Exercise limitations in a competitive cyclist twelve months post heart transplantation

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Abstract
It has been well documented that for heart transplant recipients (HTrecipient) post transplantation exercise capacity does not exceed 60% of healthy age-matched controls. Few studies have been undertaken to determine the cause of exercise limitations following heart transplantation (HT) for an elite athlete. Participant was a 39 year old elite male cyclist who suffered an acute myocardial infarction after a cycling race and received a heart transplant (HT) four months later. Six weeks prior to his AMI fitness testing was completed and a predicted VO2max of 58 mL·kg⁻¹·min⁻¹ and HRmax of 171 bpm was achieved. The participant underwent maximal exercise testing 6 and 12 months post transplant to determine exercise limitations. His results 6 and 12 months post transplant were a VO2max of 33.8 and 44.2 mL·kg⁻¹·min⁻¹ respectively, and a HRmax that was 97% and 96% of HRmax measured. The participant showed an increase in both HRmax and VO2max 12 months post HT compared to previous testing. Results suggest that the limiting factors to exercise following HT are likely due to peripheral function, which became diminished as a result accumulated from 4 months of congestive heart failure, the strain of HT, and 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 HT.

Key words: Transplant rehabilitation, orthotopic transplant, aerobic capacity.

Introduction
The heart transplant recipient (HTrecipient) 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 a HT are trading the medical management of one chronic disease for another. For example, 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 et al, 1995). The triple drug immunosuppressive regimen (cyclosporine, prednisone and azathioprine) 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 organ rejection. These and other adverse events have been shown to be positively effected by chronic bouts of physical activity (Braith and Edwards, 2000).

Changes in cardiac and 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 et al, 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 healthy age-match controls and peak HR is significantly reduced (66% of predicted) (Marconi and 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 (Marconi and Marzorati, 2003).

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.

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. Prior to the participant’s surgery he was a highly active endurance athlete that competed regionally and nationally in triathlons and was a CAT 3 cyclist. Leading up to the AMI his fitness and lifestyle would suggest a very healthy individual. Training records for the year prior to the cardiac event suggest an average of one hour of aerobic conditioning per day, with 147 hours logged on his cyclocr.computer (Cat Eye). Six weeks prior to his AMI he completed the Army Physical Fitness Test achieving 294 points out of a possible 300, including the two mile run aerobic fitness test in a time of 12 min 43 sec, equiva-
lent to a predicted VO\textsubscript{2max} of 58 mL·kg\textsuperscript{-1}·min\textsuperscript{-1} (Army, 1992). Additionally, he participated in an aerobic power test (3.1 miles in 7.6 min, with an average work capacity of 344 Watts) and an anaerobic power test (0.2 miles with a peak power output of 1010 Watts) as part of his normal training routine. The results of both tests are considered superior scores (Power to Weight Ratio of 10.4 W/kg) (Faria EW et al., 2005). The maximal HR achieved was 171 beats per minute (bpm). At six months post transplantation he participated in an exercise study at Wichita State University. Further details of the individual and aerobic capacity assessment are described by the authors in an earlier publication (Patterson et al., 2007).

The participant’s post surgery rehabilitation was more active than a traditional cardiac rehabilitation program. Cardiac rehab started 13 days after transplantation by walking 45 minutes at a peak of 3 mph with the normal restrictions due to the surgery (no upper body exercises by walking 45 minutes at a peak of 3 mph with the normal restriction increased to 150 beats per minute). On day 47 he was allowed to jog-walk-jog-walk or cycle keeping to the same HR restrictions due to the surgery (no upper body exercises) by walking 45 minutes at a peak of 3 mph with the normal HR below 140 beats per minute for two weeks). At 27 days post surgery, he was permitted to jog-walk-jog-walk or cycle keeping to the same HR restrictions, but with no time limitations. On day 31 the HR restriction increased to 150 beats per minute. On day 47 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.

Testing was completed at six (results presented in Patterson et al., 2007) and twelve months post HT surgery. At six months 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.

**Methods**

Maximum total body oxygen consumption (VO\textsubscript{2max}) tests was determined during a symptom-limited graded exercise test on an electronically-braked cycle ergometer (Ergomed, Siemens, Erlangen, Germany), commencing at 75 W and increasing by 25 W every 3 minutes 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 (# ir1507) was used. The gas analyzer and flow meter was calibrated according to the manufacturer’s recommendations before each test. Resting measures were collected for seven minutes while sitting on the bike without pedalling following 10 minutes of sitting comfortably in a chair.

**Results**

Maximal PWC (VO\textsubscript{2} and workload) and HRs at 6 and 12 months are presented in Table 1. At 6 and 12 months, VO\textsubscript{2max} was 92% and 121% of predicted and HR was 97% and 96% of the maximum HR measured prior to his AMI. Workload increased from 250 W at six months to 275 W at 12 months. This is only a 25 W increase, however time to exhaustion increased by 5 min, at six months he stopped at 21 min (1 min into the eighth stage) and went to 26 min at 12 months (stopped at the completion of stage 9). Relative VO\textsubscript{2} increased from 3316 mL·min\textsuperscript{-1} at six months to 4294 mL·min\textsuperscript{-1} at 12 months with no significant change in body weight (98.1 kg and 97.3 kg respectively).

**Discussion**

This is an extremely unique case study dealing with an elite athlete who underwent HT and there is limited literature to support the outcomes of this case. In an online search for articles studying HT 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 HT were conducted late post transplantation, upwards of 10 years. No other studies assessed how a highly active individual may respond to exercise shortly after HT.

In the healthy human heart the sinoatrial node is richly innervated 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 graded exercise, and after the cessation of exercise the heart rate drops rapidly due to the reduction of sympathetic discharge.

### Table 1. Cardiopulmonary exercise test results at 6 (and 12) months post-transplant.

<table>
<thead>
<tr>
<th></th>
<th>Maximum achieved</th>
<th>Maximum predicted</th>
<th>% predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO\textsubscript{2} (mL·kg\textsuperscript{-1}·min\textsuperscript{-1})</td>
<td>33.8 (44.2)</td>
<td>36.7 (36.5)</td>
<td>92.2 (121.2)</td>
</tr>
<tr>
<td>VO\textsubscript{2} (mL·min\textsuperscript{-1})</td>
<td>3316 (4292)</td>
<td>3606 (3550)</td>
<td>92 (121)</td>
</tr>
<tr>
<td>VE (L·min\textsuperscript{-1})</td>
<td>133.3 (109.4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>VE/VO\textsubscript{2} (L/L)</td>
<td>41.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>VE/VCO\textsubscript{2} (L/L)</td>
<td>34.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Freq (br·min\textsuperscript{-1})</td>
<td>63 (69)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>165 (163)</td>
<td>171 (170)</td>
<td>97 (96)</td>
</tr>
<tr>
<td>Workload (W)</td>
<td>250 (275)</td>
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healthy age matched controls (Bengel et al., 1999). Even partial reinnervation possible in 1 to 2 years and complete case with the transplanted heart. In HT total denervation (Squires et al., 2002; Wilson et al., 2000). This is not the case with the transplanted heart. In HT total denervation persists in the human heart following HT procedure with partial reinnervation possible in 1 to 2 years and complete reinnervation in 15 years (Bengal et al., 2001). 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 catecholamines.

Due to the blunted heart rate response stroke volume during submaximal exercise 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 (Brath and 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).

There are only a few studies that have assessed the relationship between exercise and heart transplantation and these studies suggest that both endurance and resistance training are well tolerated in heart transplant patients (Braith and Edwards, 2000; Rajendran et al., 2006). Endurance training has been shown to restore lean tissue, increase cardiac function, and peak oxygen transport (Rajendran et al., 2006). Usually exercise prescription following transplantation is regulated by walking distance, pace, ventilatory response, blood pressure response, and ratings of perceived exertion (Marconi and Marzorati, 2003). These typical HT exercise prescriptions are 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).

The individual presented here 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 for 3 to 15 years following HT. (Mancini et al., 1991). It was expected that exercise HR response to increased activity 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 HTrecipients suggest that peak HR is significantly higher in healthy controls compared to HTrecipients (~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 6 and 12 months show that the participant has a good relationship between HR and the increasing workload as seen in Figure 1.

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 same time range. There is no literature to explain how an endurance athlete will adapt to exercise shortly after orthotopic HT. As discussed in our previous article, there are reports of HTrecipients that enter strenuous long-term endurance training programs and eventually achieve peak HR and VO2peak values similar to those reported in this case (Braith et al., 2005; Richard et al., 1999). Participants in the study by Richard et al. (1999) had peak HRs of 159 ± 16 bpm with 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.

Figure 1. Heart rate responses to graded exercise tests at 6 and 12 months post heart transplantation versus the expected blunted heart rate response.

It is possible that patients in the Richard et al. study benefited from partial to complete reinnervation of the sinus node, which would provide an improved response to increasing workload, maximum workload, and recovery. 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. (2001) 20 HTrecipients were assessed for reinnervation and no evidence of reinnervation was found earlier than 18 months after HT. In most cases studies find that patients that experience complete reinnervation are in the range of three to 15 years post HT, and state that absolute complete restoration was not found until 15 years post HT (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 sug-
suggested that a younger donor heart of $31 \pm 13$ years and a recipient age of $56 \pm 12$ years resulted in reinnervation rates of $4.4 \pm 1.7$ 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 reinnervation, 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).

The case study presented here supports those reported by Richard et al. (1999; 2007) concluding that maximum HR cannot be a limiting factor to the exercise tolerance of HT recipients and chronotropic competence can return to normal. The 6 and 12 month follow-ups suggest that this can return at a more rapid pace than once thought. 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 (6 months vs. $36 \pm 24$ months).

It is likely that this individual was limited due to his peripheral dysfunctions rather than central mechanisms. Muscular deconditioning leading to a cachectic state can contribute to the reduced exercise capacity immediately following HT (Anker et al., 1997; Bussières et al., 1995). Peak oxygen consumption decreases $\sim 26\%$ within the first one to three weeks of bed rest (Braith et al., 2005), exacerbating the poor exercise capacity and cardiac functioning. The effects of long durations spent in congestive heart failure (CHF) with a sedentary lifestyle prior to surgery combined with the immunosuppressive therapy (Cyclosporine A) issued after transplantation alter muscle metabolism (Hokanson et al., 1995). Hokanson et al. (1995) showed that muscle mitochondrial respiration is impaired in rats that are given Cyclosporine A. Additionally, muscle oxidative function has been shown to be reduced while in a state of CHF, and is widely accepted that this is a major cause of exercise intolerance in this patient group (Williams et al., 2007). Endothelial dysfunction has been consistently reported after HT (Geny et al., 1999), 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 et al., 1998). Patients with endothelial 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 HT recipients 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 inhibition 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 et al., 1994; Wang et al., 1993) and upregulates NO-synthase expression in animals (Sessa et al., 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. Although this was not assessed, it is not likely that the lifelong dedication to fitness attenuated the physiological effects of CHF, in fact Selig et al. (2004) showed peripheral blood flow reductions after three months. It is possible though that the CHF related impairments may have been more severe if the individual had lived a sedentary lifestyle. We hypothesize that the participant was affected by the period of CHF, but had much of his endothelial function intact following this period and the transplantation due to a combination of the individual’s young age, long history of being physically active and the short time spent in congestive heart failure.

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 HT, 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 VO2peak was measured before and after the eight week exercise program and there was an average increase of 13% in VO2peak. 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 conditions (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 HT is much less than CHF, but these HT studies do show similar improvements when compared to studies performed on CHF patients.

In conclusion this case evaluation suggests exercise limitations following HT are 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 affecting exercise after HT.

Conclusion

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 HT, and possibly the effects of the immunosuppressive therapy leading up to the exercise test.

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.

References


Key points

- Physical work capacity following heart transplantation is not limited by cardiac denervation.
- Heart transplant rehabilitation should focus efforts on endothelial and muscular limitations.

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