Quadriceps muscle strength and body mass index are associated with estimates of physical activity post-heart transplantation

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Abstract

When we stop and think about what is truly important in life, most of us would say that it is quality time spent with family and friends and the ability to do what we enjoy. This is also the primary goal for those with end-stage heart failure (HF) fortunate enough to get a second chance at life through heart transplantation (HTx). Management post-HTx is complex with many factors including lifestyle playing a role. Some people get a little more time, others get decades, but how is this extra time spent? Some HTx recipients have completed events such as an ironman triathlon, which is so mentally and physically gruelling that even the majority of people who haven’t had a HTx would never attempt this. These are exceptional cases, but how physically active are the majority of HTx recipients? We know that in the general population many people are not physically active enough to gain health benefits and that there is a worldwide obesity epidemic, yet little is known about levels of physical activity in the HTx population.

Whilst exercise capacity improves post-HTx, it remains unclear how physically active HTx recipients are once they have recovered post-surgically. Just because someone has an improved exercise capacity post-HTx, they may not have an improved level of physical activity. The aims of this thesis are to (1) describe physical activity levels and (2) identify factors which may be associated with levels of physical activity post-HTx. A prospective observational cross-sectional study was conducted at a single centre HTx outpatient clinic. Medically stable adult HTx recipients ≥6 months post-HTx were recruited. Exclusion criteria were left ventricular ejection fraction (LVEF) less than 50% by any imaging modality, a rejection episode within the past two months or any injury or illness that could be reasonably expected to reduce mobility. Physical activity level (PAL) and average daily time spent performing at least moderate intensity activity (≥3 metabolic equivalents (METs)) were estimated using a multi-sensor device (SenseWear Pro3). Factors investigated were demographic (age, sex, body mass index (BMI), time post-HTx and reason for HTx), corticosteroid use, exercise capacity (six minute walk distance (6MWD)) and quadriceps muscle strength corrected for body weight (QS%). Eighty-seven HTx recipients were recruited between February 2013 and August 2014. Of these, 12 were excluded. Therefore, seventy-five participants, (20 female, 26.7%) and time post-HTx 9.2 ± 7.0 years (0.5 to 26 years) were included.
Twenty-seven (36%) were classified as extremely inactive (PAL <1.40); 26 (34.6%) sedentary (PAL 1.40 to 1.69) and 22 (29.3%) active (PAL ≥1.70). Multivariable analysis showed greater QS% (β=0.004 (0.002 to 0.006), p=0.001) to be independently associated with increased PAL. For increased time ≥3 METs, both greater QS% (β=0.0164 (0.003 to 0.029), p=0.014) and lower BMI (β=-0.0626 (-0.115 to -0.0099), p=0.021) were independently associated. These results highlight that quadriceps muscle strength is an important factor with regard to physical activity however causation cannot be stated in this observational study. Additionally, regular participation in physical activity can contribute to weight maintenance, and physical inactivity along with excessive energy intake often results in increased BMI and obesity.
Statement of Originality

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

Signed_____________________________

Rebecca Kelly
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List of abbreviations

ACEI, angiotensin-converting enzyme inhibitor
AEE, active energy expenditure
ARB, angiotensin receptor blocker
ARNI, angiotensin receptor neprilysin inhibitor
BMI, body mass index
BP, blood pressure
CAD, coronary artery disease
CAV, cardiac allograft vasculopathy
CO, cardiac output
CR, cardiac rehabilitation
CRT, cardiac resynchronization therapy
CVD, cardiovascular disease
DLW, doubly labelled water
EE, energy expenditure
HF, heart failure
HFrEF, heart failure with reduced ejection fraction
HTx, heart transplantation
HTN, hypertension
ICD, implantable cardioverter-defibrillator
IHD, ischaemic heart disease

ISHLT, international society of heart and lung transplantation

LVEF, left ventricular ejection fraction

LTx, lung transplantation

MAP, mean arterial pressure

MET, metabolic equivalent

MRA, mineralocorticoid/aldosterone receptor antagonist

NYHA, New York Heart Association

PAL, physical activity level

QS%, quadriceps muscle strength corrected for body weight

QoL, quality of life

RAAS, renin-angiotensin-aldosterone system

RCT, randomised controlled trial

REE, resting energy expenditure

SWA, SenseWear Pro3 armband

6MWD, six minute walk distance

6MWT, six minute walk test

SNS, sympathetic nervous system

TEE, total energy expenditure

T2DM, type 2 diabetes mellitus

̇V̇O₂peak, peak oxygen uptake

WHO, world health organisation
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Related publications and presentations

Peer reviewed publication included in this thesis (Chapter 3)

The candidate’s contribution to this co-authored paper is outlined at the front of the relevant chapter along with the contributions of the co-authors. The bibliographic details for this paper including all authors are:


Wolters Kluwer Health, Inc. was contacted by the corresponding author regarding the inclusion of this published paper as part of this thesis and this request was granted.

Conference abstracts based on this thesis


Chapter 1. Introduction

Heart failure (HF) is the number one cause of death in the Western world\(^4\). Approximately 480 000 Australians have HF\(^5\). Australia-wide, HF contributes to more than 147 000 hospital admissions annually and an estimated current annual direct health care cost of $2.6 billion\(^5\). Despite advances in medical management, the 5 year survival in people with end-stage HF is only 20%\(^6,7\). HF is a clinical syndrome resulting from a structural and/or functional cardiac abnormality that impairs the ability of the ventricle(s) to fill with, or eject, blood\(^2\). This causes cardiac output (CO) to be reduced and/or intra-cardiac pressures to be elevated at rest or during stress\(^2\). Symptoms including breathlessness, particularly on exertion, and fatigue may be accompanied by signs of elevated jugular venous pressure, pulmonary crackles and peripheral oedema\(^2\).

Heart transplantation (HTx) is now a well-accepted treatment for end-stage HF\(^8\). Despite the number of people with end-stage disease increasing over the past 20 years, the rate of HTx has remained relatively steady due to improvements in medical management of HF and limited donor organ availability\(^9\). Since the first successful human to human HTx was performed by Dr Christiaan Barnard in South Africa in 1967\(^10\), there have been considerable advances and survival has significantly improved worldwide\(^9,10\). During the early HTx era, 1 and 2 year survival rates were only 18% and 11% respectively\(^11\). Many HTx recipients died due to complications secondary to acute graft rejection\(^12\). While survival rates improved from 1970 to 1980, it was not until the introduction of cyclosporin A in the early 1980s that the incidence of severe life-threatening rejection episodes were significantly reduced\(^11\). According to the International Society of Heart and Lung Transplantation (ISHLT) registry, median survival rates have increased from 8.3 years during the 1980s to 10.4 years during the 1990s\(^9\) and to 11 years currently\(^10\) with a median survival of 14 years for those who survive the first year post-HTx\(^13\). Whilst survival rates in the first year post-HTx have improved, long-term survival of HTx recipients who are alive at 1 year has not significantly improved\(^9\). After the first year post-HTx, an attrition rate of 3 to 4% has remained stable\(^10\). The interaction of a range of factors may contribute to this attrition rate with long-term complications post-HTx. Cardiac allograft vasculopathy (CAV) which is an accelerated form of coronary artery disease (CAD) and malignancies account for approximately 35% of all deaths after 10 to 15 years post-HTx\(^10\).
It is becoming increasingly evident that modifiable factors such as obesity and physical inactivity are likely to contribute to limited improvement in long-term morbidity and mortality post-HTx. The combined impact of obesity and physical inactivity on health and all-cause mortality in the general population are well described\textsuperscript{14,15}. Environmental and societal changes including the sedentary nature of many forms of work and leisure, increased urbanisation, advances in technology, passive modes of transportation and the consumption of energy-dense, high fat foods have contributed to an increased incidence of obesity and physical inactivity worldwide\textsuperscript{16}. In addition to environmental factors linked to urbanisation, a lack of policies in various sectors including agriculture, urban planning, food processing, education, health, transport, distribution and marketing may contribute\textsuperscript{16}.

The World Health Organisation (WHO) defines overweight and obesity as abnormal or excessive fat accumulation that presents a risk to health\textsuperscript{16}. Overweight is defined as BMI $=25$ to 29.9 kg/m$^2$ and obesity is defined as BMI $\geq30$ kg/m$^2$\textsuperscript{16}. Fundamentally, overweight and obesity are largely preventable and are typically a result of overeating and physical inactivity\textsuperscript{17}. In the general population, obesity is considered one of the most serious modifiable public health challenges today\textsuperscript{18}. Environmental, behavioural, metabolic and genetic factors and their inter-relationships contribute to the development of obesity\textsuperscript{18,19}. However, it has been suggested that due to the rapid increase in the prevalence of obesity worldwide, behavioural and environmental factors predominate rather than inherent biological changes\textsuperscript{18}. Obesity is associated with increased mortality\textsuperscript{16} and increased risk of developing some cancers, musculo-skeletal disorders (especially osteoarthritis), hypertension (HTN), hyperlipidemia, cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM)\textsuperscript{16,18,20}.

Metabolic syndrome is a term used for a collection of conditions that often occur together and rarely occurs in those with a BMI $<25$ kg/m$^2$\textsuperscript{21}. This complex syndrome is defined as the presence of at least 3 of the following risk factors: waist circumference $>102$ cm in men and $>88$ cm in women, or BMI $\geq30$ kg/m$^2$; triglycerides $\geq150$ mg/mL; fasting glucose $\geq100$ mg/dL; blood pressure (BP) $\geq130/85$ mmHg and high-density lipoprotein $<40$ mg/dL in men and $<50$ mg/dL in women\textsuperscript{22}. Although metabolic
syndrome is associated with increased CVD and all-cause mortality\textsuperscript{23}, in a recent cohort study of 71,527 participants, an increased risk of myocardial infarction and ischaemic heart disease (IHD) was found to be associated with being overweight and obese independent of the presence of metabolic syndrome\textsuperscript{24}. This highlights the negative impact of excess body weight which is an independent risk factor for cardiac disease in the general population\textsuperscript{25}. Unfortunately, the prevalence of obesity post-HTx is similar to the general population\textsuperscript{26}. The WHO state that the world-wide prevalence of obesity nearly tripled between 1975 and 2016, with 13\% of the world’s adult population classified as obese in 2016\textsuperscript{16}. However, according to the Australian Bureau of Statistics 2017-2018 National Health Survey 31\% of Australian adults are obese (up from 19\% in 1995) and 67\% are classified as overweight or obese (up from 56\% in 1995)\textsuperscript{27}.

Physical activity is defined as any bodily movement produced by skeletal muscles which results in energy expenditure (EE) above resting levels of EE\textsuperscript{28}. Physical activity is a measure of functional performance that has a strong behavioural component as well as a physical component\textsuperscript{29}. Participation in physical activity can be influenced by many factors\textsuperscript{30} including exercise-associated symptoms, peripheral muscle strength, training and disease status, mood, past behaviours, health beliefs, personality characteristics and socio-economic, cultural and external factors\textsuperscript{29,31-33}. Compared to those who are sufficiently physically active, people who are insufficiently active have a 20 to 30\% increased risk of death\textsuperscript{34}. Low levels of physical activity are associated with a higher risk of CVD\textsuperscript{35}, T2DM\textsuperscript{36}, mental illnesses (dementia and depression)\textsuperscript{37,38} and some cancers\textsuperscript{39}. It is estimated that physical inactivity causes 6 to 10\% of the major non-communicable diseases (CAD, T2DM and breast and colon cancers) world-wide\textsuperscript{40}, causing 9\% of premature mortality and having a similar impact as the risk factors of smoking and obesity\textsuperscript{40,41}. Whilst the impact of low levels of physical activity have been well-documented in healthy and chronic heart disease populations\textsuperscript{35,42-44}, this has not been well-described in the post-HTx population. Moreover, the factors which relate to physical activity post-HTx remain unknown.
In healthy and chronic disease populations, increased exercise capacity and higher levels of physical activity have been found to reduce the risk of HTN, CAD, stroke, T2DM, some cancers (including breast and colon) and depression, decreasing the risk of all-cause and CVD mortality. There is strong evidence demonstrating individuals who are more physically active are more likely to achieve weight maintenance and have a healthier body mass and composition. Regular and adequate levels of physical activity are also fundamental to bone health, reduced risk of falls and fractures (hip and vertebral) and result in improved cardiovascular and muscular fitness.

For health benefits, the WHO recommends a minimum of 150 minutes of moderate intensity physical activity or at least 75 minutes of vigorous physical activity, or an equivalent combination of moderate and vigorous intensity physical activity per week. More health benefits are gained by increasing physical activity to 300 minutes of moderate intensity activity or equivalent per week and including major muscle group strengthening activities twice or more per week. All activities should be performed in bouts of at least 10 minutes duration for cardiovascular benefits. In addition to these guidelines, reducing the amount of uninterrupted time spent sedentary during waking hours is also important to reduce the risk of developing CVD and metabolic diseases. One would surmise that post-HTx, participation in regular, adequate levels of physical activity would be just as important if not more important than for those in the general population.

Including major muscle group strengthening exercises twice or more per week is important for health benefits in the general population. Post-HTx, skeletal muscle mass if often markedly reduced due to various factors including immunosuppression and deconditioning. Quadriceps muscle strength is important for functional activities including sit to stand and walking. Walsh et al (2013, n=35) found that impaired exercise capacity as measured by 6MWD was related to delayed recovery of quadriceps muscle strength post-lung transplantation (LTx) and not related to delayed improvement in graft function. Although quadriceps muscle strength has not been investigated post-HTx, it is likely that recovery of skeletal muscle strength plays an important role in outcomes for this patient group.
Aims
Obesity and physical inactivity are risk factors for poor long-term health in the general population. Currently, there is a limited body of knowledge relating physical activity and obesity in HTx and the factors relating to each. Hence, the aims of this thesis are to:

1. review the relevant literature related to obesity, levels of physical activity and exercise capacity post-HTx (Chapter 2)
2. describe physical activity levels post-HTx using a multi-sensor device (SenseWear Pro3) (Chapter 3)
3. identify factors that may be associated with estimates of physical activity (physical activity level (PAL) and average daily time spent at least moderately active (≥3 METs)) post-HTx. The factors to be studied include demographic (age, sex, BMI, time post-HTx, reason for HTx (aetiology of HF) and corticosteroid use at time of assessment) and routine clinical measures (quadriceps muscle strength corrected for body weight (QS%) and 6MWD) (Chapter 3)

The hypotheses of this thesis are:

1. For individuals post-HTx, PAL and average daily time spent performing activities ≥3 METs will be:

   a. directly related to exercise capacity (as determined by 6MWD and quadriceps muscle strength)
   b. inversely related to participant age, BMI, time post-HTx and presence of ischaemic cardiomyopathy
   c. unrelated to other aetiologies of cardiomyopathy, sex or corticosteroid use at time of assessment (Chapter 3)
Chapter 2. Literature review

Heart failure

Aetiology and pathophysiology
The main known causes of HF are diseased myocardium, abnormal loading conditions or arrhythmias\(^2\). Diseased myocardium may be due to IHD, toxic damage, immune-mediated and inflammatory damage, infiltration, metabolic derangements or genetic abnormalities\(^2\). Abnormal loading conditions may be due to HTN, valvular and myocardial structural defects (acquired or congenital), pericardial and endo-myocardial pathologies, high output states or volume overload\(^2\). Arrhythmias may be tachy-arrhythmias or brady-arrhythmias\(^2\). Aetiology is diverse (Table 1) and individuals may have several cardiovascular and non-cardiovascular pathologies causing their HF\(^2\). For the purpose of this study, HTx recipients will be grouped into the following 3 categories: ischaemic cardiomyopathy, idiopathic dilated cardiomyopathy and other (including restrictive cardiomyopathy, familial, Fabry disease, hypertrophic obstructive cardiomyopathy, amyloid, congenital heart disease, sarcoidosis and valvular heart disease).

The pathophysiology of HF involves an initial insult to the myocardium which leads to a decrease in cardiac output (CO). This results in a cascade of events, many of which are aimed at maintaining mean arterial pressure (MAP). Both the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) are activated to increase systemic vasoconstriction and blood volume through sodium and water retention\(^53\). Activation of the SNS also increases heart rate (HR) and myocardial contractility in an attempt to increase CO\(^53\). While some of these changes may be effective in maintaining MAP in the short-term, in the long-term there may be substantial ventricular remodelling as the affected chamber struggles to cope with the increased preload and afterload\(^1\). If left untreated, the ongoing effects of these adaptations are counterproductive leading to catastrophic ventricular remodelling and further reduction of CO and increased endothelial dysfunction, skeletal muscle myopathy and renal impairment\(^1\). Deteriorating blood flow, chamber dilation and wall stress contribute to ventricular dysfunction and the signs and symptoms commonly seen in HF\(^1\). See Figure 1.
**Classification of heart failure**

Individuals with HF are classified as those with preserved left ventricular ejection fraction (LVEF) (HFpEF) defined as LVEF $\geq 50\%$ and those with a reduced LVEF (HFrEF) defined as having LVEF $<50\%$\textsuperscript{54}. Individuals with HFpEF are generally elderly with several comorbidities\textsuperscript{54}. Whilst there are some well-defined pharmacological treatment options for HFrEF, specific pharmacology for HFpEF remains an ongoing challenge\textsuperscript{54}. Treatment options for HF will be discussed in the upcoming sections. The severity of HF based on symptoms is described according to the New York Heart Association (NYHA) functional classification four point scale\textsuperscript{2,3}. This is used to describe physical function and symptom severity (See Table 2).
Table 2: New York Heart Association (NYHA) Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td><strong>No limitation of physical activity</strong></td>
</tr>
<tr>
<td></td>
<td>Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath).</td>
</tr>
<tr>
<td>II</td>
<td><strong>Slight limitation of physical activity</strong></td>
</tr>
<tr>
<td></td>
<td>Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath).</td>
</tr>
<tr>
<td>III</td>
<td><strong>Marked limitation of physical activity</strong></td>
</tr>
<tr>
<td></td>
<td>Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea.</td>
</tr>
<tr>
<td>IV</td>
<td><strong>Unable to carry on any physical activity without discomfort</strong></td>
</tr>
<tr>
<td></td>
<td>Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.</td>
</tr>
</tbody>
</table>

**Management of heart failure**

Management of HF is complex and ranging from conservative to non-conservative, treatments include multidisciplinary HF disease management programs, pharmacological therapies, cardiac resynchronisation therapy (CRT), implantable cardiac defibrillators (ICDs), mechanical circulatory support and HTx. In addition, it is recommended to encourage participation in regular aerobic exercise to improve symptoms, functional capacity and reduce hospitalisation in people with stable HF.
Pharmacological therapies
Pharmacotherapy has been shown to improve survival and reduce hospitalisation in individuals with HFrEF by modulating neurohormonal systems associated with disease progression. Pharmacological therapies that have been shown to improve mortality and morbidity in those with HFrEF are angiotensin-converting enzyme inhibitors (ACEI) which act to inhibit the RAAS, resulting in dilation of blood vessels and a reduction in BP. An angiotensin receptor blocker (ARB) is only recommended as an alternative for individuals who do not tolerate an ACEI. Beta-blockers and mineralocorticoid/aldosterone receptor antagonists (MRA) have also been shown to improve outcomes in HF. A new class of pharmacological therapy (angiotensin receptor neprilysin inhibitor (ARNI)) targets the RAAS and the neutral endopeptidase system and is prescribed instead of an ACEI or an ARB in those with HFrEF who despite receiving maximally tolerated or target doses of an ACEI or ARB and a beta-blocker still have an LVEF ≤40%. Diuretics are used to control symptoms of fluid retention and maintain euvolaemia in individuals with HFrEF or HFpEF. For individuals with HFpEF, the aims of treatment are to improve quality of life (QoL) by managing symptoms and reduce hospitalisation.

Implantable cardioverter-defibrillator
Implantable cardioverter-defibrillators (ICD) are effective in preventing bradycardia and correcting potentially lethal ventricular arrhythmias. An ICD may be inserted for primary prevention of sudden cardiac death and secondary prevention for individuals who have experienced sustained symptomatic ventricular arrhythmias or are survivors of cardiac arrest.

Cardiac resynchronization therapy
Cardiac resynchronization therapy (CRT) delivers electrical impulses to the left and right ventricles facilitating co-ordinated ventricular contraction with the aim of improving CO in appropriately selected individuals with HF. In order to improve symptoms and reduce morbidity and mortality, CRT is recommended for individuals with symptomatic HF who are in sinus rhythm, who despite receiving optimal medical (pharmacological) therapy have a LVEF ≤35% and a QRS duration ≥150 msec and left bundle branch block QRS morphology.
**Mechanical circulatory support**

Mechanical circulatory support is considered in individuals with chronic refractory (end-stage) HF or acute cardiogenic shock who cannot be stabilised with medical (pharmacological) therapy in order to unload the failing ventricle and maintain end-organ perfusion. Mechanical circulatory support is used as either a bridge to HTx, or during recovery, candidacy, decision, or for destination therapy. In all the scenarios outlined above, mechanical circulatory support with a left ventricular assist device is the most commonly used. However, biventricular devices are used in some individuals as a bridge to HTx.

In those with an acute but reversible cause of HF such as acute myocarditis, mechanical circulatory support (usually left ventricular assist device) may be used as a bridge to recovery and the device removed once left ventricular function improves. Although advances in technology are lessening the impact of living with such devices, the level of independence and QoL achieved with HTx is greater. Long-term outcomes for individuals on mechanical circulatory support are impacted by possible complications including: pump thrombosis, bleeding, thromboembolism (all of which increase the risk of stroke), driveline infections and device failure.

**Heart transplantation**

In appropriately selected individuals with end-stage HF, there is consensus that HTx significantly increases survival, exercise capacity, return to work capacity and QoL. Indications for HTx include: cardiogenic shock requiring either continuous intravenous inotropic support or mechanical circulatory support; persistent NYHA functional class III or IV, congestive HF symptoms despite optimal medical therapy, $\bar{VO}_{2\text{peak}} < 12$ ml/kg/min (or < 50% of predicted), intractable severe anginal symptoms in those with CAD not amenable to percutaneous or surgical revascularization; and intractable life-threatening arrhythmia unresponsive to medical therapy or catheter ablation. Individuals with a $\bar{VO}_{2\text{peak}}$ between 12 and 14 ml/kg/min (or 50% of their age predicted) who also have a major limitation to their activities of daily living are categorized as having a probable indication for HTx.
The HTx surgical procedure involves sternotomy, cardiopulmonary bypass, recipient cardiectomy (leaving a left atrial cuff that spans the four pulmonary veins) and anastomoses to bring together donor and recipient inferior vena cava, superior vena cava, left atrium, aorta and pulmonary artery. Post-HTx survival has significantly improved due to advances in immunosuppression, refinement of donor and recipient selection, donor heart preservation methods, the performance and interpretation of myocardial biopsies and cytomegalovirus prophylaxis. Most of the recent survival improvement is related to mortality reduction during the first year post-HTx.

CVD events are reported as the leading cause of death post-solid organ transplant. After the first post-HTx year, CAV and malignancy are the most prevalent long-term complications and leading causes of death. In the HTx population, CAV is partially attributed to the presence of traditional CVD risk factors (older age, male, HTN, T2DM, obesity, hyperlipidemia and smoking). Immunosuppression therapy may contribute to CAV by causing hyperlipidemia and HTN if left untreated. Rejection and chronic inflammation may also play a role in the development and progress of CAV. Since CAV post-HTx is partially attributed to CAD risk factors, identifying and managing these modifiable risk factors may reduce progression and incidence of CAV and thus improve long-term outcomes post-HTx.

**Obesity post-heart transplantation**

Weight gain and obesity post-HTx are common with HTx recipients reported to gain approximately 10kg in the first year post-HTx. In one study, Williams et al (2006) reported a (mean ± SD) 10.3 ± 10.6 kg (p<0.05) increase in weight at 1 year post-HTx from mean weight at time of HTx of 76.3 ± 14.6 kg. Nineteen of 148 (12.8%) HTx recipients were obese (BMI ≥30 kg/m²) at the time of HTx and this increased to 51 of 144 recipients (35.4%) at 1 year post-HTx. This weight gain was found to be typically maintained 3 years post-HTx. Although resolution of pre-HTx cachexia may in part contribute to weight gain in the first year post-HTx, the increase in percentage of those classified as obese at 1 year post HTx (13 to 35%) is high. However, this rate is similar to the prevalence of obesity in the general adult population in Australia (currently approximately 31%) in contrast to these results, a longitudinal study investigating changes in body weight up to 3 years post-solid organ transplant in Switzerland (n=1359) reported a relatively low mean weight gain compared to
international data, with the majority of participants weight plateauing at approximately 2 years post-solid organ transplant. The prevalence of obesity in the HTx cohort (n=89) in this study peaked at 2 years post-HTx at 20% (n=18).

The cause of weight gain post-HTx is likely to be multifactorial. Immunosuppressant therapy, an essential therapeutic management required to prevent rejection of the donor heart, has been identified as one cause. Glucocorticoids (a class of corticosteroids) alter body fat distribution and lipid metabolism, independent of weight effects. Prednisone (a glucocorticoid), especially when dosed >5 mg/day is associated with craving sweets and increased weight. The use of glucocorticoids and other immunosuppressive therapy may also increase the risk of developing CVD risk factors including HTN, hyperlipidemia and T2DM.

Whilst the management of HTx may be a potential cause, nonetheless the level of obesity remains a potent risk factor for mortality post-HTx. A recent systematic review and meta-analysis of five registries/studies (United Network for Organ Sharing Registry; ISHLT registry; one multi-centre study and two single centre reports) reported a significantly increased risk of mortality in HTx recipients with BMI >30 kg/m². The greater risk was across all age categories, independent of transplant era and study source (BMI 30 to 34.9 kg/m²: HR 1.10, 95% CI = 1.040 to 1.170; BMI ≥35 kg/m²: HR 1.24, 95% CI = 1.120 to 1.380) when compared to HTx recipients in the healthy BMI range.

Post-HTx, complications associated with obesity may contribute to the significant increase in all-cause mortality. Obesity post-HTx has been found to be associated with increased risk of CVD, CAV, transplant rejection and T2DM.

Milaniak et al (2014, n=169) found a significant association between higher BMI and elevated fasting glucose level (r=0.35; p<0.050), total cholesterol (r=0.27; p<0.050) and presence of CVD (p=0.006), with increased BMI predicting increased CVD (OR=2.18; 95% CI = 1.022 to 4.500; p=0.044) and higher fasting glucose level (OR=1.758; 95% CI = 0.866 to 3.341; p=0.040) in a logistic regression. Carlos et al (2008) found mean values of glucose, total cholesterol, low-density lipoprotein and triglycerides to be higher in HTx recipients who were overweight or obese when compared with those of healthy weight or underweight. In a small study by Cristiano et al (2012, n=25), more than 80% of participants at 5 years post-HTx were classified as overweight or obese (BMI >25 kg/m²), with 42% having raised systolic blood pressure and more than 25%
having T2DM\textsuperscript{84}. High blood pressure, which is often associated with obesity, may negatively impact long-term survival post-HTx by increasing the risk of left ventricular hypertrophy\textsuperscript{85}.

Not only is obesity affecting individuals with HF in the post-HTx phase, the number of obese individuals awaiting HTx also appears to be increasing. This increase in pre-HTx BMI affects BMI post-HTx. In a group of 3,540 HTx recipients, Grady et al (2005) found increased BMI at time of HTx to be associated with increased BMI post-HTx\textsuperscript{81}. For the first 5 years post-HTx, relationships between morbidity and mortality and post-HTx BMI were examined by recording acute rejection episodes, infections and prevalence of CAV\textsuperscript{81}. Compared with those of healthy weight or overweight, those who at one year post-HTx were obese or underweight were found to be at a greater risk of developing transplant rejection over time (p=0.009)\textsuperscript{81}. The same study found that ethnicity may affect the likelihood of developing obesity. Individuals with darker skin gained significantly more weight post-HTx than Caucasians. Moreover, individuals with darker skin post-HTx may be at greater risk of rejection than white recipients\textsuperscript{81}. Clark et al (2007) reported HTx recipients whose body weight varied greatly from the healthy weight range had worse outcomes post-HTx; however, they found no significant relationship between BMI and survival\textsuperscript{86}. Beckmann et al (2015) have more recently published their study protocol for a systematic review of weight gain, overweight and obesity in solid organ transplant recipients\textsuperscript{76}. Whilst the systematic review is yet to be published, important evidence regarding these influencing factors and associations with outcomes and comorbidities may come to light\textsuperscript{76}.

Pre and post-HTx BMI seem to be important predictors of outcomes post-HTx. In addition to screening for obesity and other CVD risk factors, multidisciplinary interventions designed to improve health-status post-HTx by encouraging healthy eating habits and participation in regular and adequate physical activity may improve long-term morbidity and mortality outcomes in the HTx population\textsuperscript{73,87}. 
Measuring physical activity

Several non-invasive methods exist to measure physical activity in both clinical and athletic populations. In addition to questionnaires, other methods include interviews, diaries and physiological markers including HR and calorimetry. There are commercially available devices from pedometers and load transducers which measure walking activity, to accelerometers and multisensor devices which monitor total physical activity, all of which have limitations. Direct calorimetry, more specifically the doubly labelled water (DLW) method, is the gold standard for measuring EE. DLW allows measurement of total energy expenditure (TEE) in unrestrained individuals over 1 to 2 weeks. In combination with a measurement of resting energy expenditure (REE), active energy expenditure (AEE) can be calculated as AEE = 0.9TEE - REE. Although EE does not equate to body movement, body movement results in EE. This methodology, however, is invasive and limited by cost and lack of temporal resolution.

Whilst not without limitations, accelerometers offer a practical and effective compromise between accuracy and feasibility for measuring physical activity level (PAL). For this thesis, the SenseWear Pro3 armband (SWA) was chosen which is a multi-sensor device using a 2-axis accelerometer, combined with additional physiological parameters (e.g. skin temperature) to estimate EE. Compared with questionnaires, this device provides a more objective measurement of EE, is relatively inexpensive, well tolerated and provides temporal resolution. The SWA has been validated against other techniques measuring EE including indirect calorimetry and the DLW method in the healthy population and in chronic disease populations. For example, Johannsen et al (2010), using intra-class correlation analysis, reported significant agreements between the SWA and DLW estimates of EE in healthy adults (ICC = 0.80; 95% CI = 0.890 to 0.700, p<0.001). Studies evaluating the accuracy of the SWA compared with DLW method to measure EE suggest reasonable agreement on the basis of intra-class correlation analysis and Bland-Altman plots. However, an overestimation of daily EE for subjects with low EE values and an underestimation of daily EE for subjects with high EE values were observed with the SWA in both of these studies.
The SWA device provides an estimate of EE and time spent above different PALs as defined by different levels of metabolic equivalents (METs), where 1 MET is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 ml per kilogram of body weight per minute for an average adult. In addition, time lying down and sleeping are reported. Output parameters of physical activity include: PAL, minutes performing at least moderate intensity activity (defined as any physical activity ≥3 METs) and steps per day. PAL is defined as TEE in twenty-four hours divided by basal metabolic rate derived from the average sleeping metabolic rate. Average daily PAL can be expressed as an index, comparing EE whilst sleeping with activity for the day as a whole (i.e. daily EE/sleeping EE).

Using PAL, participants can be grouped into the following activity categories: extremely inactive (PAL <1.40), sedentary (PAL =1.40 to 1.69) and active (PAL ≥1.70). Monitoring for 3 days or more has been found to be useful for reliably estimating habitual physical activity. In their study of 302 high-functioning, community-dwelling older adults (aged 70-82 years), Manini et al (2006) reported that a PAL of >1.78 was strongly associated with a lower risk of mortality.

Physical activity post-solid organ transplantation

Information regarding physical activity post-HTx remains limited, with only four studies published in this area to date. Myers et al (2003) used a physical activity questionnaire to estimate EE of 47 HTx recipients (mean 4.8 ± 3.0 years post-HTx) from recreational activities over one year. This study reported that participants were engaged in a moderate level of physical activity, expending a mean of 1100 kcal/week in recreational activities. Whilst this study provides important, preliminary data regarding physical activity in the HTx population, questionnaires may not accurately reflect physical activity patterns with self-reporting often subject to recall bias. Typically individuals who are less physically active tend to overestimate physical activity, whilst individuals who are more physically active typically tend to underestimate.

A few small studies have described levels of physical activity post-HTx using accelerometers. Jakovljevic et al (2014) investigated the effects of HF, left ventricular assist device and HTx on physical activity and QoL. This prospective, observational, repeated measures study included a total of 40 subjects, 12 of which were
post-HTx (age 48 ± 17 years)\textsuperscript{60}. The SWA was used to estimate levels of physical activity over the first year post-HTx\textsuperscript{60}. Subjects demonstrated improved QoL and physical activity (52\%) within the first 3 months post-HTx. However, these measures remained unchanged in the following 9 months\textsuperscript{60}. In this study, physical activity was measured using total number of steps per day, physical activity duration (mins/day >3 METs) and AEE (kcal/day)\textsuperscript{60}. Number of steps remained significantly lower than healthy matched subjects at 12 months post-HTx, yet inaccurate detection of steps especially at slower walking speeds has been found to be a limitation of the SWA\textsuperscript{105}. At 12 months post-HTx, physical activity duration (min/day >3 METs) and AEE (kcal/day) were approaching that of healthy matched subjects (93\% and 80\% respectively)\textsuperscript{60}.

Evangelista et al (2005) used an Actiwatch 2 and diaries to assess physical activity levels of 27 women post-HTx over one week in a descriptive, cross-sectional study. Mean time post-HTx was 5.2 ± 4.4 years\textsuperscript{104}. The Actigraph data demonstrated extremely low levels of physical activity, with 55\% of participants inactive and only 15\% of participants reporting that they engaged in moderate to high levels of physical activity\textsuperscript{104}. It is unclear how the different physical activity levels were determined as the authors did not provide a description of how many activity counts define being inactive, moderately active or highly active. It is also worth noting that this study only included a small sample of women and although the Actiwatch 2 has demonstrated good reliability in previous studies (r = 0.80 to 0.96) there is little published research on the validity of the Actiwatch 2 for estimating physical activity\textsuperscript{104}. However, it has been shown that motion sensors correlate highly with HR and EE by calorimetry (r = 0.68 to 0.90), and thus have the ability to detect different intensities of physical activity and can distinguish activity by time of day\textsuperscript{106}.

Yardley et al (2017) recently used the SWA to record physical activity frequency and intensity of subjects who had previously participated in a randomised controlled trial (RCT) by Nytroen et al (2012, n=52) in which the effectiveness and safety of high intensity interval training up to 12 months post-HTx was investigated\textsuperscript{107}. Forty-one of the 52 participants from the original study took part in the follow-up study (including both control and intervention subjects), with Yardley et al (2017) reporting that participants were involved in more than 1 hour of moderate intensity physical activity (defined as 3.0 to 5.9 METs) per day\textsuperscript{103}.  

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Use of multi-sensor devices to investigate levels of physical activity has been more prevalent in the chronic lung disease and LTx populations. In a study of 170 medically stable subjects with chronic obstructive pulmonary disease, physical activity measured using an activity monitor was the strongest predictor of 4-year survival\textsuperscript{108}. In this study, physical activity provided better prognostic evidence than 6MWD, doppler-assessed peripheral vascular disease, BMI and fat-free mass index, dyspnoea, health status, depression symptoms, multiple systemic biomarkers and lung function\textsuperscript{108}. Troosters et al (2010), when investigating levels of physical activity in 70 individuals with chronic obstructive pulmonary disease using the SWA, reported that a decrease in exercise capacity was associated with a decline in physical activity level\textsuperscript{109}. In this study, time spent in activities of at least moderate intensity, set at ≥4.5 METs for those up to age 65 years and ≥3.6 METs for those older than 65 years as proposed by Pollock and Haskell\textsuperscript{110} was used as the main outcome in this study\textsuperscript{109}.

In a RCT by Langer et al (2012) which included LTx recipients aged 40 to 65 years, 21 LTx recipients were allocated to 3 months of thrice weekly exercise training sessions post-discharge from hospital and 19 recipients were allocated to the control intervention (received standard inpatient mobilisation program and but did not attend a supervised exercise program on discharge)\textsuperscript{111}. Both groups attended 6 individual counselling sessions (15 to 30 minutes duration) post-discharge, which included instructions to increase daily physical activity levels. Physical activity levels were assessed using 2 activity monitors (DynaPort and SWA) worn for at least 4 days at pre-LTx, baseline, 3 months and 1 year post-discharge\textsuperscript{111}. At 3 months and 1 year post-discharge, statistically significant differences in 6MWD (p=0.008; p=0.002), quadriceps muscle strength (p=0.001; p=0.001), walking time (p=0.008; p=0.006), time spent ≥3 METs (p=0.077; p=0.047) and steps (p=0.004; p=0.002) were found between the two groups, with higher values in the intervention group for all outcome measures\textsuperscript{111}.

Another cross-sectional study by Langer et al (2009) that compared levels of physical activity at least one year post-LTx (n=22) with those of 22 healthy age and gender-matched control subjects found moderate intensity activity (≥3 METs), steps and standing time were significantly reduced in the LTx group\textsuperscript{112}. There was also a 30% greater daily sedentary time in the LTx group compared with the control group\textsuperscript{112}. The study found statistically significant differences between groups in quadriceps muscle...
strength (p<0.01), 6MWD (p<0.01) and VO_{2peak} (p<0.01)\textsuperscript{112}. The data from this study shows that most individuals do not return to a normally active lifestyle post-LTx\textsuperscript{112}. The authors suggest that reduced exercise capacity is unlikely to be due to pulmonary dysfunction and more likely to be primarily limited by impaired skeletal muscle function\textsuperscript{112}. It is suggested that impaired skeletal muscle function may be caused not only by the negative impact of immunosuppression medications, but also by pre-LTx deconditioning and levels of physical activity post-LTx, with higher levels of physical activity found to be related to greater quadriceps muscle strength (r=0.660; p<0.010), exercise capacity (6MWD)(r=0.680; p<0.010) and self-reported physical functioning(r=0.810; p<0.010) in this LTx group\textsuperscript{112}.

A recent study by Gustaw et al (2017) investigated levels of physical activity in 113 adults post-solid organ transplant (including 27 (23.9%) post-HTx) using an internet-based questionnaire including the validated 10 item Physical Activity Scale for the Elder (scores range from 0 to over 400, with a higher score corresponding to more physical activity)\textsuperscript{113}. This study found a large variation in levels of physical activity amongst solid organ transplant recipients with a median Physical Activity Scale for the Elder score of 190.2 with a range of 49.6 to 482.7 for the HTx group\textsuperscript{113}. The authors observed that the LTx and HTx recipients engaged in higher levels of physical activity compared to the other solid organ transplant groups\textsuperscript{113}. Limitations of this study include the use of a voluntary convenience sample which may have resulted in selection bias, along with the fact that supervised exercise programs are well established in Canada for HTx and LTx recipients\textsuperscript{113} with participation in an early structured rehabilitation program found to have a positive impact on levels of physical activity post-LTx\textsuperscript{112} and on mortality post-HTx\textsuperscript{114}.

Increased mortality risk has been associated with low levels of physical activity in other solid organ transplant populations\textsuperscript{115,116}, with low levels of physical activity found to be associated with poor graft function\textsuperscript{117} and strongly associated with increased risk of CVD and all-cause mortality (measured using validated questionnaires (Tecumseh Occupational Activity Questionnaire and the Minnesota Leisure Time Physical Activity Questionnaire)) in a study of 540 renal transplant recipients\textsuperscript{116}. In all of the studies outlined above, PAL has not been described. Moreover, no studies have investigated whether clinical variables such as quadriceps muscle strength and exercise capacity are
associated with levels of physical activity in the HTx population when measured by a multi-sensor device.

**Barriers and facilitators to physical activity**

A few studies have investigated barriers and facilitators to physical activity post-solid organ transplant. Gustaw et al (2017) found that the most common factors influencing levels of physical activity post-solid organ transplant were ‘a feeling of health from physical activity (94%; n=106), support from family and friends (76%; n=86), high level of motivation to stay healthy (88%; n=99), knowledge and confidence about physical activity (74%; n=84), proximity to an exercise facility (73%; n=82) and physician recommendation (59%)’113. Notably the most common barriers to involvement in physical activity post-solid organ transplant were a feeling of having less strength (37%; n=42), post-transplant side-effects including those relating to medications (41%; n=46), cost (42%; n=47) and lack of exercise guidelines (37%; n=42)113. Gordon et al (2009) demonstrated at approximately 2 months post-renal transplant, 78% of 82 subjects reported being sedentary with reported barriers to physical activity including fatigue, illness, post-operative effects, medications and lack of clinical guidance118. In order to ensure participants were recovered from surgery, HTx recipients who were at least 6 months post-HTx were only included in the current study. In addition, those with a LVEF less than 50%, a rejection episode within the two months prior to assessment or any injury or illness that could be reasonably expected to reduce mobility were excluded to minimise confounding variables.

A study post-renal transplant reported ‘lack of motivation’ and ‘preferring to spend time otherwise’ as barriers to physical activity, and ‘feeling healthy’ and ‘wanting to feel better’ as facilitators to physical activity119. In a more recent study, Adrichen et al (2016) found physical limitations, insufficient energy level, fear and comorbidities to be the most important barriers to participation in physical activity post-solid organ transplant (n=16, HTx =4), with motivation, coping, consequences of inactivity, routine/habit, goals/goal priority and responsibility for the transplanted organ being the most common facilitators of physical activity120. A high level of self-efficacy and expertise of personnel were also found to be facilitators120. Although this was a very small study that included only 4 HTx recipients, several barriers and facilitators to
physical activity outlined in the study are similar to those found in the general population\textsuperscript{121-123}.

**Measuring exercise capacity**

Cardiopulmonary exercise testing (CPET) combined with an incremental exercise test remains the gold standard in determining exercise capacity\textsuperscript{124}. CPET provides measures of oxygen uptake, carbon dioxide output and ventilation by analysing gas exchange at rest, during exercise and during recovery\textsuperscript{125}. Peak oxygen uptake ($\dot{V}O_2\text{peak}$), defined as the highest achieved oxygen intake per unit of body weight, is the gold standard measure of cardiorespiratory fitness (exercise capacity)\textsuperscript{126}. $\dot{V}O_2\text{peak}$ can be determined during an incremental CPET and may be expressed in METs\textsuperscript{97}. However, CPET requires specialist equipment and interpretation, is costly and is difficult to administer clinically\textsuperscript{124}.

In contrast, field tests such as the six minute walk test (6MWT) and incremental and shuttle walk tests are low cost and easy to perform clinically\textsuperscript{29}. For this study, 6MWT was used as a surrogate measure of exercise capacity as it is a sub-maximal, validated test that is well-tolerated and more reflective of activities of daily living\textsuperscript{127,128}. 6MWD has been shown to have a moderately high correlation with $\dot{V}O_2\text{peak}$ in a range of cardiorespiratory populations\textsuperscript{127,129}. In one of these studies, multivariable analysis of characteristics of participants with HF awaiting HTx showed 6MWD to be the strongest independent predictor of $\dot{V}O_2\text{peak}$ with a reliability of ICC 0.96\textsuperscript{130}. In their evaluation of various walk tests (including 29 studies on 6MWT), correlations between $\dot{V}O_2\text{peak}$ and 6MWD ranged from 0.51 to 0.90 with a change of 54m in distance walked found to be clinically significant in regard to functional status\textsuperscript{127}. However, 30m may be enough to demonstrate a clinically significant difference, with Singh et al (2014) reporting this as the minimal important difference for the 6MWD in adults with chronic respiratory disease in a systematic review\textsuperscript{131}.

**Exercise capacity post-heart transplantation**

Several studies have investigated exercise capacity by measuring $\dot{V}O_2\text{peak}$ post-HTx. In a review article, Marconi et al (2003) examined 30 studies investigating $\dot{V}O_2\text{peak}$ values of HTx recipients\textsuperscript{132}. In the first two months post-HTx, a sharp increase in $\dot{V}O_2\text{peak}$ was
found (\(\pm 30\%\) pre-HTx value), mainly due to improved cardiac function and an increase in oxidative capacity and cross-sectional area of skeletal muscle fibres\textsuperscript{132}. \(\dot{V}O_2\text{peak}\) was found to gradually increased over the next 1 to 2 years before levelling off\textsuperscript{132}. Despite these improvements in \(\dot{V}O_2\text{peak}\) post-HTx\textsuperscript{132}, values rarely exceed \(~60\%\) of the value for healthy age-matched controls with a similar level of activity\textsuperscript{132-135}. Whilst 6MWD has been demonstrated to have a significant positive correlation with \(\dot{V}O_2\text{peak}\) post-HTx\textsuperscript{136,137}, there are no studies to our knowledge that have investigated recovery in 6MWD post-HTx. A recent study by Tucker et al (2018) has outlined the impairments in body systems (cardiac, vascular and skeletal muscle) post-HTx that contribute to reduced \(\dot{V}O_2\text{peak}\)\textsuperscript{138}. These authors found that post-HTx all body systems may be limited and that exercise training may be effective in improving \(\dot{V}O_2\text{peak}\) by enhancing peripheral body systems\textsuperscript{138}.

**Cardiac function**
Post-HTx, CO is normal or slightly reduced at rest; however, the observed reduction in exercise capacity post-HTx, as measured by \(\dot{V}O_2\text{peak}\), appears to be related to several factors. Post-HTx, during peak exercise, CO has been found to be 30 to 40% lower than that of age-matched controls\textsuperscript{132,139-141}. Factors found to contribute to this include reduced peak stroke volume (80% predicted)\textsuperscript{139-141}, reduced end-diastolic volume (80% predicted, due to left ventricular stiffness and altered relaxation kinetics)\textsuperscript{139,142} and chronotropic incompetence\textsuperscript{132} (delayed and blunted increase in HR during exercise due to cardiac allograft denervation, which also results in an increased resting HR(average 140bpm range 110-174))\textsuperscript{139,143,144}. Elevated left ventricular filling pressures at rest and during exercise caused by diastolic dysfunction (impaired filling) contribute to reduced stroke volume and may develop late post-HTx\textsuperscript{139}. Causes may include mismatch between the donor heart size and the recipient’s body size, number of rejection episodes, HTN and myocardial infarction from CAV\textsuperscript{132}.

**Vascular**
Post-HTx, peak exercise systemic vascular resistance has been found to be 50% greater than that observed in healthy, age-matched controls\textsuperscript{139,140}. Vascular resistance is increased due to endothelial dysfunction and peripheral vasoconstriction (caused by an exaggerated sympathetic response during exercise)\textsuperscript{145}. This greater increase in vascular
resistance leads to a reduction in oxygen delivery to skeletal muscles and an overall lower $\text{VO}_2\text{peak}^{140,146-148}$. Chronic immunosuppression therapy may also contribute to vascular impairment post-HTx$^{149,150}$ by causing endothelial dysfunction, which contributes to the development of intimal hyperplasia and plaque build-up that may lead to CAV$^{149,151}$. Impaired vasodilatory capacity and reduced capillary density also contribute to abnormal blood supply to the exercising muscle$^{145}$.

**Skeletal muscle**

Various pre and post-HTx factors that contribute to abnormalities in skeletal muscle mass, oxidative capacity (ability to extract oxygen from the blood) and morphology may contribute to reduced skeletal muscle strength and $\text{VO}_2\text{peak}$ post-HTx$^{138,143,145}$. At rest, oxygen extraction from metabolically active body tissues is normal post-HTx$^{133}$. However, during exercise, the arterio-venous oxygen difference (the amount of oxygen taken up from the blood by the body’s tissues) does not increase in a typical manner and reflects abnormalities with both the delivery of oxygen at the capillary level of the exercising skeletal muscles and impairment of skeletal muscle oxidative capacity$^{139,152}$. Kao et al (1994) reported that the maximal exercise arterio-venous oxygen difference was significantly lower (-24%) in HTx recipients compared to healthy, age-matched controls$^{139}$. Skeletal muscle oxidative capacity has been found to be significantly reduced pre-HTx$^{153,154}$ and remains reduced post-HTx$^{153-155}$. Moreover, Braith et al (1993) showed a significant decrease in total lean body mass and muscle strength post-HTx, which was associated with a lower $\text{VO}_2\text{peak}$ when compared with sedentary age-matched controls$^{156}$.

In people with chronic HF, skeletal muscle structural and biochemical abnormalities develop and oxygen delivery to the periphery is impaired, leading to diminished muscle strength and endurance$^{143}$. These changes may include reduced mitochondrial volume, capillary density, oxidative enzyme capacity$^{157,158}$, endothelial dysfunction (impaired vasodilation during exercise), reduced muscle mass, a shift in muscle fibre type I (slow twitch oxidative) to type IIB fibres (fast twitch glycolytic), and a greater reliance on anaerobic than aerobic energy production$^{133}$. Such abnormalities generally persist post-HTx and can contribute to reduced exercise capacity$^{159}$; however, there may be partial improvement after several months for some recipients$^{51,160}$. In addition, skeletal muscle atrophy due to deconditioning as a result of chronic HF is common.
**Immunosuppressant therapy**

Immunosuppression therapy is essential, particularly immediately post-HTx. This therapy can negatively impact skeletal muscle morphology and function, especially cyclosporine (a calcineurin blocker)\(^{161}\) and corticosteroids\(^{133,162}\), with pathways associated with expression of oxidative muscle fibres and capillarisation found to be inhibited with their long-term use. Cyclosporine seems to reduce the oxidative capacity of both type I and type IIB muscle fibres by impairing mitochondrial function\(^{47,161,163}\). As a result, the ability of the working skeletal muscle to utilise oxygen is impaired and there is an early shift from oxidative metabolism (low power/long duration) to anaerobic (glycolytic) metabolism (moderate power/short duration) and early onset of lactic acidosis, thus limiting \(\text{VO}_2\text{peak}\)\(^{47,161,163}\). Corticosteroids can cause proximal muscle weakness (thought to be caused by type IIB muscle fibre atrophy) and interfere with skeletal muscle’s ability to utilise oxygen and fuel\(^{162,164,165}\).

Other factors that may negatively impact \(\text{VO}_2\text{peak}\) post-HTx include increased body fat and BMI\(^{143}\) and prolonged intensive care unit length of stay\(^{166}\). Prolonged intensive care unit length of stay leads to skeletal muscle atrophy\(^{166,167}\) and has been found to be a risk factor for mortality in the general and renal-transplant populations\(^{168,169}\).

**Effects of exercise training**

Post-HTx studies have demonstrated an increase in lean body mass\(^{170-172}\) and \(\text{VO}_2\text{peak}\)\(^{107,171,173-177}\) with endurance or endurance combined with strength training. In one long-term study, fourteen middle-aged male HTx recipients (mean time post-HTx = 46 months) who participated in 4 hours per week of endurance training for a mean duration of 3 years reached peak HR and \(\text{VO}_2\text{peak}\) similar to age-predicted values\(^{178}\). In another study, using a crossover design, the effect of 12 weeks of high intensity interval training compared with moderate intensity continuous training on \(\text{VO}_2\text{peak}\) were investigated (n=16; mean time post-HTx = 6.4 years)\(^{175}\). \(\text{VO}_2\text{peak}\) improved with both training methods but the change was greater after high intensity interval training (4.9 ml·kg\(^{-1}\)·min\(^{-1}\)) versus continuous training (2.6 ml·kg\(^{-1}\)·min\(^{-1}\))\(^{175}\). Pokan et al (2004) reported male HTx recipients who participated in high intensity and long-term endurance training (n = 12) (7 to 10 hours per week for \(\geq\)2 years; except 2 subjects 15 to
20 hours per week) had a VO\textsubscript{2peak} (45 ml.kg\textsuperscript{-1}.min\textsuperscript{-1}) 29% higher than age-matched healthy sedentary males\textsuperscript{179}.

The extent of cardiac allograft re-innervation seems to play an important role in determining VO\textsubscript{2peak}. Cardiac re-innervation has been shown to occur in 40 to 70% of HTx recipients, with sympathetic re-innervation observed to occur at the earliest at 5 to 6 months post-HTx and parasympathetic re-innervation occurring more than 1 to 3 years post-HTx\textsuperscript{180,181}. An increase in heart rate variability (defined as the beat to beat variation in HR) is used as a sign of parasympathetic re-innervation\textsuperscript{182,183}. Awad et al (2016) stated that sympathetic re-innervation of the left ventricle is necessary to improve ventricular function, improve regulation of blood flow and exercise performance, and sympathetic re-innervation of the sinus node is required to restore resting HR and the chronotropic response to exercise, and both of these do not necessarily occur at the same time\textsuperscript{184,185}. Bengel et al (2001, 2002) reported a modest positive univariable association between sympathetic re-innervation and time post-HTx\textsuperscript{186,187}. Those HTx recipients who had a re-innervated cardiac allograft displayed significantly greater peak exercise power output, HR, LVEF, and LVEF reserve (peak minus rest) compared with those without re-innervation\textsuperscript{186,187}. These authors determined the presence and extent of cardiac allograft re-innervation by using positron emission tomography\textsuperscript{184,186,188,189}.

Improvements in VO\textsubscript{2peak} post-HTx with high intensity interval training performed for 1 year were found to be attributable to skeletal muscle changes, with changes in CO contributing less than 5% to the increase in VO\textsubscript{2peak}\textsuperscript{107}. Other studies reinforce this finding, with no association between CO and increased VO\textsubscript{2peak} found with ≤1 year of exercise training performed post-HTx\textsuperscript{135,171}. These peripheral improvements seem to be primarily attributed to favourable skeletal muscle adaptations\textsuperscript{171} including increased oxidative enzyme capacity, increased type I muscle fibres\textsuperscript{172} and increased mitochondrial volume density\textsuperscript{190}. Furthermore, improved muscular exercise capacity and reduced body fat have been found to be the strongest predictors of increased VO\textsubscript{2peak} one to eight years post-HTx\textsuperscript{143}.

The highest ever VO\textsubscript{2peak} recorded post-HTx is 64 ml.kg\textsuperscript{-1}.min\textsuperscript{-1} measured at 32 months post-HTx\textsuperscript{191}. This male HTx recipient was a professional cyclist with a VO\textsubscript{2peak} of 71 to 75 ml.kg\textsuperscript{-1}.min\textsuperscript{-1} prior to being diagnosed with HF (non-ischaemic cardiomyopathy)\textsuperscript{191}.
This remarkable $\dot{V}O_{2\text{peak}}$ was attributed to greater stroke volume, skeletal muscle oxygen extraction and high pre- and post-HTx levels of aerobic power and endurance training$^{191}$. A recent study by Rosenbaum et al (2016, n=201) has found long-term survival to improve with participation in an exercise-based cardiac rehabilitation (CR) program early post-HTx (mean 14 sessions) when adjusted for baseline debility$^{114}$, with participation also found to reduce hospital readmission rates (up to 29% reduction in 1 year readmission)$^{192}$.

Training intensity and duration seem to impact the extent of the improvement in $\dot{V}O_{2\text{peak}}$ post-HTx$^{138,175,179}$, with other likely contributors being pre-HTx fitness and level of exercise training, cardiac allograft re-innervation and restoration of chronotropic potential$^{138}$. These findings suggest that, similar to the general non-athletic population, peripheral factors largely determine exercise capacity post-HTx$^{143}$, with regular participation in adequate levels of exercise training vital.

**Measuring muscle strength**

Two of the more common options for objectively measuring muscle strength are isokinetic testing or hand-held dynamometry$^{193}$. Isokinetic dynamometers are computerized machines capable of generating strength curves and providing multiple elements of measuring muscle strength, including peak force, endurance, power, angle of maximal force and occurrence$^{194}$. Unfortunately, due to the high cost and complexity of this equipment it is difficult to use in the clinical setting. Hand-held dynamometry has been shown to be suitable for monitoring changes in muscle strength in people with chronic obstructive pulmonary disease$^{195}$. Isometric measurements using hand-held dynamometry are simple, easy to use in the clinical setting, provide quality information$^{196}$ and have been shown to be a valid and reliable measure of quadriceps muscle strength when compared to isokinetic dynamometry$^{193,197}$.

For this study the Lafayette manual muscle test system hand-held dynamometer was used to assess quadriceps muscle strength, with peak force recorded in kilograms. Quadriceps muscle strength corrected for body weight (QS%) was used as a surrogate measure of lower limb strength (addition of best attempt of 3 on each leg divided by body weight). Walsh et al (2013) used this measure of QS% and found an increase in QS% predicted 6MWD improvement post-LTx$^{52}$. In another study, baseline QS% was
the strongest independent predictor of responders to pulmonary rehabilitation as defined by improvement in 6MWD\textsuperscript{198}. No studies to date have investigated whether quadriceps muscle strength is associated with levels of physical activity in the HTx population. The aim of this thesis is to investigate factors that may be associated with estimates of physical activity post-HTx. It is expected that exercise capacity as measured by 6MWD and QS\% will be positively associated with estimates of physical activity, and BMI will be negatively associated with estimates of physical activity.

**Summary**

This chapter has covered the first aim of this thesis i.e. to review the relevant literature related to obesity, levels of physical activity and exercise capacity post-HTx. In this chapter the aetiology, pathophysiology, classification and management of HF from pharmacological therapies through to HTx have been addressed. In addition, the role of obesity and physical (in)activity post-HTx in term of exercise capacity, and the impact of HTx and immunosuppression therapy on this have been discussed, as have the effects of exercise training post-HTx and measuring muscle strength. The following chapter (Chapter 3) will examine aims two and three i.e. describe levels of physical activity in a group of individuals post-HTx and identify factors that may be associated with estimates of physical activity (physical activity level (PAL) and average daily time spent performing at least moderate intensity activity (\(\geq 3\) METs)) post-HTx.
Chapter 3. Quadriceps muscle strength and body mass index are associated with estimates of physical activity post-heart transplantation

QUADRICEPS MUSCLE STRENGTH AND BODY MASS INDEX ARE ASSOCIATED WITH ESTIMATES OF PHYSICAL ACTIVITY POST-HEART TRANSPLANTATION

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Abstract

BACKGROUND: Whilst exercise capacity improves post-heart transplantation (HTx), it remains unclear if the level of physical activity shows similar improvement. The purpose of this study was to (1) describe physical activity levels and (2) identify factors which may be associated with levels of physical activity post-HTx.

METHODS: A prospective observational cross-sectional study was conducted at a single centre HTx outpatient clinic. Medically stable adult recipients ≥6 months post-HTx were recruited. Physical activity level (PAL) and average daily time spent at least moderately active (≥3 metabolic equivalents (METs)) were estimated using a multi-sensor device. Factors investigated were demographic (age, sex, body mass index (BMI), time post-HTx and reason for HTx), corticosteroid use, exercise capacity (six minute walk distance) and quadriceps muscle strength corrected for body weight (QS%).

RESULTS: The mean post-HTx time of the 75 participants was 9.2 ± 7.0yrs (0.5 to 26yrs). Twenty-seven (36%) were classified as extremely inactive (PAL<1.40); 26 (34.6%) sedentary (1.40< PAL ≤1.69) and 22 (29.3%) active (PAL >1.70). Multivariable analysis showed greater QS% (β=0.004 (0.002 to 0.006) p=0.001) to be independently associated with increased PAL. For increased time ≥3 METs both greater QS% (β=0.0164 (0.003 to 0.029), p=0.014) and lower BMI (β=-0.0626 (-0.115 to -0.0099), p=0.021) were independently associated.

CONCLUSIONS: The degree of observed sedentary behaviour post-HTx is surprising, with the majority of participants not reaching levels of physical activity recommended for health benefits. QS% and BMI were the only factors found to be independently associated with estimates of physical activity. Further quality trials are required to demonstrate the long-term benefits of regular physical activity and investigate ways of increasing adherence to physical activity post-HTx.
INTRODUCTION

Heart transplantation (HTx) is a well-accepted treatment for end-stage heart failure (HF)\(^6\). Whilst survival rates in the first year post-HTx have improved; long-term survival has remained essentially unchanged for the last 20 years\(^9\). Cardiovascular (CVD) events are a leading cause of death post-HTx\(^6\), with cardiac allograft vasculopathy (CAV) affecting 50% of recipients by 10 years post-HTx\(^19\).

Obesity (Body mass index (BMI) ≥30 kg/m\(^2\)) is common post-HTx\(^7\), with recipients reported to gain approximately 10 kg one year post-HTx\(^7\). Obesity post-HTx is associated with increased risk of CVD\(^7\), CAV\(^8\), rejection\(^8\), and diabetes\(^8,8\). The impact of obesity and physical inactivity on all-cause mortality in the general population is well described\(^14,15\). In healthy and chronic disease populations, increased exercise capacity and higher levels of physical activity have been found to have a favourable effect on CVD risk factors including blood pressure, diabetes and obesity\(^20\). Whilst the impact of low levels of physical activity has been reasonably well-documented in healthy and chronic heart disease populations\(^3,4,4\), this has not been well-described in the post-HTx population. There is evidence to suggest that exercise capacity improves post-HTx\(^1\)–\(^3\). Studies have demonstrated the benefits of exercise training post-HTx, with exercise training reportedly improving long-term survival\(^1\) and peak oxygen consumption\(^1,3\), and resistance training improving skeletal muscle mass\(^1\), strength\(^1\) and bone density\(^2\). Andersen et al (2017) in a recent Cochrane review reported that exercise-based cardiac rehabilitation (CR) improves exercise capacity compared with no exercise post-HTx\(^1\), yet they concluded that further adequately powered and high quality trials are needed to demonstrate the longer-term benefits of exercise post-HTx\(^1\).

Physical activity is defined as any bodily movement produced by skeletal muscles during every day functioning\(^3\), reflecting both the physical and behavioural performance of the individual\(^2\). Initiating and maintaining involvement in regular physical activity is determined by many variables\(^3\) including exercise-associated symptoms, peripheral muscle strength, training and disease status, mood, past behaviours, health beliefs, personality characteristics and socio-economic, cultural and external factors\(^2,3\). There are a variety of ways of measuring levels of physical activity, but multi-sensor devices that provide an estimate of energy expenditure (EE) normalised for resting EE offer several advantages\(^9\). In particular, using this approach,
the physical activity level (PAL) can be derived. This measure, which takes into account differences in body size, expresses daily EE as a function of overnight EE\textsuperscript{98,203}. Leading health agencies, including the World Health Organisation, have developed 3 broad PAL classes to categorise physical activity: extremely inactive (PAL < 1.40)\textsuperscript{91}, sedentary (PAL 1.40 to 1.69)\textsuperscript{99} and active (PAL ≥1.70)\textsuperscript{99}. Healthy individuals who are extremely inactive (PAL <1.40) and sedentary (PAL 1.40 to 1.69) have been shown to have increased risk factors for CVD with those who are extremely inactive (PAL <1.40) at increased risk of CVD, diabetes and some types of cancer\textsuperscript{15,204}. The mean PAL range for adults aged 18 to 64 years in western populations has been documented as approximately 1.60 to 1.75 (sedentary to moderately active)\textsuperscript{91}.

Only a few small studies have attempted to describe physical activity levels in the post-HTx population\textsuperscript{60,101,104}. A greater body of evidence exists for the post-lung transplant (LTx) population, with studies reporting reduced time spent walking and reduced time spent moderately active (≥3 METs)\textsuperscript{111,112,205,206}, with higher levels of daily physical activity related to greater exercise capacity, physical functioning and preserved muscle strength\textsuperscript{112}. Whilst it is likely that similar factors are related to levels of physical activity in the HTx population, to date no study has reported the normalised PAL in a large group of HTx recipients using a reliable multi-sensor device or investigated factors that may be associated with estimates of physical activity. Therefore, the purpose of this study was to (1) describe physical activity levels post-HTx using a multi-sensor device (SenseWear Pro3 armband (SWA)) and (2) identify factors which may be associated with estimates of physical activity (PAL and average daily time spent at least moderately active (≥3 METs)) post-HTx. We hypothesize that PAL and average daily time spent ≥3 METs will correlate directly with six minute walk distance (6MWD) and quadriceps muscle strength corrected for body weight (QS%), inversely with age, BMI, time post-HTx and ischaemic cardiomyopathy and no correlation with sex or other aetiologies of cardiomyopathy.
MATERIALS AND METHODS

Patient selection

In this prospective observational cross-sectional study, medically stable adult HTx recipients were recruited from a single centre HTx outpatient clinic (The Prince Charles Hospital, Brisbane, Australia). Inclusion criteria were participants ≥6 months post-HTx and able to wear the SWA ≥22 hours/day for ≥3 days. Exclusion criteria were left ventricular ejection fraction (LVEF) (by any imaging modality), less than 50%, a rejection episode within the past two months or any injury or illness that could be reasonably expected to reduce mobility. This study was approved by the institutional ethics committee (HREC/13/QPCH/34) and informed written consent was gained from each participant.

Study parameters

Primary outcome measures of PAL and average daily time spent ≥3 METs were estimated using the SWA. Participants were asked to wear the SWA continuously for one week except when participating in water-based activities. The SWA has been validated against other techniques measuring EE including indirect calorimetry and the doubly labelled water method in healthy and chronic disease populations. Output parameters include PAL, average daily time spent ≥3 METs, steps and time spent lying down and sleeping. Based on PAL, participants were classified as: extremely inactive (PAL <1.40), sedentary (PAL 1.40 to 1.69) or active (PAL ≥1.70). Note whilst the SWA reports daily steps (also an indicator of physical activity), there is some evidence in other clinical populations that the device is inaccurate at detecting steps, particularly at slow walking speeds. Hence, we did not report daily steps for this study.

Measures

Demographics

Age, sex, height, body weight, BMI, time post-HTx, reason for HTx (aetiology of cardiomyopathy), immunosuppression regime at time of assessment and most recent post-HTx LVEF within 12 months of assessment time point were recorded.
**Quadriceps muscle strength**

Quadriceps muscle strength was measured using a handheld dynamometer (Lafayette Manual Muscle Test System) as per published protocol\(^{195}\) with an adjustable strap secured behind the participant’s leg and held to the dynamometer to ensure an isometric contraction as previously described\(^{198}\). In a seated position on a plinth with 90 degrees hip flexion, feet not touching the floor and the knee positioned at 70 degrees flexion, the participant was instructed to extend their knee maximally for four seconds with the peak force of the isometric contraction recorded in kilograms (kg). Three attempts were conducted on each leg alternating between legs each time with at least one minute rest between attempts as per the published protocol\(^{52}\). To standardise for body weight, quadriceps muscle strength was expressed as a percentage (QS%) by adding together the best attempt on each leg and dividing by the participant’s body weight (kg) as per Walsh et al (2014)\(^{198}\).

**Six minute walk test**

Exercise capacity was measured using the six-minute walk test (6MWT) conducted on a thirty metre track in a hospital corridor as per standardised protocol\(^{128}\). Time was monitored using a stopwatch and participants were instructed to walk at their own pace whilst attempting to cover the greatest distance possible in the six minutes. Standard encouragement was provided every minute as per recommended guidelines\(^{128}\).

**Study protocol**

Following recruitment, participants performed the quadriceps strength test, 6MWT and had the SWA fitted on their right upper arm. Instructions were given to participants to wear the SWA in their home and community environment for one week. Upon return of the SWA the physical activity measures were uploaded and PAL and average daily time spent $\geq 3$ METs were estimated and recorded. These assessment measures are clinically relevant and easily reproducible.

**Statistical analysis**

Statistical analysis was performed using linear regression and spearman correlation as appropriate to determine predictors of PAL and average daily time spent $\geq 3$ METs. Data was log transformed where it did not comply with normality. Univariable (p$<0.1$)
and multivariable analysis was conducted with demographics and routine clinical measures thought likely to impact PAL and average daily time spent ≥3 METs analysed. Variables included were age, sex, time post-HTx, BMI, reason for HTx (aetiology of cardiomyopathy), corticosteroid use at time of assessment, 6MWD and QS%. Data is expressed as mean ± SD unless otherwise stated.

RESULTS

Participants

Eighty-seven HTx recipients were recruited between February 2013 and August 2014. Of these, 9 were excluded due to wear time of the SWA device <22 hrs/day for <3 days, 1 for reduced LVEF (42%) and 2 for device failure. Therefore, seventy-five participants, (20 female, 26.7%) and time post-HTx 9.2 ± 7.0 years were included (Table 3). Reasons for HTx were 27 (35.5%) ischemic cardiomyopathy, 28 (37.3%) idiopathic dilated cardiomyopathy and 20 (26.3%) other (restrictive cardiomyopathy, familial, Fabry disease, hypertrophic-obstructive cardiomyopathy, amyloid, congenital heart disease, sarcoidosis and valvular heart disease).
Table 3: Demographics

<table>
<thead>
<tr>
<th>Demographics (n=75)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56 ± 14</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>20, 26.7</td>
</tr>
<tr>
<td>Body Mass (kg)</td>
<td>82.6 ± 19.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.0 ± 8.7</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.7 ± 6.1</td>
</tr>
<tr>
<td>Time post-transplant (years)</td>
<td>9.2 ± 7.0</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>60.8 ± 7.2</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>488 ± 100</td>
</tr>
<tr>
<td>Quadriceps strength corrected for body weight (QS%)</td>
<td>78.8 ± 24.6</td>
</tr>
</tbody>
</table>

Table 3: Demographic data, exercise capacity (6MWD) and quadriceps strength corrected for body weight (QS%).

Immunosuppression

All participants were on an immunosuppression regimen including a calcineurin inhibitor and at least one agent from a different class. The majority of recipients were on a combination of cyclosporin (n=55) and mycophenolate mofetil (MMF) (n=36). Other immunosuppression medications used were tacrolimus (n=18), everolimus (n=11), sirolimus (n=6), myfortic (n=7) and azathioprine (n=18). Most participants were not taking any oral corticosteroids (prednisolone) at the time of the study (65%) with approximately 35% taking at least 1 mg per day (1 -10 mg) (Table 4).
Table 4: Comparison of corticosteroid use of active (PAL≥1.7) and inactive (PAL<1.7) groups

<table>
<thead>
<tr>
<th>Corticosteroid (prednisolone) use at time of assessment</th>
<th>Active group (PAL≥1.7)</th>
<th>Inactive group (PAL&lt;1.7)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>5</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>No</td>
<td>17</td>
<td>32</td>
<td>49</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>53</td>
<td>75</td>
</tr>
</tbody>
</table>

Table 4: Corticosteroid (prednisolone) use at time of assessment.

Outcomes

The physical activity parameters are included in Table 5. The mean PAL for the group was 1.66 ± 0.47 and the mean average daily time spent ≥3 METs was 143 ± 155 minutes. Using the PAL categories, 25 (33.3%) participants were classified as extremely inactive (PAL <1.40), 28 (37.3%) sedentary (PAL 1.40 to 1.69) and 22 (29.3%) active (PAL ≥1.70). There was a similar distribution of participants on oral corticosteroids (prednisolone) at time of assessment in the physically active (PAL ≥1.70) and inactive (PAL <1.70) groups (Table 4). When we looked at corticosteroid use as a categorical value, we found no difference in PAL between those on prednisolone or not (p=0.60). When we looked at corticosteroid dose as a continuous variable, no difference was found between PAL and daily dose (r=-0.070, p=0.560). When we compared demographic data, clinical measures (6MWD, QS% and LVEF) and corticosteroid use of the physically active (PAL ≥1.70) and inactive (PAL <1.70) groups, QS% (p<0.001) and BMI (p=0.020) were the only factors assessed found to differ significantly between the two groups (Table 6).
<table>
<thead>
<tr>
<th>Outcomes (n=75)</th>
<th>%</th>
<th>PAL</th>
<th>Mean daily time spent ≥3 METs (mins)</th>
<th>BMI</th>
<th>Age</th>
<th>QS%</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL GROUP (n=75)</td>
<td>100</td>
<td>1.66 ± 0.47</td>
<td>143 ± 155</td>
<td>27.7 ± 6.1</td>
<td>56 ± 14</td>
<td>78.8 ± 24.6</td>
</tr>
<tr>
<td>Extremely inactive (&lt; 1.40)</td>
<td>33.3</td>
<td>1.28 ± 0.06</td>
<td>24.56 ± 16.95</td>
<td>30.45 ± 7.18</td>
<td>57.64 ± 13.64</td>
<td>69.57 ± 25.35</td>
</tr>
<tr>
<td>(n=25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary (1.40-1.69) (n=28)</td>
<td>37.3</td>
<td>1.52 ± 0.09</td>
<td>88.14 ± 44.00</td>
<td>26.96 ± 4.78</td>
<td>54.19 ± 13.18</td>
<td>76.04 ± 19.91</td>
</tr>
<tr>
<td>Active (≥1.70) (n=22)</td>
<td>29.3</td>
<td>2.27 ± 0.41</td>
<td>346.77 ± 133.95</td>
<td>25.15 ± 4.64</td>
<td>55.54 ± 16.99</td>
<td>94.21 ± 23.17</td>
</tr>
</tbody>
</table>

Table 5: Physical activity level (PAL), mean daily time spent ≥3 METs, BMI, age and QS%. 
Table 6: Characteristics of active (PAL ≥1.70) and inactive (PAL <1.70) groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Active group (n=22)</th>
<th>Inactive group (n=54)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.5 ± 17.0</td>
<td>56 ± 13.4</td>
<td>0.90</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>7, 32</td>
<td>13, 24</td>
<td>0.57</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2 ± 4.6</td>
<td>28.7 ± 6.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Time post-transplant (years)</td>
<td>9.9 ± 7.2</td>
<td>8.7 ± 7.0</td>
<td>0.52</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>60.3 ± 6.2</td>
<td>61 ± 7.5</td>
<td>0.72</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>501.8 ± 117.8</td>
<td>483 ± 93.4</td>
<td>0.47</td>
</tr>
<tr>
<td>Quadriceps strength corrected for body weight (QS%)</td>
<td>94.2 ± 23.2</td>
<td>72.5 ± 22.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Taking corticosteroid (n, %)</td>
<td>5, 22.7</td>
<td>21, 39.6</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Table 6: Demographic data, exercise capacity (6MWD), quadriceps strength corrected for body weight (QS%) and corticosteroid use at time of assessment.

The results of the univariable analysis examining the relationship between PAL and clinical measures are shown in Table 5 and Figure 2. Both the 6MWD and QS% were positively associated with PAL (p<0.1) and BMI negatively associated with PAL (p<0.1). Multivariable results are shown in Table 7 with greater QS% identified as the only measure independently associated with increased PAL.
Table 7: Univariable & multivariable analysis: Predictors of PAL

<table>
<thead>
<tr>
<th>Univariable: PAL</th>
<th>B</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>-0.015</td>
<td>-0.024 – -0.007</td>
<td>0.001</td>
</tr>
<tr>
<td>6MWD</td>
<td>0.001</td>
<td>0.000 – 0.012</td>
<td>0.024</td>
</tr>
<tr>
<td>QS%</td>
<td>0.004</td>
<td>0.002 – 0.006</td>
<td>&lt;0.001</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Multivariable: PAL</th>
<th>B</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>QS%</td>
<td>0.004</td>
<td>0.002 – 0.006</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 7: Physical activity level (PAL): dependent variable. Independent variables evaluated: Participants’ age, sex, time post-HTx, body mass index (BMI), reason for HTx, 6-minute walk distance (6MWD) and quadriceps muscle strength corrected for body weight (QS%).
Figure 2: Physical activity level (PAL) (left panels) and mean daily time spent at least moderately active (≥3 METs) (right panels) are plotted against body mass index (BMI), 6-minute walk distance (6MWD) and quadriceps muscle strength corrected for body weight (QS%).
The results of the univariable analysis examining the relationship between average daily time spent ≥3 METs and clinical measures are shown in Table 8 and Figure 2. In univariable analysis, 6MWD and QS% were found to be positively associated with average daily time spent ≥3 METs (p<0.1) and age and BMI were found to be negatively associated with average daily time spent ≥3 METs (p<0.1). In multivariable analysis greater QS% and lower BMI were identified as the only measures independently associated with increased average daily time spent ≥3 METs (Table 8).

Table 8: Univariable & multivariable analysis: Predictors of mean daily time spent ≥3 METs

<table>
<thead>
<tr>
<th>Univariable: Time spent ≥3METs</th>
<th>B</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.021</td>
<td>-0.041 – -0.001</td>
<td>0.042</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.102</td>
<td>-0.145 – -0.059</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6MWD</td>
<td>0.005</td>
<td>0.003 – 0.008</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QS%</td>
<td>0.026</td>
<td>0.015 – 0.037</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multivariable: Time spent ≥3METs</th>
<th>B</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>QS%</td>
<td>0.016</td>
<td>0.003 – 0.029</td>
<td>0.014</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.063</td>
<td>-0.115 – -0.010</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Table 8: Mean daily time spent ≥3METs: dependent variable. Independent variables evaluated: Participants’ age, sex, time post-HTx, body mass index (BMI), reason for HTx, 6-minute walk distance (6MWD) and quadriceps muscle strength corrected for body weight (QS%).

On inspection of the different PAL categories, as PAL increased, average daily time spent at least moderately active (≥3 METs) and QS% increased and BMI decreased (Table 5 & Figure 3). The active group (PAL ≥1.70) were extremely active (mean PAL for this group 2.27 ± 0.41) (Table 5 & Figure 3).
Figure 3: Mean daily time spent ≥3 METs and quadriceps muscle strength corrected for body weight (QS%) for each of the three physical activity level (PAL) groups: extremely inactive (PAL <1.40), sedentary (PAL 1.40 to 1.69) and active (PAL ≥1.70). a: time spent ≥3 METs significantly different (p<0.01) from the other groups; b: quadriceps (quads) strength significantly different from the other groups.

Discussion

This study provides baseline information on the levels of physical activity of a broad range of adult HTx recipients. Our sample had similar numbers of subjects from each of the 3 PAL and BMI categories. The majority of participants were male (73.3%), which is consistent with our hospital HTx cohort where 82% are male. The mean PAL for the whole group was greater than 1.60 (PAL = 1.66 ± 0.47) suggesting that on average, HTx recipients are sedentary to moderately active. However, closer inspection of the data suggests that the majority of participants (71%) were essentially inactive (PAL <1.70) and that 33% were extremely inactive with a PAL of <1.40. The average PAL for the group was increased due to the small number of HTx recipients who were highly active. This active group (PAL ≥1.70) were in some instances extremely active with many exceeding the recommended guidelines of at least 150 minutes of moderate
physical activity per week. Indeed the mean daily time spent moderately active (≥3 METs) for this group was 347 ± 134 minutes.

Our results reflect the level of physical activity recorded in the general adult population in western countries (PAL 1.60 to 1.75)\textsuperscript{91} and reinforce the findings of previous smaller studies post-HTx. A similar amount of daily time spent ≥3 METs was recorded using the SWA in 12 HTx recipients at one year post-HTx\textsuperscript{60}, sedentary behaviour was observed using mean activity counts from an accelerometer (Actiwatch 2) and self-reporting in 27 women post-HTx (5.2 ± 4.4 years)\textsuperscript{104} and physical activity levels of 47 HTx recipients (4.8 ± 3.0 years) was reported to be in the low to moderate range of EE assessed using a questionnaire\textsuperscript{101}. In contrast, Gustaw et al (2017) in a study assessing physical activity levels in 113 adult post-solid organ transplant recipients via an internet-based questionnaire found adult HTx recipients (24%; n=27) were engaged in above limited levels of physical activity, but stated that this difference may be due to the use of a voluntary convenience sample and participant characteristics\textsuperscript{113}.

Not surprisingly, we found higher QS% to be independently associated with higher PAL and more average daily time spent at least moderately active(≥3 METs). We are unable to determine if the higher QS% is causally related to increased PAL or vice versa, i.e. if PAL results in higher QS%. We can report that our results are similar to those previously described post-LTx with Langer et al (2009) reporting better quadriceps muscle strength related to higher levels of daily physical activity\textsuperscript{112} and Walsh et al (2013) reporting improvements in exercise capacity (measured by 6MWD) largely explained by improvements in QS% and by recipients’ pre-LTx exercise capacity\textsuperscript{52}.

We did find an inverse and independent association between BMI and average daily time spent ≥3 METs, suggesting that those with a lower BMI were potentially more active and physically fit. This would appear counter to the ‘obesity paradox for HF’ (which suggests that higher body weight individuals with HF have better exercise capacity and better chances of survival). Our results are however consistent with the smaller study by Evangelista et al (2005), who also reported an inverse relationship between physical activity and obesity in 27 women post-HTx (5.2 ± 4.4 years), with more obese individuals being less active\textsuperscript{104}.
Interestingly, greater 6MWD (measure of exercise capacity) although found to be related to increased PAL and average daily time spent ≥3 METs was not found to be independently associated with either PAL or time spent ≥3 METs in our HTx sample. This may reflect the fact that 6MWD is an index of exercise capacity and may not necessarily be directly related to physical activity. Whilst individuals may have the capacity to perform exercise, they may choose not to for a variety of reasons such as motivation and comorbidities, and hence have a low PAL.

Unfortunately, we did not assess quality of life (QoL). Poor QoL may be a reflection of mental health or physical inability and may be more predictive of physical activity than other physical measures. Assessment of this should be included in future studies. Although the majority of participants were classified as extremely inactive or sedentary they may have been content with their level of physical function. Contrary to our hypothesis, time post-HTx and age were not found to be associated with estimates of physical activity nor was type of cardiomyopathy.

Other limitations of this study should be acknowledged. First, the design is explorative and cross sectional weakening the strength of conclusions, and due to the very nature of the study, we would have had a survivor bias in our sampling. It is possible and likely that physical activity may change over time, and those who previously led an active lifestyle may be more likely to be more active post-HTx. Unfortunately pre-HTx physical activity and BMI data were not available. Those with a longer history of HF may be less physically active post-HTx due to having a longer period to become accustomed to being less physically active. Current and previous psychological and behavioural factors that may impact levels of physical activity such as interests, motivation, anxiety and depression were not investigated either. Diastolic dysfunction was not assessed which may impact levels of physical activity in those with preserved LVEF.

Medication regimes may impact physical activity levels, and although no relationship was found between corticosteroid use at time of assessment and PAL, we were not able to accurately determine the relationship between immunosuppression load post-HTx and physical activity as time post-HTx varied greatly in our dataset. One may argue that time post-HTx could be a potential surrogate for immunosuppression load (i.e. longer period post-HTx would likely have greater immunosuppression load). We also
acknowledge as a potential limitation not acquiring information on the role of complications or change in weight in the first year post-HTx and eventual outcomes due to nine participants receiving HTx away from our site and seven participants being <12 months post-HTx at time of assessment.

Although participants were mean 9.2 ± 7.0 years post-HTx, participation in a post-HTx cardiac rehabilitation (CR) program and current involvement in a formal exercise program were not recorded. However, early exercise rehabilitation is commenced routinely post-HTx with the aim to mobilize recipients as early as possible post-extubation. Daily walking and lower-limb strengthening exercises (sit to stand, squats and stair climbing) are commenced and gradually progressed during the initial hospital admission. On discharge from hospital, all recipients are referred to their local outpatient CR program if there is one available. Individualised home exercise programs consisting of walking and lower-limb strengthening exercises are also provided which are monitored and progressed during regular outpatient consultations. As all participants were ≥6 months post-HTx it is unlikely that any participants were actively enrolled in a CR program at the time of assessment. A recent retrospective review by Rosenbaum et al (2016) reported an association between increased participation in early CR and long-term survival in HTx recipients, while adjusting for baseline debility, with attendance early post-HTx corresponding to approximately 10% decreased risk of death while controlling for baseline 6MWT results, rejection episodes (early graft failure) and corticosteroid dose\textsuperscript{201}.

We can conclude that management post-HTx is complex. The degree of observed sedentary behaviour post-HTx is surprising, highlighting the need to actively intervene on physical activity as the majority of participants assessed were not reaching levels of physical activity recommended for health benefits. Quadriceps muscle strength corrected for body weight and body mass index were the only factors found to be independently associated with estimates of physical activity (PAL and average daily time spent at least moderately active (≥3 METs)). By encouraging increased levels of physical activity and by targeting muscle strength recovery in this patient population we may improve long-term health outcomes. Further quality trials are required to demonstrate the long-term benefits of regular physical activity and investigate ways of increasing adherence to physical activity post-HTx.
Chapter 4. Discussion

Summary of findings
The main goal of this thesis was to describe levels of physical activity and identify factors associated with levels of physical activity post-HTx. Demographic factors (age, sex, BMI, time post-HTx, reason for HTx), corticosteroid use at time of assessment, QS% and exercise capacity (6MWD) were assessed to determine if they were associated with estimates of physical activity. A physical activity monitor (SWA) was utilised to estimate levels of physical activity (PAL and average daily time spent at least moderately active (≥3 METs)). This chapter summarises the main findings from our study in Chapter 3 in the context of relevant literature and addresses clinical implications and future directions.

This study is the first to estimate levels of physical activity using the SWA with a large cohort of HTx recipients. As outlined in Chapter 3, most participants (71%) were classified as inactive (PAL <1.70), with 33% classified as extremely inactive (PAL <1.40) and 38% sedentary (PAL =1.40 to 1.69). Twenty-nine percent (29%) of participants were classified as active (PAL ≥1.70). The level of physical inactivity found is surprising; however, based on PAL, results for the whole cohort of participants (PAL =1.66 ± 0.47) reflects the level of physical activity recorded in the general adult population in western countries (PAL =1.60 to 1.75)\textsuperscript{91}. In addition, the findings of this study are similar to those found in previous smaller studies post-HTx\textsuperscript{60,101,104}.

Study Hypotheses
With regards to the original hypotheses stated in chapter 1, the study found the following:

For individuals post-HTx, PAL and average daily time spent ≥3 METs will be:

a. directly related to exercise capacity (as determined by 6MWD (REJECT) and quadriceps strength (ACCEPT))
b. inversely related to participant age (REJECT), BMI (ACCEPT), time post-HTx (REJECT) and presence of ischaemic cardiomyopathy (REJECT)
c. unrelated to other aetiologies of cardiomyopathy, sex or corticosteroid use at time of assessment (ACCEPT)
**Quadriceps Strength**

When factors associated with estimates of physical activity were investigated in multivariable analysis, greater QS% was found to be independently associated with higher PAL, and greater QS% and lower BMI were both independently associated with more average daily time spent at least moderately active (≥3 METs). There is no literature related to HTx and quadriceps strength. The results in Chapter 3 are similar to those previously described in post-LTx recipients i.e. Langer et al (2009) who reported better quadriceps muscle strength was related to higher levels of daily physical activity and Walsh et al (2013) findings of improvements in exercise capacity (measured by 6MWD) largely explained by improvements in QS% and recipients’ pre-LTx exercise capacity.

In community dwelling older adults, Foong et al (2016, n =636) studied the relationship between accelerometer-determined physical activity levels, muscle mass and lower limb strength. These authors found physical activity to be positively associated with lean body mass percentage and lower limb strength, with those who participated in ≥150 minutes of moderate/vigorous physical activity per week having greater lean body mass percentage and lower limb strength, with the largest effect for vigorous activity. Similar to the current study, these studies highlight the importance of ambulatory muscle strength, with the latter study highlighting the importance of adequate levels of physical activity for healthy maintenance of weight and strength in older adults.

Frailty is a clinical syndrome ‘characterised by an increased vulnerability to stressors with a decline in reserve and function of multiple physiologic systems’. Frailty has been associated with functional impairment and adverse health outcomes, such as disability, falls, decreased mobility, hospitalization and death. The Fried frailty phenotype is a measure that is used to assess frailty, with frailty defined as the presence of at least 3 of the following: unintentional weight loss (≥4.54 kg in past year), self-reported exhaustion, weakness (measured by grip strength), slow walking speed and low levels of physical activity. The Short Physical Performance Battery is another assessment of physical performance which includes a functional leg strength measurement by timing how long it takes for an individual to stand up and sit down 5 times without stopping. In order to enhance mortality predictions and identify who will benefit most from transplantation, centres have incorporated such measures of frailty into transplant candidate evaluation (in conjunction with cognitive assessments,
such as the Montreal Cognitive Assessment with cognitive impairment defined as a score of <26/30\textsuperscript{211-213}. Frailty pre-solid organ transplant (including HTx) has been found to be associated with increased morbidity and mortality post-solid organ transplantation\textsuperscript{211-215}. However, in a recent study by Rozenberg et al (2019, n =50) no difference was found in 1-year mortality or hospital outcomes between frail and non-frail LTx candidates\textsuperscript{216}. Some transplant centres provide rehabilitation interventions pre- and post-solid organ transplantation with the aim of reducing frailty and improving physical function.

The results in Chapter 3 outline that those who were less physically active had weaker quadriceps muscles (QS%). However, we are unable to determine if the stronger quadriceps muscle strength is causally related to increased levels of physical activity or vice versa, i.e. if increased levels of physical activity results in stronger quadriceps muscles. An earlier study by Rozenberg et al (2017, n =50) evaluating skeletal muscle function pre-LTx showed that the quadriceps muscle was the most common muscle observed to be weak pre-LTx\textsuperscript{217}. Using QS% as an indicator of frailty, those who are less frail (stronger quadriceps) may have the ability to be more physically active. However, muscle function is only one component of frailty and other factors also need to be considered. Currently, hand grip strength is the only measure of strength used in the Fried frailty phenotype\textsuperscript{209}. Adding QS%, utilizing previously published protocols\textsuperscript{195,198} could potentially improve concurrent validity. A QS% measure could be more widely utilised as part of the transplant candidate evaluation process and to monitor progress post-HTx. It has been shown to have good reliability, with test-retest reliability of this measure on a pilot study of LTx recipients of (ICC; 3.1) r=0.996 with a coefficient of variation of 2.7%\textsuperscript{52}.

**Obesity/BMI**

As outlined in Chapter 3 and Table 3, an inverse and independent association between BMI and time spent at least moderately active (≥3 METs) was found, suggesting those who had a higher BMI were less active and therefore potentially less fit. Obesity post-HTx has been found to be associated with increased morbidity and mortality\textsuperscript{73, 79-81, 218}. Foroutan et al (2018) also reported a BMI >30 kg/m\textsuperscript{2} pre-HTx associated with increased mortality risk post-HTx in a large systematic review and meta-analysis\textsuperscript{79}. In essence, to lose weight an individual needs to move more and eat less so that more energy is expended than consumed\textsuperscript{17}. Unfortunately, in our western, time-poor, consumerist
society, in which energy dense foods are readily available and individuals need to be intrinsically motivated to get enough physical activity in their day, the solutions are more complex than it seems. This is highlighted by the current world-wide obesity epidemic\textsuperscript{16}. As outlined in Chapter 1, many factors including environmental, behavioural, metabolic and genetic factors and their inter-relationships play a role in the development and maintenance of obesity\textsuperscript{18,19}. In order to reduce the incidence of obesity post-HTx, all of the contributing factors need to be addressed.

Obesity has more than doubled in the last decades in the general adult population\textsuperscript{16}, with a similar trend in the post-HTx\textsuperscript{26} and other solid-organ transplant populations\textsuperscript{219-221}. Zelle et al (2013, n=26) investigated the role of diet and physical activity in post-renal transplant weight gain\textsuperscript{116}. The authors found that weight gain over the first year post-renal transplant was mainly due to an increase in body fat (−2.4 to 19.5 kg) and those whose level of body fat remained stable were more physically active (p=0.014), consumed less sugar (p=0.021) and energy from drinks and dairy (p=0.054), and ate more vegetables (p=0.043) when compared with those who gained body fat\textsuperscript{116}. At one year post-renal transplant, gain in body fat was strongly related to total cholesterol (r=0.46, p=0.017) and triglycerides (r=0.511, p=0.011)\textsuperscript{116}. Although this is a small study, it demonstrates that lifestyle factors (high consumption of energy-rich food and drinks and low levels of physical activity) contribute to increased levels of body fat post-renal transplantation, and those who are more physically active are more likely to have a lower body fat percentage and more stable weight\textsuperscript{116,214}. This is also likely post-HTx.

Although greater exercise capacity as measured by 6MWD was found in univariable analysis to be related to increased PAL and more average daily time spent performing activities ≥3 METs, it was not found to be independently associated with these estimates of physical activity. This finding is contrary to the hypothesis and may reflect the fact that 6MWD is a surrogate for exercise capacity and may not be necessarily directly related to physical activity. HTx recipients may have the capacity to be more physically active post-HTx but due a variety of reasons such as motivation, psychosocial factors and comorbidities may have a low PAL and spend minimal time at least moderately active (≥3 METs). This finding highlights the complex nature of physical activity and supports the finding that physical activity is not a surrogate measure of exercise.
capacity, but reflects a range of behavioural, environmental and other factors. The findings of this study provide clinicians with important information when considering the impact of levels of physical activity in HTx recipients i.e. that higher exercise capacity (measured using the 6MWD) does not mandate higher levels of physical activity\textsuperscript{29}.

Contrary to the hypothesis, time post-HTx, age and ischaemic cardiomyopathy were not found to be independently associated with estimates of physical activity. It was hypothesised that as time post-HTx increased, physical functioning and therefore physical activity participation would decline due to the possibility of having more complications. However, this was not found to be the case. Frailty associated with reduced function and physical ability is more prevalent in the older population. It was therefore hypothesised that increasing age would be associated with a decline in physical activity levels. This was not found in the study, which may have been attributed to the relatively younger participant cohort i.e. only one participant was older than 75 years and nine participants were aged 70 to 75 years, with participant ages ranging from 22 to 78 years. It may be that, in the old (>75 years) and the old-old age groups (85-94 years), physical activity levels markedly decline. Ischaemic cardiomyopathy, caused by the presence on CAD, which can be caused by unhealthy lifestyle behaviours, was also not found to be associated with reduced physical activity levels. It was hypothesised that those who may have led an unhealthy lifestyle prior to HTx may have continued such behaviours post-HTx. This finding may be limited by the small sample size of the study and therefore more large-scale studies would be necessary to further investigate the impact of these factors.

**Immunosuppression**

A limitation of this thesis is that the relationship between immunosuppression load post-HTx and physical activity was not able to be accurately determined. It was difficult to compare the use and duration of corticosteroids as participants varied greatly in time post-HTx (9.2 ± 7.0 years). Since high doses of corticosteroids are typically used early post-HTx and during rejection episodes, those who had had a rejection episode within the past 2 months and those who were less than 6 months post-HTx were excluded to reduce this potential confounding effect. One may argue that time post-HTx could be a potential surrogate for immunosuppression load i.e. longer period post-HTx would likely have greater immunosuppression load. However, there was no relationship found
between time post-HTx and estimates of physical activity. When the demographic data, clinical measures (6MWD, QS% and LVEF) and corticosteroid use of the physically active (PAL ≥1.70) and physically inactive (PAL <1.70) groups were compared, QS% (p<0.001) and BMI (p=0.02) were the only factors found to differ significantly between the two groups (Table 4 in Chapter 3). Another limitation of this study is that due to the small numbers of participants the use of other medications that may impact physical activity levels such as sirolimus (which can affect skeletal muscle protein synthesis pathways) or beta blockers (which blunt the heart rate response during exercise) were not investigated.

**Limitations**

There are other limitations of this study. By the very nature of the study design, there would be an inherent survivor bias in the subject selection. Whilst it is likely that levels of physical activity may change over time, the relationship between time post-HTx and estimates of physical activity was assessed and no associations were found. It would have been useful to ascertain CR attendance rates post-HTx amongst participants and self-reporting of pre-HTx and current levels of physical activity, including participation in exercise and sports. In addition, it may have been helpful to assess pre-HTx physical activity levels using the SWA. Another limitation is that body weight at time of HTx was not reported, nor was the change in body weight from HTx to the assessment time point. To reduce confounding variables, anyone with a reduced LVEF and other co-morbidities that would otherwise impact usual level of physical activity were excluded. The presence of left ventricular diastolic dysfunction was not investigated, which may also negatively impact physical activity levels.

Psychological factors (including depression, anxiety and fear of exercising) and QoL, which may negatively impact levels of participation in physical activity, were not assessed. Future studies should include assessment of QoL as this is an important variable that may reflect mental health and physical ability and, hence, predict levels of physical activity more than factors assessed in Chapter 3. When using the SF-36 questionnaire to assess health-related QoL in the post-renal transplant population, those who were physically active had similar health-related QoL scores to active healthy control subjects and demonstrated better physical functioning and general and mental health scores when compared with sedentary renal-transplant recipients (n=317)\textsuperscript{222}. 
Moreover, higher sport participation in the post-renal transplant population was associated with greater health-related QoL\textsuperscript{222}.

Using the SF-36 questionnaire in LTx recipients, Langer et al (2012, n=34) observed better self-perceived health status (in 2 of the physical subcomponents) in the intervention group (who attended 3 months of exercise rehabilitation post-discharge from hospital) compared to the control group at 1 year post-hospital discharge\textsuperscript{111}. Daily time spent walking in the intervention group was 85 ± 27 mins and in the control group 54 ± 30 mins (adjusted difference 26 mins [95% CI 8 to 45 mins, p=0.006]). Quadriceps force (p=0.001), 6MWD (p=0.002) and self-reported physical functioning (p=0.039) were significantly higher in the intervention group and average ambulatory blood pressures were significantly lower in the intervention group (p≤0.01)\textsuperscript{111}. The authors suggested that the significant improvements in muscle strength and physical fitness in the intervention group may have enhanced the ability of those participants to be more physically active in their daily lives\textsuperscript{111}. Participating in exercise training programs has also been shown to improve self-efficacy (i.e. the confidence to perform certain behaviours) for participation in regular physical activity\textsuperscript{223}. Langer et al (2012) state that this improvement in self-efficacy may also have played a role in increasing daily levels of physical activity of the intervention group\textsuperscript{111}. This study highlights several benefits of participating in a post-transplant exercise-based rehabilitation program and the results may also be relevant for the post-HTx population.

**Clinical implications**

The results in Chapter 3 provide foundation information regarding physical activity levels and factors associated with estimates of physical activity. This is valuable for future studies and the implementation of targeted strategies aimed at improving long-term health outcomes post-HTx. The degree of sedentary behaviour observed, with most participants not achieving levels of physical activity recommended for health benefits, highlights the importance of focused interventions to increase physical activity in this patient population.
Clinical applications of this study could involve routinely utilising accelerometer devices to estimate levels of physical activity and assessing quadriceps muscle strength using the hand-held dynamometer pre and post-HTx. This measure of quadriceps muscle strength could also be included as part of a frailty tool in addition to grip strength. These simple, reliable and clinically relevant outcome measures are easily transferrable to other transplant populations and centres. Interestingly, a recent systematic review of 35 RCTs of exercise training post-solid organ transplant, including 21 HTx recipients, reported over 60 different outcome measures were used, highlighting the need to implement consistent, simple, inexpensive, reliable outcome measures to examine outcomes post-HTx.

In addition, using objective functional outcome measures provide important information regarding suitability for HTx, as well as assisting clinicians to work collaboratively with individuals and the multidisciplinary team to provide concrete feedback on current levels of physical functioning, set specific goals and implement targeted rehabilitation interventions. Interventions may include strategies to increase physical activity levels, such as endorsement of adequate participation in physical activity by medical practitioners, individualised home exercise programs, referrals to exercise-based CR programs, psychology and dietetic support, and utilisation of technology such as apps, telehealth and the internet to enable broader access and flexible modes of service delivery. Reassessment of outcome measures including muscle strength and PAL post-interventions to track progress may act as motivational tools to assist HTx recipients to maintain or increase their level of physical activity and muscle strength.

**Exercise-based rehabilitation**

A recent Cochrane systematic review by Andersen et al (2017, n=300), that included 10 RCTs assessed the effectiveness and safety of exercise-based rehabilitation for HTx recipients in terms of mortality, hospital admissions, adverse events, exercise capacity, health-related QoL, return to work and healthcare costs. The authors found that exercise-based CR increased exercise capacity (measured by $\dot{V}O_2$peak) but did not impact health-related QoL in the short term (12 weeks). It is suggested that aerobic exercise training post-HTx may reduce the pathophysiological consequences associated with cardiac denervation and prevent immunosuppression-induced adverse effects. A retrospective review by Rosenbaum et al (2016, n=201) found long-term survival improved by 10% with participation in early exercise-based CR post-HTx, when
controlling for baseline post-HTx 6MWD and early rejection episodes. The number of CR sessions attended in the first 90 days post-HTx was also found to predict survival (HR 0.90; 95% CI = 0.82 to 0.97, p=0.007) using multivariate Cox regression, with overall survival at 1, 5 and 10 years being 98%, 88% and 82% respectively. However, Anderson et al (2017) noted that a confounding variable in this study is that HTx recipients who were motivated to be physically active early post-HTx continued to adhere to exercise over time compared to those who had low adherence early post-HTx. In addition, those with complications post-HTx are generally less likely to be able to adhere to an exercise intervention and therefore the increased survival outlined in the study by Rosenbaum et al (2016) could be due to potential to participate in exercise after the initial program and not solely due to the intervention itself.

The goal of a CR program is to build confidence and motivation so that participation in regular physical activity is maintained once the program is finished. It is hoped that an exercise-based program will motivate and provide recipients with the skills to continue to be physically active independent of the program. Attending such programs may address some of the common factors that have been described as influencing levels of physical activity post-solid organ transplant. Gustaw et al (2017) found that the most common factors influencing levels of physical activity post-solid organ transplantation were ‘a feeling of health from physical activity (94%; n=106), support from family and friends (76%; n=86), high level of motivation to stay healthy (88%; n=99), knowledge and confidence about physical activity (74%; n=84), proximity to an exercise facility (73%; n=82) and physician recommendation (59%)’.

Studies have found muscular exercise capacity to be the strongest predictor of \( \dot{V}O_2 \) post-HTx, highlighting the important role of skeletal muscle for physical functioning. Nytroen et al (2012, n=48) showed improvements in muscular exercise capacity and \( \dot{V}O_2 \) with participants (time post-HTx = 4.1 ± 2.2 years) attending 1 year of high intensity interval training compared with usual care. This study and others suggest that high intensity interval training may be an effective and safe way to improve muscular exercise capacity, \( \dot{V}O_2 \) and general health post-HTx. However, strategies to maintain motivation to participate in adequate and regular physical activity once programs are completed also need to be considered. At the five year follow-up of this study by Nytroen et al (2012) no significant difference in \( \dot{V}O_2 \) between the intervention (high intensity interval training) and usual care groups.
was found (n=41), with both groups reportedly participating in similar amounts and intensities of physical activity. In the four year post-training period, both groups did not receive any specific exercise intervention. Additionally, 45 of the 48 original study participants were still alive at the five year follow-up. The results of this study suggest that lifelong participation in exercise is necessary to maintain positive effects on exercise capacity and for the level of exercise capacity to reach age-predicted normal levels. The question that requires further investigation is how to best get those who are not meeting physical activity recommendations for health benefits to become more physically active and remain active. Motivational interviewing is one tool that may assist behaviour change. It is defined as ‘a collaborative, person-centred conversation for strengthening the motivation of those who have ambivalence about changing behaviour’.

Although no association was found between corticosteroid use at the time of assessment and estimates of physical activity, it is also important to consider the negative impact immunosuppression may have on physical activity levels and muscle strength. It has been reported that corticosteroids and calcineurin inhibitors are associated with skeletal muscle atrophy and decreased muscular oxidative capacity.

Whilst management post-HTx is complex, obesity and physical inactivity are potentially modifiable. Behavioural and environmental factors are important considerations. As such, effective interventions that address factors relevant to the individual may have a significant impact on health outcomes, not only for HTx recipients but also for the general population.

**Future directions**

Further high-quality studies are required to demonstrate the long-term benefits of regular physical activity and investigate ways of increasing adherence to physical activity post-HTx. With baseline data on levels of physical activity, strategies to increase physical activity can be examined and implemented for those who are not reaching levels recommended for health benefits. Future research exploring targeted, innovative strategies and interventions to improve adherence to adequate levels of physical activity post-HTx may assist in optimising long-term outcomes post-HTx. Anderson et al (2017) noted in their study that HTx recipients who were motivated to be
physical active early post-HTx continued to adhere to exercise over time compared to those who had low adherence early post-HTx\textsuperscript{177}. This reinforces the importance of monitoring levels of physical activity early post-HTx and using a range of strategies to establish and maintain strong physical activity habits at this initial period and in the long-term.

It is interesting to note that a small percentage of the participants in the current study were very active. Although the current study was underpowered in terms of identifying recipient factors that influence levels of physical activity and obesity, a greater understanding of these may help ensure that interventions and resources are targeted to where they are most needed. Such factors to investigate could include QoL, behavioural factors, pre-HTx physical activity levels, interests, supports, motivations, socio-economic and environmental factors. In particular, QoL may be more predictive of levels of physical activity than the measures assessed in the current study, with certain QoL domains being a likely indicator of the participant’s mental health status.

Future studies investigating the association between QS\% and levels of physical activity with outcomes such as survival, CAV and infections post-HTx may provide information that is more clinically applicable than the current observational study. Other future research could involve conducting a RCT comparing the effectiveness of different exercise rehabilitation interventions such as targeted quadriceps muscle strengthening compared to standard care on health outcomes post-HTx. In addition, studies with an extended follow-up period are needed to demonstrate the long-term benefits of physical activity on health outcomes (including morbidity and mortality) post-HTx.

Physical inactivity and obesity are significant global health issues, with similar rates in both the post-HTx and general population. As such, utilising current research evidence on lifestyle factors impacting the health of the general population such as behaviour, diet, physical activity and motivation may improve long-term health outcomes for HTx recipients. Despite this and the myriad of solutions, humans are complex beings and behaviour change doesn’t often happen easily. At an individual level, there needs to be a greater focus on understanding behaviour, motivation and readiness to change. Additionally, working collaboratively with HTx recipients who are obese and not
meeting physical activity recommendations for health benefits is fundamental to assist positive behaviour change. For those with end-stage HF fortunate enough to get a second chance at life through HTx, the ability to spend more quality time with family and friends and do what they enjoy is what’s truly important. Anything that can assist individuals to achieve this is the primary goal.
Appendices

Figure 4: Study design

87 eligible participants recruited

Excluded
12 participants (14%)
1 x data corrupted
1 x faulty Sense Wear Armband (SWA)
1 x Left ventricular ejection fraction (LVEF) <50%
9 x SWA wear time
< 22hrs/day <3 days

Included
75 participants (86%)

Outcome measures
Quadriceps muscle strength corrected for body weight (QS%)
Six minute walk distance (6MWD)
Physical activity level (PAL)
Table 1: Aetiologies of heart failure

<table>
<thead>
<tr>
<th>DISEASED MYOCARDIUM</th>
<th>Ischaemic heart disease</th>
<th>Toxic damage</th>
<th>Immune-mediated and inflammatory damage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Myocardial scar</td>
<td>Recreational substance abuse</td>
<td>Related to infection</td>
</tr>
<tr>
<td></td>
<td>Myocardial stunning/hibernation</td>
<td>Heavy metals</td>
<td>Bacteria, spirochaetes, fungi, protozoa, parasites (Chagas disease), rickettsiae, viruses (human immunodeficiency virus/acquired immune deficiency syndrome)</td>
</tr>
<tr>
<td></td>
<td>Epicardial coronary artery disease</td>
<td>Medications</td>
<td>Not related to infection</td>
</tr>
<tr>
<td></td>
<td>Abnormal coronary microcirculation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endothelial dysfunction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DISEASED MYOCARDIUM

- **Ischaemic heart disease**
  - Myocardial scar
  - Myocardial stunning/hibernation
  - Epicardial coronary artery disease
  - Abnormal coronary microcirculation
  - Endothelial dysfunction

- **Toxic damage**
  - Recreational substance abuse
  - Heavy metals
  - Medications
    - Alcohol, cocaine, amphetamine, anabolic steroids
    - Copper, iron, lead, cobalt
    - Cytostatic drugs (e.g. anthracyclines), immunemodulating drugs (e.g. interferons monoclonal antibodies such as trastuzumab, cetuximab), antidepressant drugs, antiarrhythmics, non-steroidal anti-inflammatory drugs, anaesthetics

- **Immune-mediated and inflammatory damage**
  - Related to infection
    - Bacteria, spirochaetes, fungi, protozoa, parasites (Chagas disease), rickettsiae, viruses (human immunodeficiency virus/acquired immune deficiency syndrome)
  - Not related to infection
    - Lymphocytic/giant cell myocarditis, autoimmune diseases (e.g. Graves’ disease, rheumatoid arthritis, connective
<table>
<thead>
<tr>
<th><strong>Immune-mediated and inflammatory damage</strong></th>
<th>tissue disorders, mainly systemic lupus erythematosus, hypersensitivity and eosinophilic myocarditis (Churg-Strauss)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infiltration</strong></td>
<td>Related to malignancy</td>
</tr>
<tr>
<td>Related to malignancy</td>
<td>Amyloidosis, sarcoidosis, haemochromatosis (iron), glycogen storage disease (e.g. Pompe disease), lysosomal storage diseases (e.g. Fabry disease)</td>
</tr>
<tr>
<td>Not related to malignancy</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic derangements</strong></td>
<td>Hormonal</td>
</tr>
<tr>
<td>Nutritional</td>
<td>Deficiencies in thiamine, L-carnitine, selenium, iron, phosphates, calcium, complex malnutrition (e.g. malignancy, acquired immune deficiency syndrome, anorexia nervosa), obesity</td>
</tr>
<tr>
<td><strong>Genetic abnormalities</strong></td>
<td>Diverse forms</td>
</tr>
<tr>
<td>Table 1: Aetiologies of heart failure.</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
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<th></th>
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<tr>
<td><strong>dystrophies and laminopathies</strong></td>
<td></td>
</tr>
<tr>
<td><strong>ABNORMAL LOADING CONDITIONS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Valve and myocardium structural defects</strong></td>
<td>Acquired Mitral, aortic, tricuspid and pulmonary valve diseases Congenital Atrial and ventricular septum defects and others</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pericardial and endomyocardial pathologies</strong></td>
<td>Pericardial Constrictive pericarditis, pericardial effusion Endomyocardial Hypereosinophilic syndrome, endomyocardial fibrosis, endocardial fibroelastosis</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High output states</strong></td>
<td>Severe anaemia, sepsis, thyrotoxicosis, Paget’s disease, arterio-venous fistula, pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td><strong>Volume overload</strong></td>
<td>Renal failure, iatrogenic fluid overload</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>ARRHYTHMIAS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Tachyarrhythmias</strong></td>
<td>Atrial, ventricular arrhythmias</td>
</tr>
<tr>
<td><strong>Bradyarrhythmias</strong></td>
<td>Sinus node dysfunctions, conduction disorders</td>
</tr>
</tbody>
</table>
6 February 2013

Dr Scott McKenzie
The advanced Heart Failure and
Cardiac Transplant Unit
The Prince Charles Hospital

Dear Dr McKenzie,

Re: HREC/13/QPCH/34: Obesity and Activity in heart Transplant: Is obesity post heart transplant related to patient activity levels?

Thank you for submitting your Low Risk project for ethical review. I am pleased to advise that The Prince Charles Hospital Human Research Ethics Committee reviewed your submission and upon recommendation, the Chair has granted final approval for your low risk project.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council’s (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice.

I am pleased to advise that the Human Research Ethics Committee has granted approval of this research project. The documents reviewed and approved on 30 January 2013 include:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk Application (AU/10/5BE0110)</td>
<td>1.0</td>
<td>25 January 2013</td>
</tr>
<tr>
<td>Protocol</td>
<td>1.0</td>
<td>29 January 2013</td>
</tr>
<tr>
<td>Participant Information Sheet &amp; Consent Form</td>
<td>1.0</td>
<td>29 January 2013</td>
</tr>
<tr>
<td>Letter of invitation</td>
<td>1.0</td>
<td>29 January 2013</td>
</tr>
</tbody>
</table>

This will be tabled at the next HREC meeting held 14 March 2013, for noting.

Please note the following conditions of approval:

1. The Principal Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including any unforeseen events that might affect continued ethical acceptability of the project.


3. Amendments to the research project which only affect the ongoing site acceptability of the project are not required to be submitted to the HREC for review. These amendment requests should be submitted directly to the Research Governance Office (by-passing the HREC).
4. Proposed amendments to the research project which may affect both the ethical acceptability and site suitability of the project must be submitted firstly to the HREC for review and, once HREC approval has been granted, then submit to the RGO.

5. The HREC is notified, giving reasons, if the project is discontinued at a site before the expected date of completion.

6. The Principal Investigator will provide research status reports, annually and on completion of the research, to the HREC. http://www.health.qld.gov.au/tpch/documents/tools_progres.doc

7. The Human Research Ethics Committee or Hospital and Health Service Administration may inquire into the conduct of any research it approves.

HREC approval is valid for the duration of the project.

Should you have any queries about the HREC’s consideration of your project please contact the Executive Officer on 3139 4500. The HREC terms of Reference, Standard Operating Procedures, membership and standard forms are available from http://www.health.qld.gov.au/ohmr/html/requ/requ_home.asp.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the Hospital and Health Service CEO or Delegate of that site has been obtained.

A copy of this approval must be submitted to the Hospital & Health Services Research Governance Officer/Delegated Personnel with a completed Site Specific Assessment (SSA) Form for authorisation from the CEO or Delegate to conduct this research at The Prince Charles Hospital and Health Service.

The HREC wishes you every success in your research.

Yours faithfully

Dr Russell Denman
Chair
HUMAN RESEARCH ETHICS COMMITTEE
METRO NORTH HOSPITAL AND HEALTH SERVICE
Ethics amendment approval

Physiotherapist
for Scott McKenzie
Principal Investigator
The Prince Charles Hospital
14/7/2014

Dr Philip Lee and Mr Anne Carle
Research, Ethics & Governance Unit
The Prince Charles Hospital
Rode Road, Chermside 4032

Re: HREC/13/QPCH/34: Obesity and Activity in heart Transplant: Is obesity post heart transplant related to patient activity levels?

Dear Philip and Anne,

Investigators:
Scott McKenzie, Rebecca Francis, David Platts, George Javorsky and James Walsh.

I am writing this letter seeking to amend the study protocol to include we will document the result of the patients' most recent six minute walk test as a measure that is routinely used in the heart transplant population to assess exercise capacity.

I would also like revise the investigators to those outlined above, adding:
Norman Morris and Stephanie Yerkovich.

Please find attached the amended study protocol reflecting the proposed changes. Copies of the CVs for the two additional investigators have previously been submitted to TPCH Research, Ethics and Governance Unit.

Yours Sincerely

Rebecca Francis

C/- The Physiotherapy Department
The Prince Charles Hospital
29 July 2014

Dr Scott McKenzie
The Advanced Heart Failure and
Cardiac Transplant Unit
The Prince Charles Hospital

Dear Dr McKenzie,

Re: HREC/13/QPCH/34: Obesity and Activity in heart Transplant: Is obesity post
transplant related to patient activity levels?

I am pleased to advise that, at the meeting held on 29 July 2014, The Prince Charles Hospital
Human Research Ethics Committee reviewed the amendments submitted and upon
recommendation, the Chair has granted approval for the following:

- Protocol Version 2.0 dated 19 June 2014
- Addition of Prof Norman Morris and Dr Stephanie Yerkovich as Principal Investigators

The amended protocol has been assessed as containing a higher risk and no longer meets the
criteria of a low risk project.

List of approved Sites:

<table>
<thead>
<tr>
<th>No.</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>The Prince Charles Hospital</td>
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</tbody>
</table>

Patient information collected and distributed as part of the previously approved research has
been approved in accordance with Section 62 of the Health Services Act and the recent
amendments to the Public Health Act Sections 282 and 284. Any change to the collection and or
distribution will need to be reviewed by the HREC.

This HREC is constituted and operates in accordance with the National Health and Medical
Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007),
NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and
the CPMP/ICH Note for Guidance on Good Clinical Practice.

Please be advised that in the instance of an investigator being a member of the HREC, they are
absent from the decision making process relating to that study.

On behalf of the Human Research Ethics Committee, I would like to wish you every success with
your research endeavour.
Yours truly,

Anne Carle
A/Executive Officer – Research, Ethics and Governance Unit
The Prince Charles Hospital
Participant Information Sheet

HREC No:  
Project Title: Obesity and Activity in Heart Transplant

Name of Researchers:
Dr Scott McKenzie
Rebecca Francis
Jared Bruning
Helen Seale
Dr Martin Brown
Dr George Javorksky
Dr David Platts
Jo Maddicks-Law
James Walsh

You are invited to participate in this clinical study to determine whether physical activity levels play a part in the degree of weight gain after heart transplant.

Aim:
This study aims to determine how much physical activity heart transplant recipients engage in and if there is any relationship between the amount of physical activity and how overweight patients are.

Background:
Weight gain and obesity is common post heart transplantation with patients reported to gain around 10kg by one year post heart transplant. This weight gain is typically maintained at 3 years after transplantation. Obesity after heart transplant is associated with worse prognosis. Studies investigating the cause of this weight gain have reported that being younger and being male are most predictive of greater weight gain. Your weight pre-transplant might impact upon how much weight you gain after transplant. The medications used after heart transplant may affect your tendency to gain weight, although studies show variable results. One study suggested that non-participation in cardiac rehabilitation by women resulted in greater weight gain. Importantly however no studies have directly assessed the effect of exercise levels on weight gain after heart transplant.

What to expect:
We will record your height and weight as is usually done when you come to clinic. We will measure the amount of force you can exert with your quadriceps (thigh) muscles as this is a good gauge of physical activity levels. We will then fit you with SenseWear Pro 3 Armband and show you how to use it. The armband provides information on energy expenditure, time spent above different degrees of exertion, time lying down, sleeping duration and steps per day. Average daily PAL can be expressed as an index, comparing activity whilst sleeping (1.0 METS) with activity for the day as a whole. The Armband has been validated against other techniques measuring energy expenditure and appears to be almost as accurate as far more physically invasive measurements.
We will ask you to wear the Armband constantly for a week (you may take it off when you shower) then bring it back to us so we can download and analyse the data it has recorded. We will give you a copy of your results and let you know how this compares with a normal healthy person.

Risks and Side Effects:
The Armband should not cause any discomfort and can be taken off at any time if need be. There are no risks from participation in this study.

Benefits
For you: We can tell you how your activity levels compare with the levels of activity recommended by speciality societies.
For others: In future we may be able to give more tailored advice on approaches to rehabilitation and weight loss (or weight maintenance if you are a healthy weight). This Armband may in future provide you and other transplant recipients with a tool to help maximise your exercise levels.

Data Re-Use:
We will maintain de-identified data (data that has no information that could allow someone to link that data to an individual person) which we may use again to add to the data for similar projects (to avoid needing to recollect it all over again).

Confidentiality and Privacy
Patients enrolled in the trial will be assigned a trial number, and all data are recorded without reference to your name. The Prince Charles Hospital ensures all records will be treated with full confidentiality as per Queensland Health guidelines.

If you have any concerns or questions regarding this trial, please contact
Dr Scott McKenzie
Cardiologist
Ph 3139 4000

Independent Contact Person:
If you wish to discuss your involvement with someone not connected with the study you may contact:

The Executive Officer, Research and Ethics on 07 3139 4500

They will forward your concerns to the Chair of the Human Research Ethics Committee.
# Participant Consent Form

<table>
<thead>
<tr>
<th>HREC No:</th>
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</thead>
<tbody>
<tr>
<td>Project Title:</td>
<td>Obesity and Activity in Heart Transplant</td>
</tr>
</tbody>
</table>
| Name of Researchers: | Dr Scott McKenzie  
Rebecca Francis  
Jared Bruning  
Helen Seale  
Dr Martin Brown  
Dr George Javorsky  
Dr David Platts  
Jo Maddicks-Law  
James Walsh |

I agree to participate in the above named clinical study and in so doing acknowledge that:

- I have been informed as to the nature and extent of any risk to my health or well-being.
- I am aware that, although the project is directed to the expansion of medical knowledge generally, it may not result in any direct benefit to me.
- I have been informed that my refusal to consent to participate in the study will not affect in any way the quality of treatment provided to me.
- I have been informed that I may withdraw from the project at my request at any time and that this decision will not affect in any way the quality of treatment.
- I have been advised that the Executive Director, The Prince Charles Hospital, on recommendation from The Prince Charles Hospital Metro North Human Research Ethics Committee has given approval for this project to proceed.
- I am aware that I may request further information about the project as it proceeds.
- I am aware that my GP may be informed that I am taking part in the project.
- I understand that, in respect of any information (which may consist of records outside of this hospital) including audiovisual records obtained during the course of the project, confidentiality will be maintained to the same extent as for my Hospital medical records. In the event of any results of the project being published, I will not be identified in any way.
- I agree that, if necessary, my medical records (in respect of my involvement in this project) may be inspected by a Research Assessor. This assessor may be external to but approved by the Hospital, provided that the Assessor does not identify me or my hospital's medical records in any way to a third party.

Patient’s name: ………………………… Signature: ………………………… Date: ___ / ___ / ____  
DD / MMM / YYYY

Name of Investigator: ………………………… Signature: ………………………… Date: ___ / ___ / ____  
DD / MMM / YYYY
# Revocation of Consent Form - Participant

<table>
<thead>
<tr>
<th>HREC No:</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Project Title:</td>
<td>Obesity and Activity in Heart Transplant</td>
</tr>
<tr>
<td>Name of Researchers:</td>
<td>Name of Researchers:</td>
</tr>
<tr>
<td>Dr Scott McKenzie</td>
<td>Dr Scott McKenzie</td>
</tr>
<tr>
<td>Rebecca Francis</td>
<td>Rebecca Francis</td>
</tr>
<tr>
<td>Jared Bruning</td>
<td>Jared Bruning</td>
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<tr>
<td>Helen Seale</td>
<td>Helen Seale</td>
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<tr>
<td>Dr Martin Brown</td>
<td>Dr Martin Brown</td>
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<tr>
<td>Dr George Javorsky</td>
<td>Dr George Javorsky</td>
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<td>Dr David Platts</td>
<td>Dr David Platts</td>
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<tr>
<td>Jo Maddicks-Law</td>
<td>Jo Maddicks-Law</td>
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<tr>
<td>James Walsh</td>
<td>James Walsh</td>
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</tbody>
</table>

I hereby wish to WITHDRAW my consent to participate in the research project described above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with The Prince Charles Hospital Metro North Health Service District.

Participant’s name (please print): ........................................................................................................

(Signature).............................................................................................................................................. Date: ___ / ___ / _____

DD / MMM / YYYY

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This Revocation of Consent should be forwarded to:

Dr Scott McKenzie  
Cardiologist  
Advanced Heart Failure and Cardiac Transplant Unit  
The Prince Charles Hospital  
Rods Rd  
Chermside QLD 4032  
Fax: 07 3139 4628
**Data record sheet**

Date: [ ] Armhand #: [ ] SUBJECT #: [ ]

1 week R/V Date & time: [ ] Date of OHTs: [ ]

Armhand instruction handout given [ ] Follow up appointment card given [ ]

AFFIX PATIENT STICKER HERE

- Height:
- Weight: initial Ax: [ ] 1 week post weight: [ ]
- Handedness:
- Smoking status:

**ASSESSMENT**

Quad Strength at initial Ax (kg)

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<th>Left</th>
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</table>

**6MWT**

**PHYSIOTHERAPY – 6 minute walk test**

Date / / Time:

<table>
<thead>
<tr>
<th>At Rest</th>
<th>During Test (Completion of Test)</th>
<th>Post Test</th>
<th>Recovery Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP (maximum)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (maximum)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BORG (max. 6-20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO2 (minimum)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Meters walked = [ ] No. of stops [ ] RM Air / O2 [ ] Lpm

Reason for Stopping Test: [ ] Limiting Symptoms: [ ]

Comment: [ ]

Name: [ ] Signature: [ ]

Designation: [ ]
SenseWear armband instructions

Sensewear Armband Instructions

1. If possible try to wear the armband for 24 hours/day for one week except for showering/swimming, etc. The device is not waterproof and should not be immersed in water.
2. The device should be worn at the back of your right arm.
3. The battery will last for approximately two weeks therefore the device needs to be uploaded prior to this time.
4. Please avoid using skin care products on the area of the skin that the armband device is worn. Unfortunately most skin care products are petroleum or oil based, or are made from an oil emulsion and therefore get absorbed by the armband’s plastic. This weakens the compound causing it to crack where the structure is under most stress (where the stainless steel sensors are stamped into the mould).

Contact details

Rebecca Francis  
Physiotherapy Department  
The Prince Charles Hospital  
Rode road  
Chermside QLD 4032

Ph 3139 5308

James Walsh  
Physiotherapy Department  
The Prince Charles Hospital  
Rode road  
Chermside QLD 4032

Phone 3139 4443 - pager 0366
Griffith ethics correspondence

Re: Ethics approval for completed project

You replied on 12/02/2016 11:15 AM.

Rick Williams [rick.williams@griffith.edu.au]

Sent: Monday, 11 July 2016 12:38 PM
To: Rebecca Kelly
Cc: rumori@griffith.edu.au

Ms Kelly

Thank you for the clarification.

If your remaining research involves only analysis of collected data and/or preparation for publication (including submission to MPhil reviewers) then further human ethics approval is not required.

However, please note that any commitments to participants included in the consent materials (e.g. to provide summary feedback of results to participants) must be met.

Regards

On 11 July 2016 at 12:25, Rebecca Kelly <Rebecca.Kelly2@health.qld.gov.au> wrote:

Dear Rick,

Thank you for your prompt reply.

I am not engaging in additional data collection and do not require continuing access to hospital patients, staff, records or facilities.

Kind regards,

Rebecca Kelly

From: Rick Williams [mailto:rick.williams@griffith.edu.au]
Sent: Monday, 11 July 2016 11:16 AM
To: Rebecca Kelly
Cc: rumori@griffith.edu.au
Subject: Re: Ethics approval for completed project
Ms Kelly

Thank you for your enquiry.

The TPCH HREC letter says that "HREC approval is valid for the duration of the project." In the circumstances, if you are still collecting participant data then I recommend that you contact the TPCH HREC to discuss renewing or extending the protocol approved as HREC/13/QPCH/34. If that is feasible it will be the quickest and simplest path to continuing or recommencing your research.

If the TPCH HREC approval is extended or renewed the GUHREC will recognise and endorse that approval without additional review. The process for GUHREC recognition is set out here please scroll down to "1.6 Research that has already been ethically reviewed" and follow the guidance provided.

If you are not engaging in additional data collection and/or do not require continuing access to hospital patients, staff, records or facilities, then please let me know and I will advise additional options, including whether ethics approval is required.

I hope this information is helpful.

Regards
Re: Ethics approval for completed project

You replied on 12/07/2016 11:15 AM.

Rick Williams [rick.williams@griffith.edu.au]

Sent: Monday, 11 July 2016 12:58 PM
To: Rebecca Kelly
Cc: n.moms@griffith.edu.au

On 11 July 2016 at 09:18, Rebecca Kelly <Rebecca.kelly2@health.qld.gov.au> wrote:

Dear Rick,

I am enrolled in my MPhil at Griffith University. I am undertaking a project at The Prince Charles Hospital which has ethics approval.

The project however was completed prior to enrolling in my MPhil and the ethics approval has now expired (see attached documents).

Would I still need to apply for a 'prior approval' for my project?

Kind regards,

Rebecca Kelly
Senior Physiotherapist
Heart Failure Service
The Prince Charles Hospital
Metro North Hospital and Health Service
Reede Rd
Chermside, QLD, 4032

P: (07) 3139 5644
Rebecca.kelly2@health.qld.gov.au

Metro North Hospital and Health Service
**Data storage**

In compliance with Queensland Health regulations, all records will be kept for seven years. The original data is securely stored on a password-protected computer in a secure office. Participant details have been de-identified in published documents. Guidelines for the Protection of Privacy in the conduct of medical research have been complied with under the Commonwealth Privacy Commission Section 95A of the Privacy Act 1988 and the Privacy Amendment (Private Sector) Act 2000.
References


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