/min)	1.5	2.1
Body Surface Area	2.31	2.31
Transpulmonary Gradient	20	14
PA Saturation	46	59
Ao Saturation (%)	92	92
Pulmonary Vascular Resistance	5.7	2.9
Systemic Vascular Resistance	19.7	13.5
Ao Pressure	117/84, mean 95	97/65, mean 80

Notes: Results obtained 9-16-2005

Subjectively the patient demonstrated maximal effort; however VO_2 plateau was not observed. Peak VO_2 achieved was 13.7 ml·kg^{-1}·min^{-1} (47% of age predicted). Maximum respiratory exchange ratio was 1.00 and maximum oxygen pulse was 18 ml per beat. This test did provoke clinical symptoms of dyspnea; however it was inadequate for inducing target heart rate and exercise level. The patient's heart rate and blood pressure response to exercise was normal, however exercise capacity was subnormal. It should be noted that the patient was prescribed digitalis, beta-blocker, diuretic, and ACE inhibitors which may influence or alter heart rate response, exercise response, as well as the interpretation of test results. This is due to the negative inotropic effects, reduced neurohormonal activation, suppression of heart rate and conduction velocity resulting from beta blockers, decreased vascular volume secondary to diuretics, and impaired capacity for vasoconstriction caused by ACE inhibitors (Sullivan et al., 1998; Ndumele et al., 2003; Bell, 2003)

A follow-up echocardiogram was performed on December 1, 2005 using 2D echo with Doppler M-mode echocardiography. As seen in Table 4.4, results showed the left ventricle to be markedly enlarged, measuring 8.81 cm. The left atrium was also enlarged measuring 5.9 cm compared to normal measures of 1.9-4.0 cm. Left ventricular function was decreased with an ejection fraction of approximately 20% and severe global hypokinesis. The aortic valve demonstrated no significant insufficiency or stenosis, however mitral valve insufficiency was moderate to severe. Tricuspid jet velocity was increased and pulmonary artery systolic pressure measured 50 mmHg, indicating severe pulmonary hypertension. However pulmonary hypertension was not fixed as demonstrated by pulmonary vascular resistance of 2.9 after Nipride infusion.

TABLE 4.3

PRE LVAD CARDIOPULMONARY STRESS TEST-1

VO2 Plateau	Not achieved
Max Watts	79 watts
Peak VO2 (ml·kg^{-1}·min^{-1})	13.7
% Predicted VO2	47
RER	1.00
Max O2 pulse (ml/beat)	18
Baseline Blood pressure (mmHg)	90/60
Baseline Heart rate (bpm)	68
Exercising blood pressure	No significant change
Exercising heart rate (bpm)	91
Blood pressure at beginning of recovery	Not reported
Blood pressure at end of recovery	Not reported
Test duration	9 min 50 sec
Weber Class	C

Notes: Results obtained 9-28-2005. Missing information was not given in physician report

A second cardio-pulmonary stress test was conducted on December 9, 2005. The patient exercised on a cycle ergometer ramped at 10 watts per minute for a duration of 5 minutes 27 seconds. The test ceased secondary to overall patient fatigue. As seen in Table 4.5, the patient demonstrated maximal effort; however VO2 plateau was not achieved. Peak VO$_2$ decreased to 11.8 ml·kg^{-1}·min^{-1} (41% age predicted), a drop of 14% when compared to previous measures of 13.7 ml·kg^{-1}·min^{-1}. Maximum respiratory exchange ratio was 0.97 and maximum oxygen pulse was 7 ml per beat. Baseline blood pressure was 110/80 mmHg and rose to 125/100 mmHg with exercise. Throughout the recovery period blood pressure remained elevated at 120/100 mmHg and decreased to 116/60 mmHg at the end of recovery. This test was adequate for inducing target heart rate and exercise level as well as producing clinical symptoms of dyspnea. Heart rate and blood pressure responses were normal.

TABLE 4.4

PRE LVAD 2-D ECHOCARDIOGRAM WITH DOPPLAR M-MODE ECHOCARDIOGRAPHY-1

Dimensions	Patient	Normal
RV dimension (cm)	3.83	0.9-2.6
LV diastolic dimension (cm)	8.81	3.5-5.7
LV systolic dimension (cm)	7.42	Not reported
Post LV wall thickness (cm)	1.18	0.6-1.1
Septal wall thickness (cm)	1.21	0.6-1.1
Ejection Fraction (%)	22	55-75
Aortic root diameter (cm)	4.18	2.0-3.7
Left atrial dimension (cm)	5.91	1.9-4.0
Tricuspid velocity jet (m/sec)	3.2	Not reported
Pulmonary artery systolic pressure (mmHg)	50	Not reported

Notes: Results obtained 12-1-2005

TABLE 4.5

PRE LVAD CARDIOPULMONARY STRESS TEST-2

VO2 Plateau	Not reached
Max watts	Not reported
Peak VO2 (ml·kg^{-1}·min^{-1})	11.8
% Predicted VO2	41
RER	0.97
Max O2 pulse (ml/beat)	7
Baseline Blood pressure (mmHg)	110/80
Baseline Heart rate (bpm)	86
Exercising blood pressure (mmHg)	125/100
Exercising heart rate (bpm)	103
Blood pressure at beginning of recovery (mmHg)	120/100
Blood pressure at end of recovery (mmHg)	116/60
Test duration	5 min 27 sec
Weber Class	D

Note: Results obtained 12-9-2005. Missing information was not given in physician report

TABLE 4.6

PRE LVAD 2-D ECHOCARDIOGRAM WITH DOPPLAR AND M-MODE
ECHOCARDIOGRAPHY-2

Dimensions	Patient	Normal
RV dimension	Mildly enlarged	0.9-2.6
LV diastolic dimension (cm)	8.6	3.5-5.7
LV systolic dimension (cm)	7.9	Not reported
Post LV wall thickness	Not reported	0.6-1.1
Septal wall thickness	Not reported	0.6-1.1
Ejection Fraction (%)	25-30	55-75
Aortic root diameter	Not reported	2.0-3.7
Left atrial dimension (cm)	5.5	1.9-4.0
Tricuspid velocity jet (m/sec)	3.1	Not reported
Pulmonary artery systolic pressure	Not reported	

Notes: Results obtained 12-13-2005. Missing information was not given in physician report

The patient was subsequently hospitalized secondary to ventricular fibrillation on December 13, 2005. A 2-D echocardiogram with Doppler and M-mode echocardiography was again performed. Test results are similar to those from December 1, 2006, noting a markedly enlarged left atrium measuring 5.5 cm, massively enlarged left ventricle measuring 8.6 cm end diastolic and 7.9 cm end systolic, ejection fraction of 25-30%, and severe global hypokinesis, meaning that the entire heart has enlarged and taken the shape of a round ball verses an oval football. Full results are found in Table 4.6. Table 4.7 illustrates alterations to the patient's pharmacotherapy.

On January 6, 2006 a follow up echocardiogram was conducted. Findings from this test (Table 4.8) indicate a severely dilated left ventricle at 8.99 cm, severe global hypokinesis and a calculated ejection fraction of 25%. The left atrium was also severely dilated to 6.13 cm. Moderate mitral regurgitation was noted as was mild tricuspid regurgitation. Due to the severity of left ventricular dilation, the patient became eligible for immediate LVAD implantation.

TABLE 4.7

ALTERED PRE LVAD PHARACOTHERAPY

Medication	Dose
Aldactone	25 mg
Altace	2.5 mg
Amiodarone	200 mg
Aspirin	325 mg
Bumex	2 mg
Coreg	25 mg
Digoxin	0.25 mg
Magnesium oxide	500 mg
Nexium	40 mg
Potassium chloride	20 mg
Zaroxolyn	2.5 mg
Zocor	20 mg

Notes: Changes to pharmacotherapy reported in hospital discharge summary 12-15-2005.

TABLE 4.8

FINAL PRE LVAD ECHOCARDIOGRAM

Dimensions	Patient	Normal
RV dimension (cm)	4.54	0.9-2.6
LV diastolic dimension (cm)	8.99	3.5-5.7
LV systolic dimension (cm)	8.08	
Post LV wall thickness (cm)	1.15	0.6-1.1
Septal wall thickness (cm)	1.15	0.6-1.1
Ejection Fraction (%)	25.07	55-75
Aortic leaflet separation	Mild	1.5-2.6
Aortic root diameter (cm)	3.59	2.0-3.7
Left atrial dimension (cm)	6.13	1.9-4.0

Notes: Results obtained 1-6-2006

The patient underwent implantation of a Novacor® LVAS on January 12, 2006. Echocardiogram was preformed January 31, 2006 to assess cardiac function with the device. As seen in Table 4.9, results show improved left ventricular diastolic dimension of 6.64 and systolic dimension of 6.22, indicating that the heart was successfully unloaded. Ventricular wall thickness is mildly to moderately increased with severely decreased left ventricular function; however no regurgitation was noted at the device inflow cannula. LVAD outflow peak velocity was 1.52 meters per second, VIT measured at 17.9 cm, giving a stroke volume of 56 ml per beat. Both left and right atria were moderately dilated. The right ventricle was enlarged with moderately reduced systolic function. Regurgitation was present in both the mitral and tricuspid valves.

A follow-up 2D echocardiogram with Doppler M-mode echocardiography was performed on February 23, 2006. Results are detailed in Table 4.10. This test shows that the left ventricle continues to decrease in size, measuring 5.6 cm. The left atrium has also improved, measuring 4.8 cm. Left ventricular ejection fraction was approximately 20% with severe hypokinesis. Some leaflet separation of the aortic valve was noted upon opening and closure of the valve and the tricuspid valve demonstrated mild insufficiency. The LVAD was operating without significant dysfunction. Outflow peak velocity was 1.5 meters per second with a gradient of 9 mmHg. Tricuspid velocity jet was 2.0 meters per second, indicating normal pulmonary artery pressure.

Limited echocardiography follow-up examination was completed on April 12, 2006 and is detailed in Table 4.11. The left ventricle measured 5.4 cm at end diastole. Peak systolic velocity decreased from 1.5 meters per second to 0.9 meters per second and a gradient of 3.3 mmHg. Ejection fraction was approximately 20% and there was mild mitral and tricuspid insufficiency.

TABLE 4.9

INITIAL ECHOCARDIOGRAM POST LVAD IMPLANTATION

Dimensions	Patient	Normal
RV dimension	Moderately enlarged	0.9-2.6
LV diastolic dimension (cm)	6.94	3.5-5.7
LV systolic dimension (cm)	6.22	
Post LV wall thickness		0.6-1.1
Septal wall thickness		0.6-1.1
Ejection Fraction		55-75
Aortic leaflet separation	Mild	1.5-2.6
Aortic root diameter		2.0-3.7
Left atrial dimension	Moderately dilated	1.9-4.0
LVAD outflow peak velocity (m/sec)	1.52	
Stroke volume (ml/beat)	56	

Notes: Results obtained 1-31-2006, 19 days post LVAD implantation. Missing information was not given in physician report.

TABLE 4.10

2-D ECHOCARDIOGRAM WITH DOPPLER M-MODE ECHOCARDIOGRAPHY WITH LVAD SUPPORT

Dimensions	Patient	Normal
RV dimension	Mildly enlarged	0.9-2.6
LV diastolic dimension (cm)	5.6	3.5-5.7
LV systolic dimension (cm)	>5.0	
Post LV wall thickness		0.6-1.1
Septal wall thickness		0.6-1.1
Ejection Fraction (%)	20	55-75
Aortic leaflet separation	positive	1.5-2.6
Aortic root diameter		2.0-3.7
Left atrial dimension (cm)	4.8	1.9-4.0
LVAD outflow peak velocity (m/sec)	1.5	
LVAD gradient (mmHg)	9	
Tricuspid velocity jet (m/sec)	2.0	

Notes: Results obtained 2-23-2006. Missing information was not given in physician report.

TABLE 4.11

LIMITED ECOCARDIOGRAPHY REPORT WITH LVAD SUPPORT

Dimensions	Patient	Normal
RV dimension	Apparently normal	0.9-2.6
LV diastolic dimension (cm)	5.4	3.5-5.7
LV systolic dimension		
Post LV wall thickness		0.6-1.1
Septal wall thickness		0.6-1.1
Ejection Fraction (%)	20	55-75
Aortic leaflet separation		1.5-2.6
Aortic root diameter		2.0-3.7
Left atrial dimension		1.9-4.0
LVAD outflow peak velocity (m/sec)	0.9	
LVAD gradient (mmHg)	3.3	

Notes: Results obtained 4-12-2006. Missing information was not given in physician report.

On August 31, 2006 the patient was admitted to the hospital for infection of the LVAD outflow graft, demonstrating redness and inflammation as well as fever and chills. The patient was administered intravenous antibiotic therapy. After treatment completion ultrasound of the abdomen was conducted and determined that there was no fluid accumulation within the LVAD pocket. While hospitalized, the patient's cardiologist and LVAD implantation team consulted and determined that due to drastic improvements in central hemodynamic function along with the risks associated with recurrent infection, that the patient could be a candidate for LVAD explantation. The patient was discharged from the hospital on September 1, 2006 and immediately sought evaluation for explantation. The LVAD was subsequently explanted in October 2006. Complete echocardiography, cardiac Doppler, and color flow imaging were performed to determine native heart function; results are detailed in Table 4.12. The test revealed

normal sinus rhythm at 73 beats per minute, left ventricular end diastolic diameter of 6.16 cm, and end systolic diameter of 4.54 cm. The left ventricular cavity size appeared mildly to moderately increased with mild to moderate left ventricle hypertrophy. Overall ejection fraction was 49% and ventricular function was low normal. Doppler imaging showed impaired relaxation of left ventricular diastolic filling. The mid, apical, and basal septum segments appeared to be hypokinetic. The right and left atria appeared to be dilated measuring 21.0 cm^2 and 26.3 cm^2, respectively. The mitral valve appeared normal with normal leaflet mobility, however mild regurgitation was present. Tricuspid valve regurgitation was also present.

Body weight was significantly less post implantation as well as post explantation when compared to pre implantation body weight. In October of 2005 the patient's weight was 118.18 kg with a BMI of 35.7. His weight continued to increase, reaching 130 kg, until shortly after LVAD implantation. After implantation, the patient's weight slowly began to decrease reaching 101.18 kg and BMI of 32.14 at the time of device explantation. The patient's weight at the time of peak VO_2 testing was 109.1 kg and BMI of 32.1.

On February 10, 2007 the patient participated in a cycle ergometry VO_2 peak test beginning at 0 watts and ramped 25 Watts every 3 minutes. The test concluded secondary to lower extremity muscular fatigue. As seen in Table 4.13, the patient demonstrated maximal effort during the test. The test duration was 15 minutes with the patient achieving a maximum resistance of 100 Watts. VO_2 increased from a pre LVAD maximum of 11.8 $ml \cdot kg^{-1} \cdot min^{-1}$ to a maximum of 17.0 $ml \cdot kg^{-1} \cdot min^{-1}$, which is 64.5% of the predicted value. Resting heart rate increased from 79 beats per minute to an exercise maximum of 109 beats per minute with maximum blood pressure of 135/70 mmHg. Maximum respiratory exchange ratio rose to 1.05.

TABEL 4.12

INITIAL ECHOCARDIOGRAM POST LVAD EXPLANTATION

Dimensions	Patient	Normal
RV dimension	Mildly enlarged	0.9-2.6
LV diastolic dimension (cm)	6.16	3.5-5.7
LV systolic dimension (cm)	4.54	
Post LV wall thickness		0.6-1.1
Septal wall thickness		0.6-1.1
Ejection Fraction (%)	49	55-75
Aortic leaflet separation	Normal mobility	1.5-2.6
Aortic root diameter (cm)	3.72	2.0-3.7
Left atrial dimension (cm)	4.88	1.9-4.0
Right atrium (cm)	21.0	
Left atrium (cm)	26.3	

Notes: Results obtained 11-20-2006. Missing information was not given in physician report.

TABLE 4.13

POST LVAD EXPLANTATION PEAK VO$_2$ TEST

|	
VO2 Plateau	Not achieved
Max watts	100
Peak VO2 (ml·kg^{-1}·min^{-1})	17.0
% Predicted VO2 (%)	46.5
RER	1.05
Max O2 pulse (L/min)	47.99
Baseline Blood pressure (mmHg)	135/90
Baseline Heart rate (bpm)	79
Exercising blood pressure (mmHg)	130/72
Exercising heart rate (bpm)	109
Blood pressure at beginning of recovery (mmHg)	135/70
Blood pressure at end of recovery (mmHg)	138/80
Exercise time (minutes)	15
Weber Class	B-C

CHAPTER 5

DISCUSSION

Despite the improvements observed in patients with LVAD support, research data are limited regarding the effects of exercise with LVAD support and bridging to recovery through reverse remodeling. A review of current literature has shown a relatively small number of studies investigating the physiological changes associated with exercise and LVAD. Of these studies, most also have a small sample size (n<20) (Perme et al., 2006; Humphrey, 1997; Mettauer et al., 2001; Arena et al., 1999; Foray et al., 1996; Nishimura et al., 1996; Jaski et al., 1997 and 1999; de Jong et al., 2001). Sample sizes are small because, although more HF patients are becoming eligible for LVAD implantation, the population of those currently with LVAD is very small. While many studies have investigated the functional capacity, VO$_2$, neurohormonal, muscular, and hemodynamic changes associated with LVAD use, a total of less than 100 LVAD patients have been tested for the purpose of determining the physiological effects of exercise while under mechanical circulatory support. Data regarding bridging to recovery through reverse remodeling are even more limited. Due to a small number of LVAD patients who recover sufficient cardiac function to undergo LVAD explantation, the concept of bridging to recovery is quite new. As of 2005, only approximately 40 patients have been reported in the literature to have undergone LVAD explantation (Dandel et al., 2005). This study serves to give insight into the recovery of exercise capacity in individuals who undergo LVAD explantation without HTx.

The patient in the current study was a 47 year old male with a past medical history of idiopathic dilated cardiomyopathy. Throughout the course of the disease, the patient experienced worsening HF characterized by increasing left ventricle dilation from 8.81 cm to 8.99 cm, left atrial dilation from 5.91 cm to 6.13 cm, severely reduced ejection fraction measuring between

FIGURE 5.1

Left Ventricular Diastolic Diameter (cm)
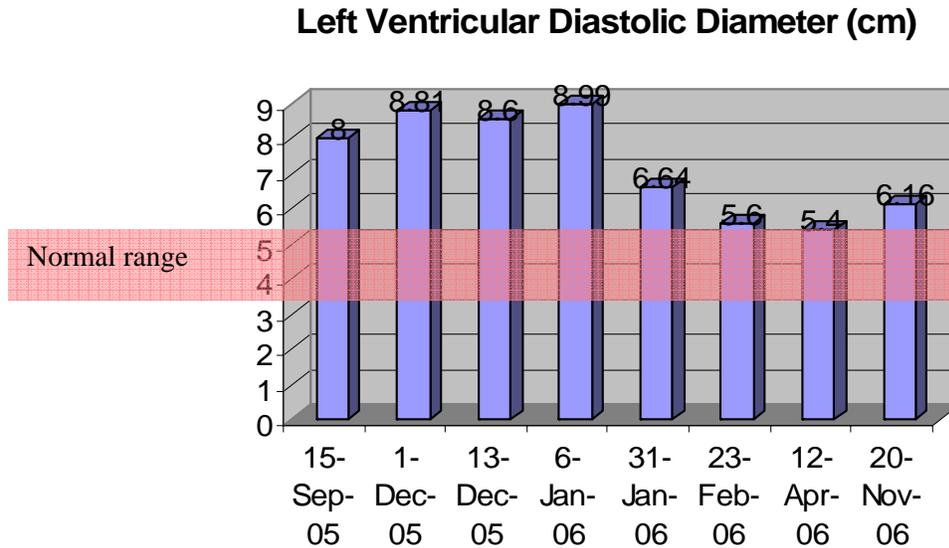
15-25%, decreased VO_2 of 11.8 ml·kg^{-1}·min^{-1}, and severely increased pulmonary artery pressure of 50 mmHg which could have potentially become permanent.

Upon implantation of a Novacor® LVAS device the patient's central hemodynamic function immediately began to improve. Left ventricular diastolic and systolic diameter decreased by 39.8% and >30%, respectively. The left atrium also decreased by 21.7%. Ejection fraction was maintained by the LVAD and stabilized at 20% and pulmonary artery pressure decreased. The LVAD successfully unloaded the heart by decreasing peripheral and pulmonary vascular resistance secondary to decreased vasoconstriction as described by Burkhoff and colleagues (2006). These researchers described that sufficient unloading of the heart leads to more normal neurohormonal activity which can lead to significant myocardial recovery (Burkhoff et al., 2006). Although the primary reason for device explantation was infection, these adaptations allowed for the patient to regain near normal heart function without requiring HTx, and was subsequently able to undergo LVAD explantation.

Post explantation, the patient's central hemodynamic function remained within functional limits. The left ventricular diastolic dimension increased to 6.16 cm, systolic dimension was within normal limits at 4.54 cm and ejection fraction was slightly below normal at 49%. Overall, this is a 31.2% reduction in diastolic dimension, 43.8% reduction in systolic dimension, and 55.11% increase in ejection fraction.

Myocardial thickness has been shown to be a good (reliable) measure of cardiac health (Grossman, 1974). As discussed in Chapter 2 regarding the Frank Starling Mechanism, wall thickness can be directly related to ventricular contraction strength, as any change in thickness or elasticity can alter the total volume of blood accepted by the chamber reducing the length of stretch to each muscle fiber. The end result is a reduced volume of blood being ejected from the ventricle (stroke volume) and an increase volume of blood remaining in the ventricle after contraction (end systolic volume).

Repeated cardiopulmonary stress tests detail the extent of worsening HF leading up to LVAD implantation. In October of 2006 the patient achieved a peak aerobic capacity of 13.7 ml·kg^{-1}·min^{-1} which quickly deteriorated to 11.8 ml·kg^{-1}·min^{-1} over the course of 32 days. It is worth noting that both VO$_2$ values qualify the patient for a HTx. This test was not repeated while the patient was under LVAD support due to the limited ability of the device to increase cardiac output to meet metabolic demand. However, three months post explantation, the patient's peak VO$_2$ had improved to 17 .0 ml·kg^{-1}·min^{-1}.

The improvements observed in the patients central hemodynamics (Table 5.1) while under LVAD support such as decreased left ventricular diastolic diameter and left ventricular systolic diameter indicates that reverse remodeling did occur secondary to reduced physiological load placed upon the myocardium. This idea is further supported by the patient's improved

cardiac function upon explantation of the device, as seen in Table 5.1. Improved co-morbidities such as weight loss may have also had an effect on improved hemodynamics.

One of the primary limitations of this study is that peak VO_2 is used to determine the functional capacity of the patient. It was previously believed that the difference between percent heart rate reserve offered an equivalent percentage of VO_2 max (ACSM, 1995). This belief stemmed from the late 1950's work of Karvonen (Swain and Leutholtz, 1997); however VO_2 was not measured in his study (Karvonen, 1957). In fact, a relationship between percent heart rate reserve and VO_2 max has not been established in the literature (Swain and Leutholtz, 1997). Swain and Leutholtz (1997) showed that the inconsistency between heart rate reserve and VO_2 max during cycle ergometry is inversely proportional to the intensity of exercise and fitness level. A later study by Swain and colleagues showed that during treadmill exercise percent heart rate reserve and VO_2 max highly correlated with each other; however, regression lines were significantly different, indicating that the same disparity seen in cycle ergometry exists with treadmill exercise (Swain et al., 1998). These researchers did report that percent heart rate reserve and VO_2 reserve were indistinguishable during cycle ergometry, and slightly different, but not significantly, during treadmill exercise (Swain and Leutholtz, 1997; Swain et al., 1998). A similar study conducted by Brawner and colleagues (2001) determined the relationship of percent heart rate reserve, VO_2 max, and percent VO_2 reserve in HF patients. They showed that in a heart disease population, percent heart rate reserve and percent VO_2 reserve do differ, but not significantly whereas percent heart rate reserve and VO_2 max are significantly different at a $P<0.001$ level (Brawner et al., 2001). Brawner et al., (2001) as well as Mezzani and colleagues (2007) have noted that the use of beta-blocking pharmacotherapy does not significantly alter the results.

TABLE 5.1

SUMMARY OF CARDIOPULMONARY STRESS TESTS

	Pre LVAD 9-28-2006	Pre LVAD 12-9-2006	Post LVAD 2-10-2007
VO2 Plateau	Not achieved	Not reached	Not achieved
Max Watts	79	Not reported	100
Peak VO2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	13.7	11.8	17.0
% Predicted VO2 (%)	47	41	64.5
RER	1.00	0.97	1.05
Max O2 pulse	18 ml/beat	7 ml/beat	47.99 L/min
Baseline Blood pressure (mmHg)	90/60	110/80	135/90
Baseline Heart rate (bpm)	68	86	109
Exercising blood pressure (mmHg)	No significant change	125/100	130/72
Exercising heart rate (bpm)	91	103	108
Blood pressure at beginning of recovery (mmHg)	Not reported	120/100	135/70
Blood pressure at end of recovery (mmHg)	Not reported	116/60	138/80
Weber Class	C	D	B-C

In the current study the patient demonstrated a peak VO_2 of 17 $ml \cdot kg^{-1} \cdot min^{-1}$, however percent VO_2 reserve was not determined. Had percent VO_2 been determined we may have a better understanding of the patient's functional level. Subjectively, a peak VO_2 of 17 $ml \cdot kg^{-1} \cdot min^{-1}$ is significantly reduced when compared to age predicted norms, which may cause one to conclude that the patient is severely functionally limited. This however is not the case for the individual presented here. Clinically the patient has undergone two major surgeries and recovered near normal central hemodynamic function. In fact, one month following the LVAD explantation his ejection fraction (49%) measured significantly above the clinically accepted criteria for HF (< 40%; normal adult is 55% - 75%). He has also been given physician clearance to participate in any physical activity that he chooses without limitation. He has

returned to work full time and takes care of his children, indicating that he is not severely functionally limited. Determining percent heart rate reserve and percent VO_2 reserve may give a more clear understanding of the patient's physical capabilities.

A second limitation to the study is the intensity with which workload was increased during the VO_2 max test. Typically during a cycle ergometry graded exercise test for a heart disease patient, work load is increased by 10 Watts per stage (Keteyian and Spring, 2003). However, due to the limitations of the cycle ergometer, workload was increased by 25 Watts per 3 minute stage. The steep increase in resistance can potentially lead to a shortened test time due the rapid increase in active muscle mass and metabolic demand. However, this did not seem to have an effect on test results as the patient was able to exercise for 15 minutes reaching a maximum work load of 100 Watts.

It is worth noting the weight loss that occurred while the patient was under LVAD support. Prior to device implantation the patient weighed as much as 122.73 kg, while weighing 101.82 kg at device explantation. A decrease in adipose tissue may have contributed to the unloading of the heart. This is because less energy is required to move the body as well as less tissue requiring perfusion which would decrease metabolic demand. This could decrease systemic hypertension as well as have an effect on preload and afterload. However, the majority of the weight lost by the patient was fluid that had been retained as a compensatory mechanism working to maintain vascular volume. Due to the clinical applications of relative VO_2 and the patient's weight loss most likely attributable to fluid loss and not the loss of tissue, relative VO_2 measures were used in this study.

In conclusion, the results from this case study indicate that significant improvements in native heart function are possible with a period of mechanical unloading through LVAD support.

In addition, symptom limited maximal graded exercise testing appears to be safe for this specific individual. This is a unique case study in that the severity of the individual's deteriorating disease would suggest the need for immediate HTx or permanent mechanical circulatory support. There were no donor hearts available and the latter was performed, however in this case the device was removed after only nine months and the patient presents with near normal heart function. LVAD mechanics have improved dramatically over the past decade and it appears that bridging to recovery is a potentially viable treatment option, but further studies with larger sample sizes are needed to describe the detailed physiological adaptations that occur within this population.

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