EXERCISE LIMITATIONS IN A COMPETITIVE CYCLIST TWELVE MONTHS POST HEART TRANSPLANTATION

A Thesis by

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The following faculty members 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 with a major in Exercise Science.

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Jeremy Patterson, Committee Chair

We have read this thesis and recommend its acceptance:

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Michael E. Rogers, Committee Member

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Nicole L. Rogers, Committee Member
DEDICATION

To my family and friends whose support and encouragement throughout the graduate program helped me succeed, and especially my father who provided me with daily advice and friendship until his final days.
ACKNOWLEDGEMENTS

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ABSTRACT

BACKGROUND: It has been well documented that for heart transplant recipients (HTR) post transplantation exercise capacity does not exceed 60% of healthy age matched controls. Few, if any studies have been undertaken to determine the cause of exercise limitations following heart transplantation (HTx) for an elite athlete who has received a new heart.

CASE SUMMARY: The participant in this study is a 39 year old professionally trained male cyclist who suffered an acute myocardial infarction after a cycling road race and received a heart transplant (HT) four months after the AMI. The participant underwent maximal graded exercise testing six and 12 months post transplant to assess recovery and exercise capacity in an attempt to determine the causes of exercise limitations following HT.

RESULTS: The participant showed an increase in both HR and VO\textsubscript{2max} 12 months post HT compared to previous testing (six months post) and those of healthy age matched controls. His results six months and 12 months post transplant were a VO\textsubscript{2max} of 33.8 and 44.2 mL·kg\(^{-1}·\text{min}^{-1}\) respectively, and HR\textsubscript{max} that was 97% and 96% of HR\textsubscript{max} measured prior to his AMI.

CONCLUSION: Results suggest that the limiting factors to exercise following HTx are likely due to peripheral function in this case, which became diminished as a result accumulated from four months of CHF, the strain of HTx, and possibly the effects of the immunosuppressive therapy leading up to the exercise testing. Lifestyle before HT and a more aggressive approach to HT recovery should be considered necessary in the improvement of peripheral functioning following HTx.
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Post-transplant versus the expected blunted heart rate response
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<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACh</td>
<td>Acetylcholine</td>
</tr>
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<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>cGMP</td>
<td>Guanosine monophosphate</td>
</tr>
<tr>
<td>CHF</td>
<td>Chronic Heart Failure</td>
</tr>
<tr>
<td>Cm</td>
<td>Centimeter</td>
</tr>
<tr>
<td>EDRF</td>
<td>Endothelium-derived relaxing factor</td>
</tr>
<tr>
<td>G-cyclase</td>
<td>Guanylyl cyclase</td>
</tr>
<tr>
<td>GTP</td>
<td>Guanosine triphosphate</td>
</tr>
<tr>
<td>HF</td>
<td>Heart failure</td>
</tr>
<tr>
<td>HT</td>
<td>Heart Transplant</td>
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<tr>
<td>HTR</td>
<td>Heart transplant recipient</td>
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<td>HTx</td>
<td>Heart transplantation</td>
</tr>
<tr>
<td>kg</td>
<td>Kilogram</td>
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<tr>
<td>min</td>
<td>Minute</td>
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<tr>
<td>ml</td>
<td>Milliliter</td>
</tr>
<tr>
<td>mm</td>
<td>Millimeter</td>
</tr>
<tr>
<td>mmHg</td>
<td>Millimeters of mercury</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>NOS</td>
<td>Nitric oxide synthase</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>Q</td>
<td>Cardiac output</td>
</tr>
<tr>
<td>VO$_2$</td>
<td>Symbol for oxygen uptake</td>
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CHAPTER 1
INTRODUCTION

The heart transplant recipient (HTR) presents as a very challenging patient for exercise rehabilitation, primarily because of the new cardiac physiology, hemodynamics and immunosuppressive status. The immunosuppressive drug regimen that patients with a heart transplant (HT) must follow is responsible for numerous co-morbidities in this population. In many cases, patients with HT are trading the medical management of one chronic disease for another. For example medications commonly administered following heart transplantation (HTx) have various adverse effects, Cyclosporine causes hypertension and Prednisone therapy produces sodium and fluid retention, loss of muscle mass, glucose intolerance, osteoporosis, fat redistribution from extremities to torso, gastric irritation, increased appetite, increased susceptibility to opportunistic infections, predisposition to peptic ulcers, and increased potassium excretion (Hokanson, Mercier, & Brooks, 1995). The triple drug immunosuppressive regimen of patients with HT manifests some of the traditional risk factors for coronary artery disease such as elevated blood lipids and hypertension. These patients are also susceptible to plaque deposition because of chronic injury to the heart and blood vessels caused by repeated episodes of acute rejection. These and other adverse events following HTx have been shown to be positively effected by chronic bouts of physical activity (Braith & Edwards, 2000).

Peripheral factors contribute to impaired physical performance in patients with congestive heart failure (CHF). Published data support the fact that peripheral physiology remains impaired in patients with HT for a prolonged period of time after HTx. Skeletal muscle biopsies six weeks post transplantation are grossly abnormal and include intracellular lipid and
glycogen accumulations and markedly thickened capillary basement membranes (Braith, Limacher, Leggett, & Pollock, 1993). Skeletal muscle contractile function remains unaltered for six weeks after transplantation. Peripheral factors, including high arterial lactates, still predominate in patients who are 15 months post-transplant. The vascular system becomes intrinsically stiff in response to the long-term, low-flow state of CHF (Braith, et al., 2005). Peripheral vasodilator capacity remains impaired for as long as four months after heart transplantation. Improvements in cardiac function act indirectly and slowly to improve peripheral vascular function. Increasing physical activity after heart transplantation (HTx) has been shown to improve impaired peripheral physiology in these patients (Marconi & Marzorati, 2003; Osada, et al., 1997).

Changes in cardiac, systemic physiology and hemodynamics over time in patients with HT are an important consideration in utilizing exercise as a therapeutic intervention. From early to late post-transplantation, patients with HT increase their average maximum MET level from approximately 5.0 to 6.0 METs (Marzo, Wilson, & Mancini, 1992). These improved physiological capacities allow the patient with HT to improve their physical work capacity on the average of 37% from early to late post-transplantation. Although these improvements are significant compared to pre-transplantation, it has been well documented that post-transplantation physical work capacity (PWC) normally does not exceed 60% of the value for healthy age-matched controls and peak HR is significantly reduced (66% of predicted) (Marconi & Marzorati, 2003). The reduced PWC has been linked to the blunted HR at peak exercise due to complete denervation of the heart causing a loss of autonomic innervation of the SA node (Bangel, et al., 2001). These benefits of physical activity post transplant are widely accepted. However, the influence of pre-transplant fitness on recovery is unknown. The purpose of this
study is to examine the physiological responses of a heart transplant recipient that had an elite aerobic capacity prior to a severe cardiac event.
CHAPTER 2
LITERATURE REVIEW

2.1 Normal Heart Function

Before understanding heart failure and the processes that lead to heart transplantation, it is necessary to understand the normal functions of the heart. During normal heart function, the four chambers of the heart undergo periods of contraction (systole) and relaxation (diastole). This series of contraction and relaxation phases makes up 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 (Dyer & Fifer, 2003). Atrial systole marks the beginning of the cardiac cycle and is initiated by the sinoatrial node (SA node). Atrial systole consists of simultaneous contraction of both the right and left atria. During these contractions blood is pushed out of the atria and into the ventricles (Dyer & Fifer, 2003). After atrial systole is complete, atrial diastole begins. During atrial diastole, deoxygenated blood is delivered to the right atrium through the superior and inferior vena cava. The vena cava is responsible for venous return from systemic structures, and oxygenated blood is delivered to the left atrium via the pulmonary vein (Keteyian & Forman, 2008). During ventricular systole, the ventricles contract and pressure increases, forcing the tricuspid and mitral valves to close. This prevents blood from entering 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 be effectively delivered to other parts of the body via the vascular system (Keteyian & Forman, 2008). When ventricular systole has concluded and diastole begins, pressure within the ventricles lowers. Once ventricular pressure falls below the pressure within the aorta and
pulmonary artery, the aortic valve and pulmonary semilunar valves close, preventing the flow of
blood into the ventricles (Maiorana, et al., 2000). When ventricular pressure falls below that of
the atria, the tricuspid and mitral valves open, allowing for the passive blood flow 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 (Dargie & McMurray, 1994). During
diastole the ventricles fill to approximately 110-120 ml. This volume is the end diastolic volume
(Kannel & Belanger, 1991). The amount of blood that is ejected from the ventricles during
systole is the stroke volume and ranges from 70-75 ml (Dyer & Fifer, 2003). The blood
remaining in the ventricle at the end of systole is the end systolic volume and is normally 40-50
ml (Kannel & Belanger, 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 (Keteyian, et al., 1996). Ejection fraction is the percentage of end
diastolic volume ejected from the ventricles during systole. Values typically fall within a range
of 55-75% for the average adult (Dargie & McMurray, 1994). Cardiac output is the volume of
blood ejected from the heart per minute and is the product of stroke volume and heart rate
(Wielenga, et al., 1999). Cardiac output 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 (Dyer & Fifer, 2003), however, with increased
physical activity this value can increase considerably depending upon exercise intensity (Dyer &
Fifer, 2003).

2.1.1 Frank-Starling Mechanism

The Frank-Starling law of the heart (also known as Starling's law or the Frank-Starling
mechanism) states that the greater the volume of blood entering the heart during diastole (end-
diastolic volume), the greater the volume of blood ejected during systolic contraction (Maiorana, et al., 2000). As the heart fills with more blood than normal, the force of the ventricular muscular contractions will increase; this is a result of an increased load on each muscle fiber due to the increased volume of blood entering the heart (Shephard, Kavanagh, & Mertens, 1998). This increased load causes a greater contraction with increased force. The increased contractile force automatically ejects the increased volume of blood, and is marked by increased stroke volume (Wielenga, et al., 1999).

In individuals with CHF, the Frank-Starling mechanism is the first compensatory mechanism that attempts to maintain a balance between stroke volume, cardiac output, and ejection fraction (Pu, et al., 2001). 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 triggers the Frank-Starling mechanism which will cause the ventricles contract with a greater force during the next contraction (Dyer & Fifer, 2003; Gupta, Sabtine, & Lilly, 2003). The increased contractile force of the heart causes an increase in stroke volume which empties the ventricle and increases cardiac output (Coats, Adamopoulos, Meyer, Conway, & Sleight, 1990). This compensatory mechanism maintains cardiac output for period of time, but as vascular volume increases the ventricular walls becomes rigid and ineffective at filling and ejecting blood (Coats, 1999). As a result, the patient will continue to have diminished aerobic capacity leading to further complications (Belardinelli, Georgiou, Cianci, & Purcaro, 1999).
2.2 Pathophysiology of Heart Failure

Heart failure is fairly common, afflicting approximately 4.8 million Americans with 400,000 new cases reported annually (Keteyian & Forman, 2008). Heart failure is the most severe final manifestation of nearly every form of cardiac disease including atherosclerosis, myocardial infarctions, valvular disease, hypertension, congenital heart disease, and cardiomyopathies (Dyer & Fifer, 2003). Heart failure can be defined as the inability of the heart to keep up with the demands of the body and, more specifically, failure of the heart to pump blood with normal efficiency (Kannel & Belanger, 1991). When this occurs, the heart is unable to provide adequate blood flow to other organs such as the brain, liver and kidneys. This lack of blood flow can lead to other complications and organ failure. Heart failure may be due to failure of either the right or left or of both ventricles. When ventricular failure occurs the heart activates compensatory mechanisms in an attempt to improve pumping capacity and cardiac output (Belardinelli, et al., 1999). These mechanisms include enlarging of the ventricles to pump more blood efficiently, developing more muscle mass to increase the force of contractions, and elevating heart rate to increase cardiac output (Keteyian, et al., 1996). While these compensatory mechanisms do help initially, over time these mechanisms will further decrease the pumping capacity of the heart making it far more inefficient than before (Kannel & Belanger, 1991). As the size of the heart increases the efficiency decreases. With this decreased efficiency comes a sharp decline in aerobic capacity as well as increased edema (fluid buildup) within the body. The location of the compensation within the heart dictates whether the heart failure is classified as left or right sided heart failure (Gupta, et al., 2003).
2.2.1 Left Sided Heart Failure

Chronic heart failure may result from a number of cardiovascular conditions that can arise separately or group together to further impair the failing heart. These conditions include impaired contractility, increased afterload, and impaired ventricular filling (Phipps, 1997). Heart failure most commonly results from conditions of impaired left ventricular function (Gupta, et al., 2003). When ventricular emptying abnormalities occur it is termed systolic dysfunction. When this occurs, the left ventricle can no longer contract with enough force to provide adequate circulation within the body. Systolic dysfunction is a result of impaired myocardial contractility or pressure overload (Gupta, et al., 2003). Pressure overload impairs ventricular ejection by significantly increasing resistance to blood flow. In this scenario the stroke volume falls, and with an increase in end systolic volume and preload there is a compensatory rise in stroke volume via the Frank Starling mechanism (Dyer & Fifer, 2003). When there are abnormalities of ventricular filling it is termed diastolic dysfunction. When this occurs, the ability of the heart to relax and allow for diastolic filling is impaired, due to a stiffening of the cardiac muscle (Dargie & McMurray, 1994). With either diastolic and systolic dysfunction or with a combination of both diastolic and systolic dysfunction, left sided heart failure can result (Keteyian & Forman, 2008).

Left sided heart failure can lead to several complications, one of the more common being pulmonary edema. When a heart is in failure, the blood flowing to the left ventricle can become backed up allowing for overflow of fluid into the lungs, resulting in pulmonary edema (Kannel & Belanger, 1991). In addition to pulmonary edema other areas of the body can experience fluid build up from the decreased contractile ability of the heart.
2.2.2 Right Sided Heart Failure

In comparison to the left ventricle, the right ventricle is a thin walled chamber that regularly accepts blood volume at a lower filling pressure and ejects against a lower pulmonary pressure (Keteyian & Forman, 2008). Because of this difference the right ventricle is susceptible to failure when a sudden increase in after load is present. The most common cause of right sided heart failure is left sided heart failure (Coats, 1999). With right sided heart failure there is excessive afterload to the right ventricle because of elevated pulmonary vascular pressure resulting from left ventricle dysfunction (Coats, 1999). When the right ventricle fails the elevated diastolic pressure is transferred to the right atrium which causes congestion of the systemic veins as well as signs and symptoms of right sided heart failure. When right sided heart failure is isolated the decreased right ventricular output reduces blood return to the left ventricle, decreasing preload potentially causing a decrease in stroke volume (Keteyian, 2001).

2.3 Diagnosis and Classification

With its complex pathophysiology and systemic intricacy heart failure presents a challenge when developing a single diagnostic method for a disease that includes a large range of signs and symptoms (Dargie & McMurray, 1994). Because of this complexity, the current diagnostic criteria for congestive heart failure are based on a functional staged classification system and exercise testing (Squires & Rodeheffer, 2008). The Webber/American Heart Association staging classification system (as listed below) quantifies heart failure patients into stages of the disease.

**Stage A:** Distinguishes individuals who are at risk of developing CHF (i.e. those with risk factors such as hypertension, coronary artery disease, diabetes, or family history of cardiomyopathy) but still have normal heart function.
**Stage B**: Pertains to individuals who have structural heart disease but remain asymptomatic.

**Stage C**: Refers to individuals who have structural disease and are intermittently symptomatic.

**Stage D**: Refers to individuals who have structural heart disease, are symptomatic at all times, and require specialized interventions (Keteyian, 2001).

Along with the Webber classifications stages of CHF is the familiar New York Heart Association (NYHA) functional classification system of heart failure. In this system patients are further classified based on their functional capacity. The NYHA classification only looks at patients in stage C and D heart failure. The functional classifications for the NYHA are as follows:

- **Class I**: No limitations: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitations.
- **Class II**: slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
- **Class III**: Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.
- **Class IV**: Inability to carry on any physical activity without discomfort: symptoms of congestive failure are present even at rest. With any physical activity, increased discomfort is experienced (Keteyian, 2001).

Using these diagnostic techniques allows for a non-invasive approach in the classification and treatment of patients with CHF. Exercise testing is also used in parallel with the staging systems detailed above determining severity of CHF (Shephard, et al., 1998). The prevalence of different classifications of CHF in America are not exactly known. An estimated 800,000 people (16% of
the CHF population) have a Class III or IV heart defect significantly increasing risk of death, and an estimated 4000 or 0.5 percent of the Class III and IV CHF population currently await a HT (Ammar, et al., 2007). A patient with severe CHF that performs a maximal graded exercise test and produces a VO$_{2\text{max}}$ less than $14 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ is determined to have severely limited aerobic capacity and be a candidate for heart transplantation (Marconi & Marzorati, 2003).

2.4 Treatment of Heart Failure

With these aforementioned factors, treatment for heart failure focuses on a five-tiered approach (Keteyian & Forman, 2008). Step one involves identification and correction of the underlying condition causing the heart failure. This could require surgical repair or replacement of dysfunctional valves, a coronary artery bypass graft, and/or treatment of severe hypertension. Step two is the elimination of acute precipitating causes of symptoms. This would include treating acute infections or arrhythmias, removing of excessive salt intake, and stopping the use of drugs that can aggravate symptoms of CHF. Step three is the management of CHF systems. This includes the treatment of pulmonary and systemic vascular congestion, as well as increased cardiac output and perfusion of vital organs. Treatment of congestion is accomplished by dietary sodium restriction and diuretic medications and vasodilators are used to aid in the perfusion of vital organs. Step four mediates the neurohormonal response to help prevent adverse ventricular remodeling via the Frank Starling Mechanism, in order to slow progression of left ventricular dysfunction. Step five focuses on the improvement of long-term survival supported by evidence that longevity is enhanced by specific interventions including the use of diuretics, vasodilators, inotropic drugs, beta-blockers, and the introduction to exercise in an attempt to slow or counter the negative remodeling encountered by heart failure patients (Witte, Thackray, Nikitin, Cleland, & Clark, 2003). Even with these treatment options heart failure can continue to progress and
physical capacity will further decline. When peak VO\textsubscript{2} drops below 14 ml•kg\textsuperscript{-1}•min\textsuperscript{-1} and patients are placed in AHA stage C and NYHA class III the next stage in treatment is to be placed on a heart transplant waiting list (Bussières, et al., 1995; Johnson, Carlson, VanderLaan, & Langholz, 1998). When a suitable donor is found and the patient is strong enough to undergo the procedure, heart transplantation can occur (Bangel, et al., 2001)

**2.4.1 Heart Medications and Exercise**

Several different types of medications are used in the treatment of both heart failure and in the period of time immediately following HTx. These medications include diuretics, vasodilators, inotropic drugs and beta-blockers as well as steroids and immuno suppressive therapy following HTx (Witte, et al., 2003). These drugs have various effects on the physiological systems of the body at rest as well as factors involving exercise capacity. Inotropic drugs such as digitalis are administered intravenously and have the effect of increasing ventricular contractions resulting in an increase in stroke volume and cardiac output. These drugs are usually used in the short term due to the lack of an orally-administered form of the drug as well as the rapid development of drug tolerance. Digitalis enhances contractility of the cardiac muscle, reduces cardiac enlargement, and helps to control the rate of ventricular contractions (Squires & Rodeheffer, 2008). Beta blockers act on the sympathetic nervous system slowing the heart rate and reducing stress on the heart (Witte, et al., 2003). Vasodialators aid in the ability of vascular smooth muscle to relax and dilate to allow for more unrestricted blood flow the vital organs of the body. A patient often remains on these medications following HTx and is also prescribed a variety of immunosuppressant drugs to help reduce the chance of an acute rejection of the new donor heart (Fraund, Pethig, Franke, & Wahlers, 1999). Typically, a patient is placed on a maintenance regimen of immunosuppressant medications which typically
includes a calcineurin inhibitor (cyclosporine), an antiproliferative agent (mycophenolate mofetil), and a steroid (prednisone). Although immunosuppressant medications greatly reduce the chance of an acute donor heart rejection, they carry several potential debilitating side effects. Cyclosporine can cause renal dysfunction, hypertension and muscle cramps. Prednisone, in the high dose range used in the prevention of acute rejection, can cause a number of problems including an alteration of body fat distribution resulting in android obesity, osteoporosis, dyslipidemia and skeletal muscle atrophy and weakness (Hokanson, et al., 1995). After the first one to two years following HTx the patient may begin to taper off of the immunosuppressant medications (specifically prednisone) due to its numerous side effects (Squires & Rodeheffer, 2008).

2.5 Endothelial Function

Endothelial function is a key discussion item within the review of the vascular system. Endothelial cells line the arterial walls and produce a number of vasoactive substances that work to regulate vascular tone (Dyer & Fifer, 2003). Endothelial cells are responsible for the production of chemical reactions that control vasodilation and vasoconstriction. Vasodilators produced by endothelial cells include nitric oxide (formerly termed “endothelium-derived relaxing factor”), prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF) (Furchgott RF & Vanhoutte PM, 1989). The endothelial cells also produce a vasoconstrictor referred to as endothelin-1. Endothelium-derived nitric oxide regulates vascular tone by releasing into the smooth muscle causing it to relax and vasodilate (Drexler, 1997). The release of NO into the smooth muscle occurs at a resting state and is additionally stimulated by many substances and conditions (Dyke, Proctor, Dietz, & Joyner, 1995). Acetylcholine, serotonin, thrombin, and shear stress can induce the release of NO from the endothelium resulting in
vasodilatation for blood vessels (Green, O'Driscoll, Blanksby, & Taylor, 1996). Acetylcholine (ACh) has two opposite actions on the smooth muscle surrounding blood vessels. Acetylcholine’s direct effect on smooth muscle cells is vasoconstriction, but when an intact endothelial lining overlies the smooth muscle cell vasodilation occurs. ACh causes the endothelial cells to release NO that quickly diffuses to the adjacent smooth muscle cells resulting in their relaxation with vasodilation of the vessel (Furchgott & Vanhoutte, 1989). When ACh or other vasodilators such as serotonin or histamine bind to endothelial cells, intracellular free calcium increases activate the enzyme nitric oxide synthase (NOS). NOS catalyzes the formation of NO from the amino acid L-arginine, then NO diffuses from the endothelium cells into the adjacent vascular smooth muscle activating guanylyl cyclase (G-cyclase), and G-cyclase forms cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP), which in turn increases intracellular cGMP resulting in smooth muscle cell relaxation as shown in Figure 1. (Drexler, 1997).

FIGURE 2.6.1
ENDOTHELIAL CELL FUNCTION
Along with the endothelial-dependent vasodilators, some agents cause smooth muscle relaxation independent of endothelial cells. For example sodium nitroprussied and nitroglycerin medications result in vasodilation by providing large sources of NO to the vascular smooth muscle activating G-gyclase and forming cGMP without endothelial cell involvement (Drexler, 1997; Gupta, et al., 2003).

2.5.1 Sheer Stress

Shear stress has been shown to play a very important role in the conditioning of endothelial cells and numerous investigators have demonstrated that shear stress (dragging frictional force created by blood flow) is one of the most powerful endothelial stimuli involved in the release of the vasodilator NO (Fischer, et al., 2005). During the cardiac cycle blood flowing against the endothelial cells that line the vascular system can stimulate the endothelial cells to release NO. This occurs at all times but, especially during exercise due to an increase in cardiac output resulting from a greater stroke volume and faster heart rate (Drexler, 1997). Increased blood volume and rate of flow places greater pressures on the endothelial cells causing an increased release of NO, thus producing greater vasodilatation (Braith, et al., 2005). The nature and magnitude of shear stress plays an important role in long-term maintenance of blood vessel structure and function required for optimal regeneration of injured endothelium cells (Traub & Berk, 1998). It has been shown that increased shear stress induced through regular aerobic exercise results in greater endothelial cell conditioning resulting in enhances to NO secretion into the smooth muscle cells (Fischer, et al., 2005; Traub & Berk, 1998). This conditioning of the endothelial cells is critical in limiting the development of atherosclerosis and endothelial dysfunction (Love & McMurray, 1996).
2.5.2 Endothelial Dysfunction

Compromised function of endothelial cells is characteristic of endothelial dysfunction, occurring when normal biochemical processes can no longer be carried out by endothelial cells (Fischer, et al., 2005). A consequence of endothelial dysfunction can be seen with the release of acetylcholine. In healthy endothelial cells, the release of acetylcholine beginning the process of NO release into the smooth muscle cells causes vasodilation. However, in conditions of endothelial dysfunction, ACh release results in vasoconstriction likely due to the reduced production of NO by dysfunctional endothelial cells (Love & McMurray, 1996). Endothelial dysfunction is associated with several cardiac diseases including systemic and pulmonary hypertension, hypercholesterolemia, diabetes, arteriosclerosis, CHF, and post HTx complications. In patients with CHF, endothelial dysfunction of coronary and peripheral arteries has been demonstrated and is associated with functional implications (Fischer, et al., 2005). A notable consequence of endothelial dysfunction results in the inability of a vessel to dilate in response to physiological stimuli, such as increases in blood flow, reflecting impaired flow-dependent vasodilation (Drexler, 1997). It has been suggested that endothelial dysfunction contributes to exercise intolerance, impaired myocardial perfusion, left ventricular remodeling in CHF, and is associated with higher incidences of hospitalization for decompensation of heart failure, cardiac transplantation, and cardiac death (Dyer & Fifer, 2003). Endothelial dysfunction appears to occur soon in both large and small coronary vessels in patients after HTx, this may contribute to the development of graft atherosclerosis, which is one of the primary problems limiting long-term survival of HTx patients. Endothelium dependent dilation appears to deteriorate over time in transplanted hearts. The blood flow response to acetylcholine is
preserved early post-transplantation and becomes impaired within three years post transplantation due to the progression of endothelial dysfunction (Fischer, et al., 2005). Endothelial function can improve and has been shown to occur in patients with CHF that perform exercise. Exercise improved endothelium-dependent vasodilation is closely correlated with achieved increases in peak oxygen uptake and exercise tolerances (Fischer, et al., 2005; Miller & Vanhoutte, 1988).

2.6 Heart Transplantation

For patients with end-stage heart failure, cardiac transplantation is the definitive treatment (Squires & Rodeheffer, 2008). Heart transplantation carries one year and five year survival rates of 83 percent and 68 percent respectively (Osada, et al., 1997). The annual mortality through 14 years of follow-up is four percent per year. Early mortality is commonly attributed to graft failure, acute rejection and infection. Late mortality is likely a result of cardiac allograft vasculopathy, malignancy, or infection (Stewart, Badenhop, Brubaker, Keteyian, & King, 2003).

Heart transplantation is a procedure in which the diseased heart in a person is replaced with a healthy heart from a deceased donor. Ninety percent of heart transplants are performed on patients with end-stage CHF (Bengel, et al., 1999). When end-stage of CHF is reached and HTx criteria is met patients are placed on the heart recipient waiting list. Since donor hearts are in short supply, patients who need a HTx go through a rigorous selection process in order to find a suitable match. Patients awaiting a heart need to be sick enough to need a new heart, yet healthy enough to receive it (Bengel, et al., 1999).

The first human heart transplant was performed by Christian Barnard at Groote Schuur Hospital, Cape Town South Africa, on December 3, 1967, and the patient survived 18 days. One
month later the second heart transplant was performed and the patient survived 20 months. The survival rates have continued to improve (DiBardino, 1999). In the 40 years following that first procedure, HTx has become a widespread therapy for end stage heart failure and more than 61,000 transplantations have been performed worldwide. In 2008 2,136 HTx were performed in the United States (Squires & Rodeheffer, 2008). Advances in surgical techniques, rehabilitation practices, and the development of the powerful immunosuppressant drug cyclosporine in the late 1980’s has led to dramatically increased survival rates, especially in the first year after HTx. Approximately 88 percent of patients survive the first year after transplant surgery, 72 percent survive for five years, the ten year survival rate is close to 50 percent, and 16 percent of heart transplant patients survive 20 years (DiBardino, 1999). After the surgery, most heart transplant recipients (about 90 percent) can come close to resuming normal daily activities, but, fewer than 40 percent return to work (Marconi, et al., 2002). With higher survival rates patients are able to resume regular physical activity and have a good quality of life (Phipps, 1997). However, it is well documented that despite HTx, their maximal aerobic power remains low and exercise tolerance is reduced when compared with healthy age matched controls (Patterson, Pitetti, Young, Goodman, & Farhoud, 2007).

2.6.1 Deinnervation of the Heart

The desired results of heart transplantation are improved survival, reduced symptoms, and increased exercise capacity. During a HT procedure, the diseased heart is removed from the patient’s body and is replaced with the heart of a donor (DiBardino, 1999). This procedure produces several conditions within the new heart. The new donor heart has now become surgically deinnervated and will no longer receive input from the autonomic nervous system (Bangel, et al., 2001; Lucia, et al., 1997). It should also be noted that the majority of heart
transplant recipients develop diastolic dysfunction (elevated filling pressures at rest and with exercise) possibly due to hypertension, acute rejection episodes, and allograft vasculopathy (disease of the blood vessels in transplanted heart), and vasodilatory capacity is impaired due to endothelial dysfunction (Bussières, et al., 1995). When the patient’s heart becomes deinnervated, heart rate increases are no longer due to activity of the autonomic nervous system, but are dependent on increases in plasma catecholamine concentration (eg, from the adrenal secretion) and peripheral demand of the working muscles (Wilson, Johnson, Haidet, Kubo, & Mianuelli, 2000). This typically results in a slow and submaximal increase in HR during exercise with a HR that continues to rise after cessation of exercise as well as a HR that falls slowly during recovery (Wilson, et al., 2000). This accounts for the reduction of peak exercise HRs by 30% to 40% of healthy age matched controls (Patterson, et al., 2007).

2.6.2 Recovery from Heart Transplantation

After recovery most patients report improved quality of life, and are able to return to activities of daily living, although exercise capacity generally remains below average. Recovery process begins with inpatient cardiac rehabilitation, during this time patients are encouraged to walk for short periods of time under the supervision of medical staff personal. Inpatient rehabilitation typically consists of low duration and intensity walking with the main goal of getting the patients mobile after surgery (Stewart, et al., 2003). In the next stage of rehabilitation, exercise is conducted three to four times per week at moderate intensities for up to 12 weeks. During this time patients can expect to see improvements in aerobic capacity ranging between 20% to 50% due to adaptations in HR and cardiac output (Stewart, et al., 2003). Resistance training is also utilized in the rehabilitation of HT patients, beginning after surgical clearance. Resistance exercises are utilized in an attempt to increase lean muscle mass and
improve bone density, thereby improving peripheral muscle capacity (Oliver, et al., 2001). This is of great importance due to muscle and bone wasting caused by time spent in CHF and side effects of immunosuppressant medications (Stewart, et al., 2003).

Following transplantation one of the chief concerns is acute rejection. Unfortunately, rejection is not the only health concern following HTx. There are several serious medical conditions that can continue to affect the HT recipient, these include infection, malignancy, hypertension, obesity, dyslipidemia, diabetes, chronic renal insufficiency, osteoporosis, and depression (Marconi, et al., 2002). After surgery, pulmonary bacterial infections are common, and late after transplantation viral, bacterial and fungal infections are a threat. Malignancy risk is high for transplant recipients. At seven years post HTx, incidence of malignancy are as high as 24% (Wilson, et al., 2000). Hypertension effects up to 95% of patients, as a possible result of immunosuppressant medications and their adverse effects on renal function (Marconi, et al., 2002). Weight gain and obesity are common following transplantation. In a study of 95 patients, BMI averaged 28± 1kg/m² at time of surgery, and one year post transplantation BMI increased by 2.1± 3.6kg/m², and weight increased an average of 6.3±8.7kg (Squires & Rodeheffer, 2008). Weight gain post HTx could be due in part to the use of corticosteroids such as prednisone. The incidence of increased blood lipids after transplantation are almost as prevalent as the development of hypertension. This could be related to renal dysfunction and diuretics prescribed for the treatment of hypertension (Squires & Rodeheffer, 2008). With the increased chances of weight gain, diabetes becomes a concern in the heart transplant recipient. It has been reported that approximately 35% of patients have developed type II diabetes up to seven years post HTx (Marconi & Marzorati, 2003). This alone is associated with a poor long term survival rates in cardiac transplant recipients. Even with the reception of a new functioning
heart, patients are at a higher risk of developing the same, if not more, of the same risk factors acquired prior to heart transplantation (Tegtbur, Pethig, Machold, Haverich, & Busse, 2003).

2.7 Exercise and Heart Transplantation

In the healthy human heart the sinus node is innervated richly by the parasympathetic and sympathetic nervous systems. These two systems regulate heart rate both at rest and during exercise (Wilson, et al., 2000). In normal individuals heart rate increases abruptly at the onset of exercise and rises progressively during exercise, and after the cessation of exercise the heart rate drops rapidly due to withdrawal of sympathetic discharge (Squires, Leung, Cyr, & Allison, 2002; Wilson, et al., 2000). This is not the case with the transplanted heart. In HTx total deinnervation persists in the human heart following HTx procedure. At rest there is a slight increase in heart rate and blood pressure, with a low to normal cardiac output when compared to healthy age matched controls (Bengel, et al., 1999). Even with these differences the donor heart remains capable of a satisfactory acute response to exercise (Johnson, et al., 1998). This is achieved through the Frank Starling Mechanism and responses to circulating hormones. During submaximal exercise stroke volume is greater than normal, but cardiac output is somewhat reduced. Peak heart rate, VO2 peak, peak stroke volume and peak cardiac output are all less than that of healthy age-matched controls (Wilson, et al., 2000). These peak values in untrained heart transplant patients remain approximately 60% to 70% of predicted values, however trained individuals late after transplantation approach aged matched norms up to approximately 95% of predicted values (Braith & Edwards, 2000). This suggests that a suitably adapted exercise prescription program following cardiac transplantation could improve quality of life and exercise tolerance in heart transplant patients (Kobashigawa, et al., 1999).
2.7.1 Aerobic Training and Heart Transplantation

Few studies have looked at the relationship between exercise and heart transplantation. In these studies ample evidence has been found suggesting that both endurance and resistance training are well tolerated in heart transplant patients (Braith & Edwards, 2000; Rajendran, et al., 2006). Endurance training has been shown to restore lean tissue, gains of cardiac function, and peak oxygen transport (Rajendran, et al., 2006). Usually exercise prescription following transplantation is commonly regulated by walking distance, pace, ventilatory response, blood pressure response, and ratings of perceived exertion (Marconi & Marzorati, 2003). These typical HT exercise prescriptions are usually limited to low volume, low intensity exercise consisting of light walking and or stationary cycling (Fink, et al., 2000).

More aggressive approaches to heart transplantation rehabilitation have been studied and suggest that long term aerobic training that is strenuous in nature can improve exercise tolerance and quality of life in heart transplant patients (Pokan, et al., 2004; Rajendran, et al., 2006; Warburton, et al., 2004). The data suggests that not only does long term training significantly improve cardiocirculatory and peripheral function, but may also enable HT patients to reach physical fitness levels similar to those of normal age-matched subjects (Auerbach, et al., 1999; Richard, et al., 1999).

2.7.2 Maximal Testing and Heart Transplantation

Studies looking at responses to exercise in heart transplant patients often use VO₂ to gauge progress. A study conducted by Richard and colleagues (1999) looked at physical work capacity in 14 endurance trained heart transplant recipients. In this study both VO₂ and heart rates were measured on cycle ergometry and treadmill protocols. This study found that treadmill testing resulted in higher values of VO₂max and HRmax compared to cycle ergometry test
(Richard, et. al. 1999). This may have been due to previous training of participants as endurance runners. For this reason cycle ergometry will be used to test VO$_{2\text{max}}$ in our participant due to his prior cycling experience and specificity of training.

### 2.8 Summary and Conclusions

CHF is the final manifestation of nearly every cardiac disease, and the final treatment option for end stages of CHF is HTx. It has been documented HTr will see improvements in quality of life shortly after HT, but PCW does not exceed 60% of the value for healthy age-matched controls (Patterson, et al., 2007). Exercise limitations following HTx are likely due to chronotropic incompetence and peripheral limitations. The complete deinnervation for the donor heart and muscle deconditioning are strongly linked to exercise intolerance following HTx. Chronotropic competence can return to pre HT levels with long term physical activity (Richard, et al., 1999). Improvements to endothelial function and peripheral conditioning are strongly correlated to increases in exercise capacity following HT (Pokan, et al., 2004). The literature review presented here could lead to a conclusion that patients with HT would benefit from long term exercise programs in an attempt to improve peripheral function thus reducing exercise limitations following HTx.
CHAPTER 3

METHODOLOGY

3.1 Case Summary

The participant in this study is a 39 year old male who suffered an acute myocardial infarction after a cycling road race. The subject underwent emergency coronary bypass surgery, and later went into CHF. After a month in CHF the subject underwent heart transplant surgery on August 5, 2005 receiving a donor heart from a 19 year old male, and participated in a previous exercise study at Wichita State University (Patterson, et al., 2007). Prior to the participant’s surgery he was a highly active athlete with an aerobic capacity equivalent to a professional cyclist. He completed the Army Physical Fitness Test six weeks prior to his AMI, achieving 294 points out of a possible 300, including the two mile run aerobic fitness test in a time of 12 min 43 sec, equivalent to a predicted $\text{VO}_{2\text{max}}$ of 58 mL·kg$^{-1}$·min$^{-1}$ (Army, 1992). His post surgery rehabilitation was more active than a traditional cardiac rehabilitation programs.

Day 1: started walking

Day 11: released from hospital (August 15$^{\text{th}}$)

Day 13: cardiac rehab began consisting of walking for 45 min at 3 mph with typical post-surgery restrictions and maintaining a HR $< 140$ bpm

Day 27: permitted to jog-walk-jog-walk or cycle w/ same HR restrictions, but without time limitations (September 1$^{\text{st}}$)

Day 31: HR restriction increased to 150 bpm (September 5$^{\text{th}}$)

Day 46: HR restriction increased to 160 bpm and all restrictions were lifted barring chest exercises (September 20$^{\text{th}}$)
Day 47: (September 21st) all restrictions were lifted and he has been exercising at high intensities and durations (in excess of 60 min) since, consistently cycling 50 miles per session, 2-3 times per week. Follow-up testing was completed at six and twelve months post HT surgery. Overall health and functional capacity had significantly improved and he was fully cleared by his team of physicians to participate in any and all forms (including maximal exertion) of physical activity and exercise testing.

3.2 Methods

Maximum total body oxygen consumption ($\text{VO}_{2\text{max}}$) tests was determined during a symptom-limited graded exercise test on an electronically-braked cycle ergometer (Ergomed, Siemens, Erlangen, Germany), commencing at 25 W and increasing by 25 W.min$^{-1}$ until the patient could no longer continue to pedal at a minimum cadence of 60 revolutions per minute. Heart rate and ECG were measured by 12-lead electrocardiographic (Marquette, USA) monitoring throughout exercise and recovery. Blood pressure was measured and recorded by research personnel using a mercury sphygmomanometer before exercise, during exercise (every two minutes) at maximum exertion, and several times throughout recovery. The Borg rating of perceived exertion (RPE) (Borg, 1973) was recorded at the end of each minute, prior to the increase of resistance (25W). 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 (Han Rudolph) leading to a mixing chamber (RFU 1975), the PhysioDyne Instrument metabolic cart with a Max II oxygen analyzer (# Pm1111E), and a carbon dioxide analyzer (# 1r1507) was used. The gas analyzer and flow meter was calibrated according to the manufacturer’s recommendations before each test. The gas meters were calibrated against gases
of known concentrations before each test. Oxygen uptake (VO₂) and carbon dioxide output
(VCO₂) was determined from the measurement of oxygen and carbon dioxide concentration in
the inspired and expired air.
CHAPTER 4

RESULTS

Prior to the AMI this competitive cyclist participated in an aerobic power test (3.1 mile in 7.6 min) and an anaerobic power test (0.2 mile) as part of his normal training routine (Table 4.1.1).

TABLE 4.1.1.
EXERCISE TESTING RESULTS PRIOR TO CARDIAC EVENT

<table>
<thead>
<tr>
<th></th>
<th>$HR_{\text{max}}$ (bpm)</th>
<th>Predicted $\text{VO}_{2\text{max}}$ (ml·kg$^{-1}$·min$^{-1}$)</th>
<th>Avg. Work Cap (Watts)</th>
<th>Peak Power (Watts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle test</td>
<td>171</td>
<td>45.3</td>
<td>344</td>
<td>1010</td>
</tr>
<tr>
<td>Time (Min.)</td>
<td>Predicted $\text{VO}_{2\text{max}}$ (ml·kg$^{-1}$·min$^{-1}$)</td>
<td>Population Avg. (ml·kg$^{-1}$·min$^{-1}$)</td>
<td>Rating</td>
<td></td>
</tr>
<tr>
<td>Army Run Test</td>
<td>12.7</td>
<td>57.3</td>
<td>41.8</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

The results of both tests are considered superior scores (Power to Weight Ratio of 10.4 W/kg) (Faria, Parker, & Faria, 2005). The maximal HR achieved was 171 beats per minute (bpm). Two weeks later he completed the Army Physical Fitness Test achieving 294 points, out of a possible 300, including the 2 mile run Aerobic Fitness Test in a time of 12 minutes 43 seconds; equivalent to a predicted $\text{VO}_{2\text{max}}$ of 58 mL·kg$^{-1}$·min$^{-1}$ (Army, 1992). Peak PWC ($\text{VO}_2$ and workload) and peak HRs at 6 and 12 months are presented in Table 4.1.2.
<table>
<thead>
<tr>
<th>Cardiopulmonary Exercise Test results 6 months post transplant</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>VO(<em>2)(</em>{\text{max}}) (ml·kg(^{-1}·\text{min}^{-1}))</td>
<td>4.5</td>
<td>33.8</td>
<td>36.7</td>
<td>92.2</td>
</tr>
<tr>
<td>VO(_2) (ml·min(^{-1}))</td>
<td>1479</td>
<td>3316</td>
<td>3606</td>
<td>92</td>
</tr>
<tr>
<td>VE (l/min)</td>
<td>42.87</td>
<td>133.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freq (br·min(^{-1}))</td>
<td>26</td>
<td>63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>115</td>
<td>165</td>
<td>171</td>
<td>97</td>
</tr>
<tr>
<td>Workload (W)</td>
<td>25</td>
<td>250</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiopulmonary Exercise Test results 12 months post transplant</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>VO(<em>2)(</em>{\text{max}}) (ml·kg(^{-1}·\text{min}^{-1}))</td>
<td>4.9</td>
<td>44.2</td>
<td>36.5</td>
<td>121.2</td>
</tr>
<tr>
<td>VO(_2) (ml·min(^{-1}))</td>
<td>471</td>
<td>4292</td>
<td>3550</td>
<td>121</td>
</tr>
<tr>
<td>VE (l/min)</td>
<td>10.06</td>
<td>109.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freq (br·min(^{-1}))</td>
<td>17</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>102</td>
<td>163</td>
<td>170</td>
<td>96</td>
</tr>
<tr>
<td>Workload (W)</td>
<td>25</td>
<td>275</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VO\(_2\)\(_{\text{max}}\) was 92% and 121% of predicted and HR was 97% and 96% of the maximum HR measured prior to his AMI.
CHAPTER 5
DISCUSSION

The major factors limiting physical work capacity (PWC) following heart transplantation are chronotropic incompetence, left ventricular dysfunction, lung limitations, and muscle limitations (Braith & Edwards, 2000; Marconi & Marzorati, 2003; Niset, Hermans, & Depelchin, 1991; Toledo, Pinhas, Aravot, Almog, & Akselrod, 2002). Other factors that may influence exercise capacity after transplantation include prolonged cold ischemia of the allograph, acute rejection episodes, muscle degeneration due to cyclosporine therapy, weight gain due to prednisone therapy, occult ischemia due to transplant vasculopathy, and peripheral deconditioning, resulting from long periods of time spent in heart failure and immunosuppressant drug therapy.

At the time of the post-transplant PWC evaluation, neither left ventricular dysfunction (i.e., cardiac allograft vasculopathy or oxidative stress) nor lung limitations (i.e., diffusion abnormalities) had been detected by his medical team. This suggests that chronotropic incompetence (i.e., central) and muscle limitations (i.e., peripheral) would remain the major limitations to PWC following HTx.

The participant underwent complete denervation of the heart. The loss of autonomic innervation of the SA node has been reported to reduce peak HR response during exercise by 30-40% of healthy controls (Mancini, et al., 1991). It was expected that exercise HR response to reactivity of the sympathetic nervous system would be limited to secretions of epinephrine and norepinephrine from the adrenal medulla (Wilson, et al., 2000). Studies examining responses to progressive exercise in HTRs suggest that peak HR is significantly higher in healthy controls compared to HTRs (~66% of predicted) and that PWC is related to HR at peak exercise (Niset, et
al., 1991). Interestingly, results of the post-HT exercise tests at six and twelve months show that the participant has a good relationship between HR and the increasing workload as seen in (figure 5.1.1.)

**FIGURE 5.1.1.**

**HEART RATE RESPONSE TO GRADED EXERCISE TESTS AT SIX AND TWELVE MONTHS POST TRANSPLANTATION VERSUS THE EXPECTED BLUNTED HEART RATE RESPONSE**

In addition, the maximal HRs achieved at 6 and 12 months (165 and 163 bpm) were close (97% and 96%) to his previously reported maximal HR (171 bpm). Not surprisingly, the authors were unable to identify any other reported HT case with a similar maximal HR response within six months of surgery. The participant’s medical team can provide no explanation for this response to exercise. Unfortunately, there is no literature to explain how a well-trained athlete will react to exercise shortly after orthotopic HTx. There are reports however, that HTRs who are
compliant during strenuous long term endurance training programs, can achieve peak HR and VO\textsubscript{2peak} values late after transplantation that are similar to those reported in this case (Braith, et al., 2005; Richard, et al., 1999).

Similar HR response to exercise can be seen in patients who have experienced reinnervatoin of the sinus node. In a study by Wilson et al. (2000) 13 subjects six months post transplant were tested for reinnervation. Out of these 13 patients none had experienced partial or complete reinnervation six months post HT (Wilson, et al., 2000). In a study conducted by Bengel et al. (2000) 20 HTRs were assessed for reinnervatoin and no evidence of reinnervation was found earlier than 18 months after HTx. In most cases studies find that patients that experience complete reinnervation are in the range of three to 15 years post HTx, and state that absolute complete restoration was not found till 15 years post HTx (Bangel, et al., 2001; Bengel, et al., 1999; Marconi, et al., 2002; Pokan, et al., 2004; Wilson, et al., 2000). It should also be noted that the age of the donor heart and recipient play a role in the rate of reinnervation. Two studies suggested that a younger donor heart of 31±13 years and a recipient age of 56±12 years resulted in reinnervation rates of 4.4±1.7 years (Bangel, et al., 2001; Bengel, et al., 1999). Even with this correlation of age of donor and recipient, reinnervation is still occurring no earlier than 30 months. It is suggested that even with partial or complete reinnervatoin, a higher peak exercise HR and larger HR reserve do not result in a better aerobic exercise capacity, but exercise capacity was largely related to improved performance of peripheral muscles that allows for improved cardiac functioning (Pokan, et al., 2004).

These results were similar to those reported by Richard and colleagues (Richard, et al., 1999). PWC was measured in 14 endurance trained HTRs. Participants in this study reported 4 ± 1 hours per week of endurance type physical activity (primarily running) for 36 ± 24 months
prior to testing. PWC evaluations occurred 43 ± 12 months following HTR. Peak exercise responses for the participant in the present study and in those reported by Richard et al. (1999) were similar for peak heart rate (165 and 163 bpm vs. 159 ± 16 bpm) and VO$_{2\text{peak}}$ (33.8 and 44.2 ml•kg$^{-1}$•min$^{-1}$ vs. 32.5 ± 7.8 ml•kg$^{-1}$•min$^{-1}$), respectively. Participants in the study by Richard et al. (1999) had an average age of 43 ± 9 years, and had been training regularly for 36 ± 24 months prior to testing and PWC evaluations occurred 43 ± 12 months following HT. In comparison, the participant in this study was 39 years old and had been cleared from all training restrictions only three months prior to the first PWC evaluation which took place six months following HT. Interestingly, seven of the 14 HTR participants of the Richard et al. study took part in an endurance relay running race where electrocadiograms were recorded. For all but one of the patients, the maximum HR achieved during the race was equivalent or higher than the maximum HR reported for their exercise testing, with a mean that was equivalent to 101% of the maximum predicted HR. Results of the case study presented here support those reported by Richard et al. (1999) concluding that maximum HR cannot be a limiting factor to the exercise tolerance of HTRs and chronotropic competence can return to normal. It is possible that the many years of maintaining a high fitness level prior to the AMI may have assisted this individual to achieve near normal chronotropic competence in a much shorter time period (Six months vs. 36 ± 24 months).

Muscle atrophy and deconditioning are other factors that may limit PWC immediately following HT (Bussières, et al., 1995). Peak oxygen consumption decreases ~26% within the first one to three weeks of bed rest (Braith, et al., 2005), exacerbating the poor exercise capacity and cardiac functioning. Along with prolonged periods of being sedentary prior to surgery, the immunosuppressive therapy (Cyclosporine A) issued after transplantation has been shown to
alter muscle metabolism (Hokanson, et al., 1995). Hokanson et al. (1995) showed that muscle mitochondrial respiration is significantly decreased in rats that are given Cyclosporine A, reducing their tolerance to exercise. Endothelial dysfunction has been consistently reported after HT (Geny, Piquard, Lonsdorfer, & Haberey, 1998), which is characterized by a decreased nitric oxide (NO) bioavailability and an increased endothelin-1 synthesis and characterized by an impaired flow-mediated dilatation (Andreassen, Gullestad, Holm, Simonsen, & Kvernebo, 1998). Patients with endothelia dysfunction are more likely to experience hypertension and decrease tolerance to exercise (Geny, et al., 1998). Beneficial effects of exercise training have been related to an improvement in the HTRs endothelial function. Comparatively, studies assessing exercise capacity in patients with CHF have suggested that the inadequate cardiac function leads to reduced skeletal muscle blood flow, deconditioning, and skeletal muscle atrophy which contributes to the profound exercise intolerance in CHF, more so than central mechanisms (Williams, et al., 2007). The importance of the endothelium in maintaining a healthy vasculature has been increasingly recognized, particularly with respect to NO and its mediated functions. In addition to regulating blood flow to skeletal and cardiac muscle at rest and during elevated metabolic demand, NO also possesses a number of antiatherogenic properties, including inhibition of platelet and monocyte adhesion to the endothelium of vessel walls and inhibituion of cellular transmigration, vascular smooth muscle proliferation and LDL oxidation (Harrison, 1997). A number of studies indicate that NO release contributes to skeletal muscle vasodilation during exercise (Dyke, et al., 1995; Green, et al., 1996). Additionally, exercise training over time improves NO-mediated responses (Laughlin, Amann, Thorne, & Pollock, 1994; Wang, Wolin, & Hintze, 1993) and upregulates NO-synthase expression in
animals (Sessa, Pritchard, Seyedi, Wang, & Hintze, 1994). This suggests that any preservation of endothelial function would be expected to prevent the progression of vascular disease.

The total duration the participant was in CHF was less than four months and not years (which is often the case and leads to severe deterioration). The rate at which endothelial dysfunction occurs is unknown, and many factors will play a role in this event making it difficult to determine. But it is likely that this individual had much of his endothelial function intact following transplantation do to a combination of the individuals’ young age, long history of being physically active and the short time spent in chronic heart failure. Together these helped him to achieve a good relationship between HR and workload.

The limiting factor of this individual’s exercise capacity was likely due to peripheral function (vascular and muscular). This was a result accumulated from four months of CHF, the strain of HTx, and possibly the effects of the immunosuppressive therapy leading up to the exercise testing. Impaired vascular function in response to exercise may contribute to impaired exercise tolerance. Interventions, which improve endothelial function, including a more rapid transition from CHF to heart transplant should be considered cardioprotective. To reverse exercise limitations rehabilitation should focus efforts on endothelial and muscular limitations. There have been several studies looking at CHF and exercise that have shown an increase physical activity can result in improved functional capacity and endothelial function (Belardinelli, et al., 1999; Coats, 1999; Maiorana, et al., 2000; Shephard, et al., 1998). In an exercise study by Belardinelli et al. (1999) functional capacity was assessed in 99 CHF patients following a long term (1 year) moderate exercise program. Belardinelli et al. (1999) found improvements in peak oxygen uptake and ventilatory threshold as high as 30% compared to the control group. More importantly these improvements in functional capacity remained stable.
throughout the year and did not decline. It was also noted that the improvements in exercise capacity following training were related to peripheral adaptations and muscular conditioning (Belardinelli, et al., 1999). Maiorana et al. (2000) studied vascular function in 14 male CHF patients that underwent an eight week circuit training program consisting of resistance training and stationary cycling. The results from Maiorana et al. (2000) suggested that aerobic and resistance training improved endothelial dependent and independent vascular function. In this study by Maiorana et al. (2000) forearm blood flow was measured to determine increases in vasodilatation, it was shown that participants that completed the eight week program had an increase in forearm blood flow as high as 20%. It should also be noted that VO$_{2\text{peak}}$ was measured before and after the eight week exercise program and there was an average increase of 13% in VO$_{2\text{peak}}$. The data suggest that exercise both aerobic and resistance training can result in a higher functional capacity for CHF patients as well as improvements in endothelial and muscular conditioning (Belardinelli, et al., 1999; Maiorana, et al., 2000). The data from CHF exercise studies suggest marked improvement in functional capacity suggesting that HT patients could gain similar improvements following long-term exercise programs. Unfortunately, the number of exercise studies involving HTx are much less than CHF, but these HT studies do show similar improvements when compared to studies performed on CHF patients.

This is an extremely unique case study dealing with an elite athlete who underwent HTx and there is limited literature to support the outcomes of this case. In an online search for articles studying HTx and exercise only 110 results were identified to the date, of those 110 only 15 were involved in sub maximal or maximal exercise testing in HT patients. Furthermore, maximal exercise was assessed in only one study with multiple subjects, and case studies involving exercise and HTx were conducted late post transplantation, up wards of 10 years.
No other studies assessed how an elite athlete may respond to exercise shortly after HTx. In conclusion this case evaluation suggests exercise limitations following HTx related to peripheral functioning. Further testing of this case study and other subjects with similar experiences is needed to aid in the determination of limiting factors effecting exercise after HTx.
BIBLIOGRAPHY


