School of Physiotherapy and Exercise Science

Quadriceps Dysfunction Following Lung and Heart-lung Transplant: Magnitude, Nature, Contributing Factors and Clinical Implications

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DECLARATION

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgement has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007 – updated March 2014). The proposed research received human research ethics approval from the Royal Perth Hospital Human Research Ethics Committee, Approval Number EC2009/120 and the Curtin University Human Research Ethics Committee, Approval Number HR 57/2010.

Carol Watson

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STATEMENT OF ORIGINALITY

This thesis is presented for the degree of Master of Philosophy at Curtin University Western Australia. Studies and preparation of this thesis were undertaken between 4th March 2010 and 30th November 2018, through the School of Physiotherapy and Exercise Science at Curtin University, in association with the Advanced Lung Disease Unit and the Department of Physiotherapy at Royal Perth Hospital.

This research project was developed in association with my supervisors who have been involved in editing this thesis and all associated publications. All material presented in this thesis is original.

ABSTRACT

Background

Lung transplant is a procedure offered to a small proportion of individuals with end-stage lung disease that results in amelioration of symptoms, improved health-related quality of life and potentially a survival benefit. Earlier work has demonstrated that whilst lung transplant results in large improvements in lung function, lung transplant recipients continue to have reduced exercise tolerance and participate in low levels of physical activity. It has been proposed that peripheral muscle dysfunction, particularly of the quadriceps femoris, contributes to these persistent limitations.

The research questions addressed in this study were, in people following bilateral lung transplant or heart-lung transplant;

1. Is the strength of the quadriceps femoris, when expressed as Nm, reduced when compared with healthy controls of similar age and gender?
2. Is the strength of the quadriceps femoris, when expressed as Nm per kilogram of muscle mass, reduced when compared with healthy controls of similar age and gender?
3. Is the strength of the quadriceps femoris (which is affected by local and systemic factors) reduced relative to the strength of the biceps brachii (which is affected predominantly by systemic factors)?
4. Is the endurance of the quadriceps femoris reduced, when compared with healthy controls of similar age and gender?
5. What component of quadriceps femoris function (i.e. strength vs. endurance) explains a greater proportion of the variance in measurements of functional exercise capacity, sedentary time and daily physical activity? Are similar relationships seen in a group of healthy controls?

Methods

The study undertaken was cross-sectional and observational in design.

Two groups of participants were recruited; (i) a transplant group which included bilateral lung transplant or heart-lung transplant recipients who were a minimum of six months following lung transplant and had no limitations to exercise testing and (ii) a control group of healthy people of similar age and gender proportion as the transplant group. Participants in both groups completed two assessment sessions that were separated by nine to 14 days. To describe the study participants, data

were collected regarding demography and anthropometry (e.g. age, weight etc), lung function (spirometry) and health-related quality of life (Quality Metric Incorporated Short Form 36 version 2). Using a highly standardised protocol and a robust dynamometer, measures of muscle function were collected. Regarding strength, measures were collected of maximum torque generated by quadriceps femoris and maximum torque generated by biceps brachii during maximal voluntary isometric contractions. To determine whether or not measures of maximum torque generated by quadriceps femoris and biceps brachii were reduced when expressed as Nm per kilogram of muscle mass, measures of lean mass were collected using dual-energy X-ray absorptiometry. Regarding quadriceps femoris endurance, using a protocol adapted from that described by Bigland-Ritchie et al, measures were collected of the time to task failure and rate of decline of the maximal torque measured during performance of a maximal voluntary isometric contraction generated at the start of each minute during the endurance protocol. Additionally, during the quadriceps femoris endurance protocol, electromyographic signals were collected from vastus medialis and vastus lateralis muscles. Other measures collected in both groups comprised exercise capacity (six-minute walk distance), sedentary time and time spent undertaking different levels of intensity of physical activity (SenseWear Pro3 Armband) and average daily steps (StepWatch™ Activity Monitor).

Results

The transplant group comprised 10 adults following bilateral lung transplant or heart-lung transplant (5 females, 43 [20] yr). The control group comprised 20 healthy adults (9 female, 39 [25] yr). Compared with the control group, those in the transplant group had minor reductions in both forced expiratory volume in one second (2.98 [0.83] L vs. 3.80 [1.00] L; $p = 0.013$) and forced vital capacity (3.55 [1.12] L vs. 4.78 [1.64] L; $p = 0.019$). The forced expiratory ratio was similar in both groups (79 [20] % vs. 81 [11] %; $p = 0.81$). Regarding health-related quality of life, when compared with the control group, those in the transplant group had lower scores on Quality Metric Incorporated Short Form 36 version 2 for physical function (90 [8] vs. 100 [5]; $p < 0.001$), general health (71 [18] vs. 82 [20]; $p = 0.017$) and role emotional domains (92 [19] vs. 100 [0]; $p = 0.049$), and a lower physical health summary score (52 [2] vs. 55 [5]; $p < 0.001$).

Regarding muscle specific measures, compared with measures collected in the control group, those in the transplant group had lower maximal torque generated by

quadriceps femoris and biceps brachii (148 [87] Nm vs. 221 [14] Nm; p = 0.022; and 34 [22] Nm vs. 45 [45] Nm, p = 0.044, respectively). However, when measures of torque were expressed per kilogram of lean muscle mass, there was no difference in maximal torque generated by quadriceps femoris and biceps brachii between the groups (25 [8] Nm/kg vs. 27 [8] Nm/kg of lean muscle mass in the lower limb; p = 0.37 and 17 [5] Nm/kg vs. 19 [4] Nm/kg of lean muscle mass in the upper limb; p = 0.48, respectively). This is consistent with data showing that, compared with the control group, those in the transplant group had less lean muscle mass in both the lower and upper limbs (7.0 [2.2] kg vs. 8.8 [4.1] kg; p = 0.011 and 2.1 [0] kg vs. 3.0 [0.2] kg; p = 0.035, respectively). Regarding the distribution of muscle weakness, when maximal torque generated by biceps brachii was expressed as a ratio of maximal torque generated by quadriceps femoris, there was no difference between the groups (0.22 [0.07] vs. 0.24 [0.07]; p = 0.56).

Regarding quadriceps femoris endurance, compared with the control group, those in the transplant group had a shorter time to task failure (90 [100] s vs. 300 [200] s; p = 0.001). Using a Kaplan-Meier analysis, time to task failure of greater than three minutes was achieved in 55% of the transplant group compared with 90% of the control group (p < 0.001). Compared with the control group, those in the transplant group demonstrated a rate of decline of the torque measured from the maximal voluntary isometric contractions generated at the start of each minute during the endurance protocol that was 60.10 Nm greater per contraction (95% confidence interval [CI] 5.5 to 114.6; p = 0.031). Analysis of electromyography demonstrated that, compared with the control group, those in the transplant group had a reduction in median frequency of the vastus lateralis muscle that was -7.29 Hz less per contraction (95%CI -13.97 to -0.61).

Regarding other outcomes, compared with the control group, those in the transplant group had a shorter six-minute walk distance (671 [107] m vs. 797 [68] m; p < 0.001) and demonstrated a tendency to take less steps on an average day (9,582 [3,620] steps vs. 13,283 [4,514] steps; p = 0.05).

In the transplant group, associations were demonstrated between maximal torque generated by quadriceps femoris and six-minute walk distance (r = 0.691; p = 0.021), sedentary time (r = -0.744; p = 0.014) and time spent participating in moderate or vigorous intensity physical activity (r = 0.738; p = 0.023). No convincing associations were reported between time to task failure and these measures.

Discussion

Data from this study demonstrated that although the transplant group had negligible impairment in lung function, when compared with a control group of similar age and gender proportion, those in the transplant group had reduced strength of the quadriceps femoris and biceps brachii, when expressed in terms of torque generated during a maximal voluntary isometric contraction. This impairment in quadriceps femoris and biceps brachii strength appeared to be, at least in part, the result of smaller muscle mass in the transplant group, as there was no evidence of a difference in strength between the groups when differences in muscle mass were considered in the analyses. The impairment in muscle strength was similar between the quadriceps femoris and biceps brachii suggesting that there may be a systemic cause to the reductions in muscle strength, such as a side-effect of immunosuppressant medications.

Further, when compared to the control group, those in the transplant group had reduced endurance of the quadriceps femoris, as measured using two effort-dependent measures of muscle endurance (i.e. time to task failure and rate of decline of the torque measured from the maximal voluntary isometric contractions generated at the start of each minute during the endurance protocol) and one effort-independent measure of fatigue (i.e. rate of decline of electromyography median frequency of the vastus lateralis muscle).

Finally, when compared to the control group, those in the transplant group had a reduction in exercise capacity and showed a tendency to undertake less steps during daily life.

In the transplant group, measures related to quadriceps femoris strength, but not quadriceps femoris endurance, were associated with functional outcomes, including six-minute walk distance, sedentary time and time spent participating in moderate or vigorous intensity physical activity. Although reduced, this study was unable to demonstrate relationships between measures related to quadriceps femoris endurance and six-minute walk distance, sedentary time and time spent participating in moderate or vigorous intensity physical activity. However, it is also possible that the lack of relationship between quadriceps femoris endurance and these outcomes reflected the high variability in the measures of quadriceps femoris endurance and the small participant numbers available for these analyses.

Conclusion

Following lung transplant, muscle strength and mass were impaired in both quadriceps femoris and biceps brachii. This suggests that during rehabilitation there may be a need to optimise muscle strength and the mass of large proximal muscles in both the lower and upper limbs rather than focussing exclusively on quadriceps femoris. Further, as quadriceps femoris endurance was also impaired, exercise modalities that serve to optimise both strength and endurance are likely to be of benefit. Additionally given the associations found in this study between muscle strength and sedentary time and time spent participating in moderate or vigorous intensity physical activity, lifestyle targets around reducing sedentary time and optimising the time spent undertaking moderate or vigorous intensity physical activity may be appropriate for this population.

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LIST OF ABBREVIATIONS

1-RM	One repetition maximum
6MWD	Six-minute walk distance
$6MWD_{\%pred}$	Percentage of predicted six-minute walk distance
6MWT	Six-minute walk test
AT	Anaerobic threshold
BB	Biceps brachii
BF	Biceps femoris
BLT	Bilateral lung transplant
BMD	Bone mineral density
BOS	Bronchiolitis obliterans syndrome
CF	Cystic fibrosis
CG	Control group
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRQ	Chronic Respiratory Disease Questionnaire
CT	Computerised tomography
DEXA	Dual-energy X-ray absorptiometry
EMG	Electromyography
ex	Exercise
FEV_1	Forced expiratory volume in 1 second
$FEV_{1\%pred}$	Percentage of predicted forced expiratory volume in one second
FEV_{1pred}	Predicted forced expiratory volume in one second
FFM	Fat free mass

FVC	Forced vital capacity
$FVC_{\%pred}$	Percentage of predicted forced vital capacity percent
FVC_{pred}	Predicted forced vital capacity
HGF	Hand grip force
HLT	Heart-lung transplant
HR	Heart rate
HRQL	Health-related quality of life
IG	Intervention group
IQR	Interquartile range
ISHLT	International Society of Heart and Lung Transplantation
K_m	Michaelis constant for the enzyme being investigated
LT	Lung transplant
max	maximum
MEP	Maximum expiratory pressure
METS	Metabolic equivalent tasks
min	minimum
MIP	Minimum inspiratory pressure
MT	Maximal torque
MT_{BB}	Maximum torque of the biceps brachii
MT_{QF}	Maximum torque of the quadriceps femoris
MT_{QF_end}	Maximum torque of the quadriceps femoris at the start of each minute during the endurance protocol
MVIC	Maximal voluntary isometric contraction
MVPA	Moderate or vigorous intensity physical activity
O_{2AT}	Rate of oxygen uptake at anaerobic threshold

PA	Physical activity
pred	Predicted
QF	Quadriceps femoris
RCT	Randomised controlled trial
ROM	Range of movement
RPE	Rating of perceived exertion
RPE_{BB}	Rating of perceived exertion during biceps brachii testing
RPE_{QF}	Rating of perceived exertion during quadriceps femoris testing
RPH	Royal Perth Hospital
SAM	StepWatch™ activity monitor
SD	Standard deviation
SF36	Short form 36
SF36v2	Short form 36 version 2
SLT	Single lung transplant
SOB	Shortness of breath
SpO_2	Arterial oxygen saturation measured by pulse oximetry
SpO_{2nadir}	Lowest measure of arterial oxygen saturation measured by pulse oximetry
ST	Sedentary time
SWA	SenseWear Armband
TG	Transplant group
$tiredness_{BB}$	Limb tiredness of biceps brachii
$tiredness_{QF}$	Limb tiredness of quadriceps femoris
T_{lim}	Time to task failure
USA	United States of America

VCO_2	Rate of carbon dioxide output
$V\dot{E}$	Rate of minute ventilation
VO_2	Rate of oxygen uptake
VO_{2max}	Maximum rate of oxygen uptake (maximum work capacity)
VO_{2peak}	Peak rate of oxygen uptake (peak work capacity)
vs.	versus
W_{max}	Maximum workload
W_{peak}	Peak workload

UNITS OF MEASUREMENT

bpm	beats per minute
cm	centimetre
dB	decibel
ft lb	foot pound
g	gram
Hz	Hertz
kg	kilogram
kHz	kilohertz
kΩ	kilo-Ohm
L	litre
lb	pound
m	metre
min	minute
mL	millilitre
mm	millimetre
mmHg	millimetres of mercury
mSv	Milli-Sievert
N	Newton
Nm	Newton metre
s	second
µm	micrometre
W	Watt
yr	year

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CONFERENCE PRESENTATIONS

2012

Thoracic Society of Australia Western Australian Branch Annual Scientific Meeting

Is muscle strength reduced in lung and heart-lung transplant recipients? Preliminary data (Poster presentation)

CHAPTER 1 INTRODUCTION

The study described in this thesis focusses on the measurement of peripheral muscle dysfunction, specifically quadriceps femoris (QF), following bilateral lung transplant (BLT) or heart-lung transplant (HLT). Data collection was undertaken across Royal Perth Hospital and Curtin University in Perth, Western Australia.

Lung transplant (LT) is a procedure offered to a small proportion of individuals with end-stage lung disease. This procedure ameliorates symptoms, improves health-related quality of life (HRQL) and may result in a survival benefit (1). Between 1st January 1995 and 30th June 2016, the International Society of Heart and Lung Transplant reported that worldwide, 62,456 (96% adult) single lung transplant (SLT) and bilateral lung transplant (BLT) and 4,745 (84% adult) heart-lung transplant (HLT) procedures were performed (2). In 2015, 11 SLT, 205 BLT and two HLT procedures were performed in the six transplant centres across Australia and New Zealand (3).

Earlier work has demonstrated that, following LT, in the presence of essentially normal lung function, recipients continue to have reduced exercise tolerance and participate in low levels of physical activity (PA) (1, 4-7). Peripheral muscle dysfunction, particularly of the QF, appears to be an important limiting factor (8). However the magnitude of impairment in muscle function compared to healthy people is unclear. It is also unclear if there is greater impact on muscle strength or endurance of this muscle, if this dysfunction is caused by local or systemic factors and how this dysfunction relates to functional impairment.

The study presented in this Masters of Philosophy thesis explored factors relating to muscle dysfunction following BLT and HLT. Bilateral lung transplant and HLT recipients were chosen because following these procedures, recipients have large improvements in lung function and they were less likely to be limited by breathlessness during the assessments. The study was cross-sectional and observational in design and compared measures of muscle dysfunction in people following BLT or HLT with measures collected under identical conditions in a group of healthy people of similar age and gender proportion. Measures were collected of QF and biceps brachii (BB) strength, QF endurance, lung function, HRQL, body composition, exercise capacity, sedentary time (ST) and PA undertaken during daily waking hours, along with demographic and anthropometric measures.

This chapter presents the research questions addressed by this thesis, provides rationale for each of these questions and outlines the significance and novelty of the work undertaken.

1.1 Research questions

The research questions addressed in this study were, in people following BLT or HLT;

1. Is the strength of the QF, when expressed as Nm, reduced when compared with healthy controls of similar age and gender?
2. Is the strength of the QF, when expressed as Nm per kilogram of muscle mass, reduced when compared with healthy controls of similar age and gender?
3. Is the strength of the QF (which is affected by local and systemic factors) reduced relative to the strength of the BB (which is affected predominantly by systemic factors)?
4. Is the endurance of the QF reduced, when compared with healthy controls of similar age and gender?
5. What component of QF function (i.e. strength vs. endurance) explains a greater proportion of the variance in measurements of functional exercise capacity, ST and daily PA? Are similar relationships seen in a group of healthy controls?

1.1.1 Rationale for research question 1 and 2

Although several studies have reported impairments in QF strength in LT recipients (4-7, 9-16), most have expressed QF strength measured in LT recipients as a percentage of that derived using regression equations that were developed in a reference population (5-7, 11). The problem with this approach is that while it accounts for age and gender related differences in muscle function, it does not account for differences in assessment protocol such as the opportunity to practice, encouragement given or equipment used. One approach to overcome this limitation is to compare QF strength in LT recipients with that measured in healthy controls of similar age and gender proportion, using an identical methodology. The few studies that have used this approach report that the QF strength in LT recipients is between 52% and 67% of that generated in healthy controls (6, 14, 15). However, two of these earlier studies included SLT recipients in their LT cohort (6, 14) and whilst SLT procedures result in improvements in lung function they do not fully ameliorate

this impairment (17). Therefore the inclusion of SLT recipients in these studies makes it difficult to determine whether or not the impairment in QF strength relates to (i) the persistent ventilatory limitation to exercise serving to constrain exercise tolerance, which in turn, limits the stimulus borne by the peripheral muscles to promote conditioning post-transplant or (ii) a specific process that occurs within the muscle itself despite amelioration of the ventilatory limitation to exercise. Of the few studies that have compared QF strength in LT recipients with healthy controls of similar age and gender proportion, only one has attempted to account for any difference in the size of the muscle between these populations (i.e. by expressing QF forces as a factor of its cross-sectional area derived from computerised tomography (CT) scan) (15). However, this study recruited a population of LT recipients that all had cystic fibrosis as their underlying disease. These data may have limited generalisability to an older sample of LT recipients given the age related decline in muscle mass. The study in this Masters of Philosophy thesis serves to overcome these potential limitations of earlier work by: (i) measuring QF strength in BLT and HLT only, procedures that produce a return to normal or near-normal lung function (17); (ii) comparing measures of QF strength in a LT group with a group of healthy people of similar age and gender proportion using identical methods to; and (iii) accounting for the lean muscle mass of QF.

1.1.2 Rationale for research question 3

Several factors have been proposed to contribute to the aetiology of QF dysfunction following LT. These factors can be broadly grouped into local and systemic factors. Local factors relate mainly to the deconditioning associated with prolonged disuse of the muscle. This is likely to have preceded the LT and arisen in response to the symptoms experienced by the person during vigorous activity. That is, people with end-stage lung disease often experience intolerable dyspnoea with exertion, and, as a consequence, they adopt a sedentary lifestyle (18). Minimisation of moderate or vigorous intensity PA over several years results in muscle deconditioning, which is characterised by atrophy as well as specific histological changes, such as reduced capillarisation of muscle fibres, reduction in oxidative enzymes and a shift in muscle fibre type that favours glycolytic energy systems (19-25). Systemic factors relate mainly to the side-effects of immunosuppressant therapy. Specifically, cyclosporine has been proposed to induce a mitochondrial myopathy (26), cause reduction in overall muscle size and cross-sectional fibre type (27) and alter calcium and potassium regulation (28) and corticosteroids are recognised to reduce muscle protein synthesis and enhance proteolysis (29). To attempt to separate local from

systemic factors, earlier work has compared dysfunction between muscles with differences in their propensity for disuse (30, 31). That is, if systemic factors are the predominant cause of any impairments in QF strength it would be expected that similar impairments would be found in other peripheral skeletal muscles, particularly those of similar type and function. In contrast, if any impairments in QF strength result from a local process, such as chronic disuse / inactivity, it would be reasonable to expect a pattern of distribution in the skeletal muscle weakness characterised by greater impairment in the lower limbs, such as the QF, with relative sparing of upper limb muscle groups. This is because, activities that condition the QF, such as climbing stairs, can be avoided during daily life, whereas activities that condition the upper limb muscles, such as overhead arm activity (e.g. showering and dressing), are often impossible to avoid. The approach of comparing the strength of lower limb and upper limbs in an attempt to comment on the role of local vs. systemic factors may play on peripheral muscle dysfunction was utilised in an earlier study of people with chronic obstructive pulmonary disease (COPD) in which the loss in force-generating capacity of the QF was compared with that of adductor pollicis (30). This study demonstrated that the impairments in QF were far greater than any seen in adductor pollicis and therefore concluded that inactivity, rather than a systemic cause, was largely responsible for the dysfunction in the QF in people with COPD (30). In the study undertaken as part of this Masters of Philosophy, BB was chosen as the muscle to compare with QF. This is because BB is characterised by similar anatomical and morphological features (32) but, when compared with QF, has a reduced propensity for disuse. Further, the strength of both QF and BB could be readily measured using the same equipment.

1.1.3 Rationale for research question 4

During daily life, the strength of QF is challenged during activities such as transitioning from sitting to standing (33). However, the endurance of QF is also challenged during moderate or vigorous intensity aerobic exercise, walking up inclines, stair climbing and running. Of note, despite the interest in evaluating the strength of QF, only one study has explored QF dysfunction following LT in terms of endurance. In this study, Mathur et al (13) measured the endurance of the QF in six SLT recipients using a sustained contraction at 80% of the maximal torque generated by QF during a maximal voluntary isometric contraction on a robust dynamometer. These data were compared with identical measures collected in six people with COPD and no difference was demonstrated between the two groups (13). To date, no study has compared measures of QF endurance in BLT and HLT

recipients, who no longer demonstrate a ventilatory limitation to exercise, with identical measures collected in healthy people of similar age and gender. Further, the study by Mathur et al (13) assessed endurance of the QF using a protocol which required a sustained contraction at 80% of the maximal force, which does not mirror the typical pattern of muscle contraction of the QF during activities of daily living. In contrast, the study undertaken as part of this Masters of Philosophy utilised a protocol characterised by intermittent muscle contractions which more accurately reflects the type of muscle contractions required of the QF during high-intensity activity, such as stair climbing. Both effort-dependent and effort-independent measures related to QF endurance were collected in those following BLT and HLT and compared with identical measures collected in a group of healthy people of similar age and gender proportion.

1.1.4 Rationale for research question 5

Early work suggests that despite having negligible ventilatory limitation to exercise, SLT and BLT recipients have reduced exercise capacity and participate in low levels of PA during their daily lives (6, 34). These reductions have been shown to persist for up to one year post-transplant and have been hypothesised to be related to the impairments in QF function (6). However to date, in LT recipients, no study has explored relationships between both QF strength and QF endurance with measurements of functional exercise capacity, ST and daily PA and compared the strength of these associations with those observed in a group of healthy controls of similar age and gender proportion. These data will assist in determining the contribution of QF dysfunction in ongoing deficits in exercise capacity and PA observed in this population.

1.2 Significance and novelty

Lung transplant procedures are complex and expensive. New South Wales Health advises the public via their website that in 2014/15 the direct cost of a LT procedure, in Australian dollars, was $134,600 (35). This cost was a conservative estimate as it did not account for ongoing costs from post-procedure care needs such as readmission and treatment associated with organ rejection. The cost effectiveness of LT is somewhat diminished however by substantial post-operative morbidity and mortality (36). Specifically, following LT, although the respiratory limitation to exercise that was present prior to the procedure is largely ameliorated, exercise capacity and daily PA remain impaired, most likely as a consequence of peripheral muscle dysfunction. This study explores the magnitude and nature of peripheral

muscle dysfunction, specifically muscle strength of QF and BB and endurance of the QF, using rigorous assessment protocols. It also explores relationships between peripheral muscle dysfunction and its implications on functional capacity, ST and levels of PA. Whilst exercise training following LT has been demonstrated to be of benefit to LT recipients (37) specific recommendations on what components should be included remain unclear (38).

The study is the first of its kind to be undertaken in a Western Australian cohort. It represents an important first step towards the development of a training strategy that will address the specific deficits in peripheral muscle function and thereby optimise functional outcomes for individuals following BLT and HLT.

CHAPTER 2 LITERATURE REVIEW

This literature review will address three main areas in relation to lung transplant (LT) procedures. The first part will provide an overview of LT procedures, including single lung transplant (SLT), bilateral lung transplant (BLT) and heart-lung transplant (HLT). Both the indications for and survival following these procedures will be addressed. The second part will address the impact of LT, with a particular focus on BLT and HLT, on lung function, exercise capacity, health-related quality of life (HRQL), sedentary time (ST) and physical activity (PA). An overview of the impact of exercise training following LT on these factors will be provided. The third part will address peripheral muscle dysfunction following LT which is the main focus of the study presented in this thesis. As in the second part, an overview of the impact of exercise training following LT on peripheral muscle function will be provided.

2.1 Overview of lung transplant procedures

This part will describe the different types of LT procedures that are undertaken for people with end-stage lung disease and will outline the indications for the LT. Survival and predictors of survival will be presented and a number of comorbid conditions that recipients may develop are discussed.

2.1.1 A description of single, bilateral and heart-lung transplant

Lung transplant is a procedure undertaken for a highly select group of people with chronic, end-stage lung disease who are deteriorating despite being on maximal medical therapy (39). Transplantation of a single lung via a posterolateral thoracotomy was first performed in a human in 1962 by a group in the United States of America (40). At this time, Dr Fritz Derom was credited as the person to have performed the most successful LT, as the recipient of this SLT survived for a further 10.5 months post-procedure (41). Single lung transplant became a surgical option for non-infective lung disease in the early 1990s (42). Bilateral lung transplant was first performed as an en bloc procedure with a tracheal anastomosis in 1985. However as a result of high rates of anastomotic breakdown resulting in death, BLT was later modified to a procedure in which one lung is replaced followed by the other i.e. bilateral sequential LT (43). Bilateral lung transplant can be performed via posterolateral thoracotomy on both sides or more recently has been performed via an incision across the anterior chest in the fourth intercostal space, requiring division of the sternum (44). The BLT procedure is now performed far more often that SLT (2), with Australian data suggesting 89% of ‘lung-only’ procedures are now BLT (45).

In addition, some people are offered a HLT, which is replacement of both lungs and the heart in one block and is performed through a median sternotomy (44). The HLT procedure is performed infrequently, with Australian data suggesting only five were performed in 2017(45). The first HLT in Australia was performed in 1986, the first SLT following in 1990 and the first BLT in 1992 (45). Some people go on to require further transplantation. People who have undergone initial SLT may undergo ipsilateral or contralateral single lung re-transplant or a bilateral lung re-transplant and people who have undergone initial BLT may receive either a single or bilateral lung re-transplant (46).

2.1.2 Indications for people to receive either lung or heart-lung transplant and number of procedures performed worldwide and in Australia

Using worldwide data in adults who had a BLT, the main underlying conditions were chronic obstructive pulmonary disease (COPD)/emphysema (26%) and cystic fibrosis (CF) (23%) with other indications including, but not limited, to alpha-1 anti-trypsin deficiency, interstitial lung disease and non-CF bronchiectasis (2). In adults who had a HLT, the main underlying conditions were pulmonary hypertension (excluding idiopathic pulmonary arterial hypertension) (38%), idiopathic pulmonary arterial hypertension (30%) and CF (14%) (2).

Whilst spirometry is not the only marker of need for LT, measures of forced expiratory volume in one second (FEV_1), and rate of decline in FEV_1 and forced vital capacity (FVC) are used in decision making regarding referral and/or progression to LT. The threshold spirometric values used to decide on appropriateness of LT may differ for different disease groups. For example, international guidelines recommend referring patients with CF for LT when their FEV_1 has fallen below 30% of predicted or when their FEV_1 rapidly declines. In contrast, patients with COPD are referred when their FEV_1 falls to below 25% of predicted values and then proceed to be listed for surgery when FEV_1 falls below 15 to 20% of predicted values. For patients with interstitial lung disease, referral for LT is considered when their FVC falls below 80% predicted and then proceed to list for surgery if there is a greater than 10% decline in FVC in the following six month period (47).

The International Society of Heart and Lung Transplant (ISHLT) report that worldwide, between 1st January 1995 and 30th June 2016, a total of 62,456 SLT or BLT and 4,745 HLT procedures were performed (2). Procedures were predominantly performed on adults with data collected for 12 months following 1st July 2015 indicating that 96% of the SLT and BLT procedures and 84% of HLT

procedures were performed on adults. Five centres in Australia and one in New Zealand contribute to the registry via the Australian and New Zealand Cardiothoracic Transplant Registry (2, 48) with 526 SLT, 2,533 BLT and 201 HLT procedures registered as having been performed in Australia since 1986 (45).

Western Australia has a single centre LT program which commenced in 2008 at Royal Perth Hospital. In February 2015 the unit transferred to a new facility and at that point in time, 100 procedures had been performed. The predominant conditions undergoing LT in the first eleven years of the service operation in Western Australia were interstitial lung disease (30%), CF (28%) and COPD (excluding alpha-1 anti-trypsin deficiency) (23%) (49).

2.1.3 Survival following lung and heart-lung transplant

2.1.3.1 Rates of survival following lung and heart-lung transplant

Lung transplant procedures have been shown to confer a survival benefit in some, but not all, people who undergo these procedures (50-52). Many people live longer and describe a better HRQL following LT (53). However statistical analysis has shown that some transplant recipients die sooner than they would have done if they had not had a transplant (52) and a significant proportion encounter adverse events and comorbidity (53) (see Section 2.1.3.3).

With SLT and BLT considered together, survival data, expressed in terms of the median survival time, has increased from 4.3 years in 1990 to 6.3 years in 2014 with an overall median survival time of 5.7 years (54, 55). Recipients who survive to one year post-LT have a median survival following this first year of 7.9 years (54). When survival data are expressed as the proportion who have survived at specific time points post-procedure, between 1990 and 1997, the three month and 12 months survival rates were 83% and 72%, respectively. These rates have improved with data collected between 2005 and 2012 indicating that the three month and 12 month survival rates were 91% and 83%, respectively. The ten year survival rate was 32% (54). When comparing survival rates with recipients grouped according to the type of LT, BLT recipients have a better survival compared to SLT recipients (median 7.4 yr vs. 4.6 yr, respectively between 1990 and 2015) (2). This overall trend towards improvement in survival post-LT is largely as a consequence of a shift away from SLT to BLT, but also due to improved surgical technique, improved early peri-operative management, antimicrobial prophylaxis and improved patient selection (50).

Using data collected between 1982 and 2015, the median survival time for HLT was 3.3 years (2). Heart-lung transplant has reported survival rates of 72% at three months declining to 32% at ten years. In comparison to lung-only transplant, HLT has a more pronounced early mortality but better long-term survival (54).

The most common causes of death in the first 30 days following LT are graft failure (lung or heart), technical complications and non-cytomegalovirus infections (54). Primary graft failure remains the leading cause of early mortality following SLT, BLT and HLT. After the first year, chronic lung allograft dysfunction and non-cytomegalovirus infections are the most common causes of mortality (54). Bronchiolitis obliterans syndrome (BOS), the most common type of chronic allograft dysfunction, is defined as "a delayed allograft dysfunction with persistent decline in FEV_1 that is not caused by other known and potentially reversible causes of post-transplant loss of lung function" (56). In adults following SLT or BLT, BOS is seen in 50% of recipients within five years of transplant, and 76% by ten years. In BLT recipients, when compared with those who did not develop BOS, those who did develop BOS had "an annual hazard for death that was ten times greater" (57). Once BOS has developed the five-year survival was estimated at only 26%" (57). Regarding the development of BOS following HLT, this is present in 42% and 57% of recipients five and ten years after HLT, respectively (54). A restrictive pattern of lung function has been recognised more recently in about 30% of patients with chronic allograft dysfunction which is characterised by "a persistent decline in FEV_1, FVC and total lung capacity, in the presence of persistent lung infiltrates, pleural thickening on thoracic computerised tomography (CT) scan and histological changes of pleuroparenchymal infiltrates and obliterative bronchiolitis" (58). Once this pattern is seen median survival becomes worse than that seen in LT recipients with BOS, with median survival being only six to 18 months compared with three to five years with BOS (58).

2.1.3.2 Predictors of survival

As outlined in Section 2.1.3.1 the type of LT procedure performed impacts on survival with those receiving BLT having better survival than those receiving SLT. Other factors that have been shown to impact survival can be broadly grouped as donor or recipient factors.

Donor factors that may negatively impact on survival include tobacco use, being positive for cytomegalovirus when the recipient is negative, being taller than the recipient, having severe illness pre-transplant other than intensive care admission

alone (e.g. the need for dialysis and ventilation prior to harvest of donor organs) and having a history of diabetes (54).

Recipient factors that impact on survival include the type of pre-existing lung disease. At three months after SLT and BLT, recipients with COPD not associated with alpha-1 anti-trypsin deficiency have the lowest mortality (9%), whereas those with idiopathic pulmonary arterial hypertension had the highest mortality (22%). For people surviving to one year, median survival was 11.1 years for CF, 10.1 years for idiopathic pulmonary arterial hypertension, 8.9 years for sarcoidosis, 8.7 years for COPD associated with alpha-1 anti-trypsin deficiency and 7.0 years for both COPD not associated with alpha-1 anti-trypsin deficiency and interstitial lung disease (54). Other recipient factors that may negatively impact on survival include being aged > 60 years, previous blood transfusion, higher supplemental oxygen requirements at rest, low FVC (expressed as a percent of predicted), the need pre-operatively for an intensive care admission and/or mechanical ventilation and the need post-operatively for extra-corporeal membrane oxygenation (54). Data regarding whether or not a high or low body mass index is a risk factor are contradictory (39).

Measures of physical function collected pre-operatively have been shown to influence survival following LT. Specifically, an analysis of 9,956 transplant recipients (64.8% BLT, 35.2% SLT) transplanted between 2005 and 2011 who were grouped into quartiles according to their pre-operative six-minute walk distance (6MWD), showed a significant difference in survival between quartiles. That is, the median survival for people with the lowest 6MWD (i.e. ≤137 m) was 4.1 years whereas the median survival for people with the greatest 6MWD (i.e. > 330 m) was 5.8 years (59). These data corroborate work showing that lower levels of functional independence was associated with poorer survival post-LT (60). That is, one-year survival rates in LT recipients who were classified as needing (i) no assistance, (ii) some assistance or (iii) total assistance were 89%, 86% and 76%, respectively (60).

Other authors have more recently considered the impact of frailty, a term used to describe biological age rather than chronological age, on survival following LT. Using a frailty index these authors found that frailty was associated with a decreased survival independent of age, gender and transplant type with frail patients having a one- and three year estimated survival rate of 71.7% and 41.3%, compared with 92.9% and 66.1% for non-frail patients (61).

2.1.3.3 Morbidity following lung and heart-lung transplant

People awaiting transplant procedures report a number of symptoms including breathlessness, fatigue, decreased exercise tolerance and reduced quality of life (62, 63) and have been shown to participate in low levels of PA during daily life (12, 64, 65). Following LT many of these symptoms are ameliorated, at least in part or for a period of time, but these benefits may come at a cost to LT recipients.

Recipients develop conditions (e.g. hypertension, renal dysfunction, hyperlipidaemia, diabetes) commonly caused or exacerbated by immunosuppressant medications and complication rates increase significantly over time (54). Using data after 1994, within 12 months of LT, 22% of SLT and BLT recipients had developed renal dysfunction and 21% had developed diabetes. The prevalence of renal dysfunction and diabetes increases between one and five years post-LT. For the same period 5%, 19% and 30% of SLT or BLT recipients had developed one or more malignancies within one, five and ten years respectively, with skin cancer being the most common (2).

Regarding HLT, within one year of procedure 20% had developed renal dysfunction and 18% had developed diabetes. As with SLT and BLT it is common for malignancy to develop with the prevalence of malignancy being 6%, 11% and 15% at one, five and ten year post-HLT. In this population, lymphoma is more commonly reported than skin cancer (2).

Another condition commonly seen following LT is osteoporosis. Osteoporosis is reported in various studies as being present in between 35% and 61% of LT candidates (66-71). Specifically, one study that reported the bone mineral density (BMD) in LT candidates suggested prevalence of osteoporosis and osteopenia in the lumbar spine to be 32% and 32%, and in the femoral neck to be 54% and 32%, respectively (72). These data concur with other work in this population (73). Following LT, osteoporosis and osteopenia has been shown to worsen with a further 4% of bone loss reported over the first six months (67). Reductions in BMD have been associated with 18% to 42% of recipients developing osteoporotic fractures (72, 74). One study explored the impact of a resistance exercise program focussing on the lumbar extensor muscles and measured BMD of the lumbar spine before, two months and eight months after LT (see Table 2.1) (75). Whilst a group of eight in the exercise group and eight in the control group demonstrated a significant reduction in lumbar BMD between study entry and two months post-LT, the control group continued to lose BMD between two and eight months while the trained group

increased lumbar BMD and returned close to their pre-LT baseline. Given these results and that exercise training involving progressive resistance and balance exercise are recommended to prevent further bone loss and/or improve BMD and decrease fall and fracture risk (76), inclusion of these components within exercise training following LT would appear to be essential.

Single lung transplant, BLT and HLT candidates and recipients are reported as also having reduced peripheral muscle mass. This reduction in muscle mass combined with impairments in peripheral muscle strength or function, termed sarcopenia (77), has been shown to result in an increased risk of physical disability, poorer quality of life and death in elderly people (78) and although a number of studies of LT recipients have explored peripheral muscle mass and strength, the prevalence of sarcopenia itself is not well explored (9). Skeletal muscle mass and skeletal muscle strength following LT will be discussed in Section 2.3.

2.1.4 Summary

Lung transplant procedures are performed in a highly select group of people with chronic, end-stage lung disease who are deteriorating despite being on maximal therapy. Whilst these procedures confer benefit in terms of survival, this benefit is not universal. A number of donor and recipient factors, along with measures of physical performance e.g. 6MWD and frailty, have been shown to predict survival. Following LT, many recipients have significant improvement in symptoms but may go on to develop comorbid conditions that significantly impact their lives.

2.2 Changes in lung function, exercise capacity, health-related quality of life, sedentary time and physical activity following lung and heart-lung transplant

This part will describe the changes in a number of physical and functional measures following LT. Specifically the impact of LT on lung function, exercise capacity and HRQL is outlined as well as the impact on recipients' ST and participation in PA. A number of LT studies report collecting these measures in groups which include both SLT and BLT. Therefore, the proportion of SLT or BLT are provided. Where possible changes in these measures in BLT and HLT specifically are highlighted. In addition an overview of the effect of exercise training following LT on these factors will be provided.

2.2.1 Effect of lung and heart-lung transplant on lung function

Following LT, repeated measures of FEV_1 and FVC are used to assess performance of the allograft. Forced expiratory volume in one second and FVC show a marked improvement in the first 12 months following procedure with values then decreasing slightly before remaining relatively constant (79). Whilst SLT recipients have been shown to achieve FEV_1 and FVC approximately one year after LT that reach 72% and 75% of predicted values, respectively, BLT recipients fare considerably better reaching 90% and 87% of predicted values, respectively (80). Bilateral lung transplant recipients have also been shown to maintain improvements in these measures for longer than those who received SLT (79). Data in HLT regarding recovery of lung function is sparse though it appears to not be as good as recovery following BLT (81).

2.2.2 Effect of lung and heart-lung transplant on exercise capacity

Following LT, dramatic improvements in exercise capacity have been demonstrated. These improvements are seen when exercise capacity is expressed as distance walked during field-based walking tests (e.g. 6MWD), and also when expressed using measures derived from laboratory-based assessment (e.g. peak rate of oxygen update [VO_{2peak}]). Specifically, in a group of 36 SLT and BLT recipients (15 SLT, 21 BLT), 6MWD measured four months post-procedure improved from (mean ± SD) 320 ± 138 m to 449 ± 128 m ($p < 0.05$) (7). Likewise, in 46 SLT recipients measures of VO_{2peak} collected prior to LT and three months after LT have been seen to increase from 9.4 ± 3.1 mL/kg/min to 12.1 ± 2.9 mL/kg/min ($p < 0.001$) and in 32 BLT recipients from 11.7 ± 4.2 mL/kg/min to 14.6 ± 3.7 mL/kg/min ($p < 0.05$) (82).

Studies reporting 6MWD in HLT are limited, with most studies only reporting values following the LT procedure. However as is seen in SLT and BLT, improvements in VO_{2peak} from 10.7 ± 4.5 mL/kg/min prior to surgery to 12.7 ± 3.0 mL/kg/min three months after surgery have been reported in 25 HLT recipients (82).

It is notable that although the improvement in exercise capacity following LT is large, measures of 6MWD and VO_{2peak} remain lower than expected in an otherwise healthy population. Specifically, in 22 LT recipients (7 SLT, 15 BLT), who were an average of 15.5 months after surgery, 6MWD was approximately 70% of that measured in an age and gender matched healthy control group (6). Additionally, BLT recipients three months following LT have been reported as having VO_{2peak} of 40% to 50% of predicted values (82, 83) with VO_{2peak} remaining at approximately 50% of predicted levels in mixed SLT and BLT populations beyond one year after LT (5, 6). Likewise

for HLT recipients, when expressed as VO_{2peak}, improvements only reached approximately 40% of predicted values at three months post-procedure (82) and approximately 60% from 14 months post-procedure onwards (4, 84, 85).

The reasons for the limited recovery in exercise capacity are multifactorial, but following BLT, do not relate to ongoing ventilatory limitation to exercise. Earlier work which has explored the factors which contribute to the persistent impairments in exercise capacity seen following LT suggest that post-LT improvements in exercise capacity were largely explained by recipients' pre-transplant exercise capacity and post-operative improvements in quadriceps femoris (QF) strength rather than changes in graft function, as measured by spirometry (16). Specifically, at two weeks following LT, 59% of the improvement in 6MWD, expressed as a percentage of that predicted in a healthy population, was explained by pre-transplant 6MWD and the magnitude of change in QF strength. The amount of variance in the improvement in 6MWD explained by these two variables increased to 68% at six weeks, 72% at 13 weeks and 75% at 26 weeks post-LT (16). These results suggest that interventions to improve pre-transplant exercise capacity and QF strength following LT may optimise recovery of exercise capacity in LT recipients.

Participation in exercise training following LT has been shown to benefit recipients in terms of 6MWD (see Table 2.1). Compared with the change in 6MWD observed in a control group who did not receive exercise training following LT, a group that received three months of exercise training following LT demonstrated significantly greater improvements (increase in 6MWD at the end of the three month intervention period of 177 m vs. 132 m; $p = 0.008$). On completion of the intervention period, the 6MWD in the exercise and control groups were equivalent to 79 ± 8% and 70 ± 10% predicted, respectively. These benefits were maintained for at least one year with 6MWD in each group being 86 ± 7% and 74 ± 11% predicted, respectively (37). Whilst this study only had small numbers, as the majority of study participants had undergone BLT (83% in the exercise group and 88% in the control group), these data support the benefit of exercise following BLT. Although data from randomised controlled trials are not available, following HLT, improvements in 6MWD from 351 ± 66 m to 422 ± 69 m have been reported on completion of 41 ± 19 days of exercise training, initiated 47 ± 23 days after discharge from hospital (4). Whilst this improvement did not reach statistical significance, improvement in 6MWD of 30 m is considered clinically significant in chronic respiratory disease (86). On discharge from the exercise training program the group continued to demonstrate significant gains in 6MWD with 6MWD being 481 ± 76 m, 511 ± 100 m and 530 ± 91 m ($p <$

0.001) six, 12 and 18 months post-LT, respectively (4). Nevertheless, without a control group, it is not clear whether this improvement is greater than would be expected with natural recovery alone.

Table 2.1 Summary of studies of exercise training in lung and heart-lung transplant.

Author	Year	Study design	Transplant type	Interventions	Outcome measures	Findings
Ambrosino (4)	1996	Prospective cohort	11 HLT	Aerobic ex Inspiratory muscle training Abdominal and lower and upper limb resistance ex	QF max isokinetic torque BF max isokinetic torque 6MWD VO_{2peak} MIP MEP	Muscle strength: Significant increase in QF max isokinetic torque after 6 months (86 ± 18 Nm vs. 48 ± 16 Nm; $p < 0.001$), after 12 months (82 ± 16 Nm vs. 48 ± 16 Nm; $p < 0.001$) and after 18 months (78 ± 20 Nm vs. 48 ± 16 Nm; $p < 0.001$). Significant increase in BF max isokinetic torque after 6 months (35 ± 10 Nm vs. 28 ± 12 Nm; $p < 0.05$), after 12 months (44 ± 7 Nm vs. 28 ± 12 Nm; $p < 0.001$) and after 18 months 42 ± 10 Nm vs. 28 ± 12 Nm; $p < 0.001$). Exercise capacity: Significant increase in 6MWD after 6 months (481 ± 76 m vs. 351 ± 66 m; $p < 0.001$), after 12 months (511 ± 100 m vs. 351 ± 66 m; $p < 0.001$) and after 18 months 530 ± 91 m vs. 351 ± 66 m; $p < 0.001$). Significant increase in VO_{2peak} after 6 months (19.6 ± 6 mL/kg/min vs. 14.2 ± 4 mL/kg/min; $p < 0.05$). Other: Significant increase in MIP at 12 months (75 ± 17 cmH_2O vs. 50 ± 5 cmH_2O; $p < 0.05$); Significant increase in MEP after 12 months.

Table 2.1 Summary of studies of exercise training in lung and heart-lung transplant (continued)

Author	Year	Study design	Transplant type	Interventions	Outcome measures	Findings
Ambrosino (continued)						(100 ± 49 cmH_2O vs. 58 ± 19 cmH_2O; $p < 0.001$) and after 18 months (82 ±31 cmH_2O vs. 58 ± 19 cmH_2O; $p < 0.001$).
Braith (87)	2007	RCT	IG 1: 10 LT IG 2: 10 LT CG: 10 LT	IG 1: Alendronate Lumbar resistance ex IG 2: Alendronate CG: No intervention	Lumbar BMD	BMD 14.1 ± 3.9% below baseline (CG; $p \leq 0.05$); 1.4 ± 1.1% above baseline (alendronate only; $p \geq 0.05$); 10.8 ± 2.3% above baseline (alendronate + resistance; $p \leq 0.05$).
Fuller (88)	2017	RCT	IG 1: 4 SLT 28 BLT IG 2: 5 SLT 29 BLT	IG 1: Supervised 7 week program > home program Aerobic ex Resistance ex Home program IG 2: Supervised 14 week program Aerobic ex Resistance ex	QF strength BF strength 6MWD HRQL	Muscle strength: IG 1: Significant increase in QF peak torque (34.09 Nm; $p < 05$) and BF peak torque (21.10 Nm; $p < 0.05$). IG 2: Significant increase in QF peak torque (34.83 Nm; $p < 0.05$) and BF peak torque (12.93 Nm; $p < 0.05$). Exercise capacity: IG 1: Significant increase in 6WMD (202 ± 72 m; $p < 0.05$). IG 2: Significant increase in 6WMD (149 ± 169 m; $p < 0.05$).

Table 2.1 Summary of studies of exercise training in lung and heart-lung transplant (continued)

Author	Year	Study design	Transplant type	Interventions	Outcome measures	Findings
Fuller (continued)						HRQL: IG 1: Significant increase in SF36 physical health summary score (40.2; $p < 0.05$) and SF36 mental health summary score (34.2; $p < 0.05$) after 6 months. IG 2: Significant increase in SF36 physical health summary score (38.5; $p < 0.05$) and SF36 mental health summary score (27.9; $p < 0.05$) after 6 months. No differences between IG 1 and IG 2.
Fuller (89)	2017	RCT	IG: 43 BLT CG: 37 BLT	IG: Supervised 12 week Aerobic ex Lower limb resistance ex Upper limb ROM and resistance ex CG: Supervised 12 week Aerobic ex Lower limb resistance ex	Shoulder flexion and abduction strength HRQL Bodily pain	Muscle strength: Significant increase in shoulder flexion peak torque (8.4 ± 4 Nm vs. 6.7 ± 2.8 Nm; $p = 0.037$) at 6 weeks. HRQL: Significantly improved SF36 bodily pain domain (76 ± 17 vs. 66 ± 26; $p = 0.05$). Other: Significantly less bodily pain (VAS 2.1 ± 1.3 cm vs. 3.8 ± 1.7 cm; $p < 0.001$) at end of 6 weeks. No difference between groups after 6 months.

Table 2.1 Summary of studies of exercise training in lung and heart-lung transplant (continued)

Author	Year	Study design	Transplant type	Interventions	Outcome measures	Findings
Guerrero (90)	2005	Controlled trial	2 SLT 9 BLT 1 HLT	Aerobic ex	Mitochondrial respiration	Other: Significant increase in bioenergetics at cellular level (apparent K_m 94 ± 34 µm vs. 203 ± 62 µm; $p < 0.001$), W_{max} (85 ± 43 W vs. 98 ± 42 W; $p = 0.04$), endurance time (20 ± 10 min vs. 31 ± 14 min; $p = 0.01$) and VO_{2max} (1.2 ± 0.56 L/min vs. 1.4 ± 0.5 L/min, $p = 0.05$).
Ihle (91)	2011	RCT	IG: 11 SLT 19 BLT CG: 10 SLT 20 BLT	IG: Inpatient program >1 year after LT. Aerobic ex Lower and upper limb resistance ex Muscle stretches ROM ex Education CG: Outpatient program > 1 year after LT Airway clearance Breathing ex Physiotherapist prescribed aerobic ex	6MWD W_{max} VO_2peak AT HRQL	Exercise capacity: IG: Significant increase in W_{max} (7.33W; $p = 0.022$), $W_{max\ \%pred}$ (4.02%, $p = 0.044$), VO_{2peak} (1.33 mL/kg/min; $p = 0.039$), AT (16.43 W; $p = 0.002$) and O_{2AT} (1.97 mL/min/kg; $p = 0.033$). CG: Significant increase in $W_{max\ \%pred}$ (8.5%; $p = 0.001$), VO_{2peak} (2.2 mL/kg/min; $p = 0.005$). AT (14.02 W; $p = 0.001$) and O_{2AT} (2.94 mL/kg/min; $p = 0.001$). No difference between IG and CG. HRQL: No difference between IG and CG.

Table 2.1 Summary of studies of exercise training in lung and heart-lung transplant (continued)

Author	Year	Study design	Transplant type	Interventions	Outcome measures	Findings
Langer (37)	2012	RCT	IG: 3 SLT 15 BLT CG: 2 SLT 14 BLT	IG: Aerobic ex QF resistance ex Counselling to participate in ex CG: Counselling to participate in ex	QF strength 6MWD W_{max} VO_{2max} ST PA HRQL	Muscle strength: Significant difference in $QF_{\%pred}$ after intervention (IG 17% [95% CI, 9 to 24] more than CG; p = 0.001) and after 1 year (16% [95% CI, 7 to 25] more than CG; p = 0.001). Exercise capacity: Significant difference in $6MWD_{\%pred}$ after intervention (IG 9% [95% CI, 3 to 5] more than CG; p = 0.008) and after 1 year (IG 16% [95% CI, 5 to 19] more than CG; p = 0.002). Significant difference in $W_{max\ \%pred}$ after 1 year (IG 16% [95% CI, 1 to 31] more than CG; p = 0.042). Physical activity: Significant difference after intervention in daily steps (IG 1376 steps [95% CI, 481 to 2269] more than CG; p = 0.004) and after 1 year (IG 3017 steps [95% CI, 1185 to 4849] more than CG; p = 0.002). Significant difference in MVPA after 1 year (IG 27 min/day [95% CI, 1 to 54] more than CG; p = 0.047). Significant difference in movement intensity after intervention (IG 0.18 m/s^2 [95% CI, 0.01 to 0.35] more than CG; p = 0.044) and after 1 year (IG 0.27 m/s^2

Table 2.1 Summary of studies of exercise training in lung and heart-lung transplant (continued)

Author	Year	Study design	Transplant type	Interventions	Outcome measures	Findings
Langer (continued)						[95% CI, 0.14 to 0.39] more than CG; p = 0.001) HRQL: Significant difference in SF36 physical functioning domain after 1 year (IG 10 [95% CI, 1 to 20] more than CG; p = 0.039) and role physical domain (IG 29 [95% CI, 7 to 51] more than CG; p = 0.011).
Maury (7)	2008	Prospective cohort	15 SLT 21 BLT	Aerobic ex Resistance ex	QF max isometric force HGF 6MWD FEV_1	Muscle strength: Significant increase in QF max isometric force (51 ± 28% vs. 59 ± 26% predicted; p < 0.05) and HGF (53 ± 20% vs. 73 ± 21% predicted; p < 0.05). Exercise capacity: Significant increase in 6MWD (140 ± 91 m; p <0.05). Other: No difference.
Mitchell (75)	2003	RCT	IG: 8 LT CG: 8 LT	IG: Lumbar resistance ex CG: No intervention	Lumbar BMD	BMD: 19.5% above baseline (CG; p ≤ 0.05); 5% below baseline (IG; p ≤ 0.05).

Table 2.1 Summary of studies of exercise training in lung and heart-lung transplant (continued)

Author	Year	Study design	Transplant type	Interventions	Outcome measures	Findings
Munro (92)	2009	Prospective cohort	7 SLT 29 BLT	Aerobic ex Resistance ex Education	6MWD HRQL (SF36) FEV_1 FVC	Exercise capacity: Significant increase in 6MWD (92 m; $p < 0.0001$). HRQL: Significant increase in HRQL ($p < 0.05$). Other: Significant increase in FEV_1 and FVC ($p < 0.0001$).
Smith (93)	2018	Prospective cohort	4 SLT 6 BLT	4 weeks: Aerobic and resistance ex Stretching Education 6 months: Home based aerobic and resistance ex IG 1: Low volume resistance ex IG 2: High volume resistance ex	QF max isometric force QF max isokinetic force QF 1-RM Leg press 1-RM HGF 6MWD	Muscle strength: Significant increase in QF max isometric force (1.20 [95% CI, 0.99 to 1.41] Nm/kg vs.1.46 [95% CI, 1.8 to 1.74] Nm/kg; $p < 0.05$) after 4 weeks. No significant increase at 6 months after home program. No difference between groups. Significant increase in QF max isokinetic torque corrected for body mass at 60^{o}/s (1.27 [95% CI, 1.09 to 1.4] Nm/kg vs.1.58 [95% CI, 1.33 to 1.81] Nm/kg; $p < 0.001$) and at 120^{o}/s (1.06 [95% CI, 0.9 to 1.23] Nm/kg vs. 1.34 [95% CI, 1.15 to 1.52] Nm/kg; $p < 0.001$) after 4 weeks. No significant increase at 6 months after home program. No difference between groups.

Table 2.1 Summary of studies of exercise training in lung and heart-lung transplant (continued)

Author	Year	Study design	Transplant type	Interventions	Outcome measures	Findings
Smith (continued)				Education Home based aerobic and resistance ex		Significant increase in QF 1-RM (98 [95% CI: 31 to 58] kg vs.73 [95% CI, 57 to 89] kg; p <0.001) after 4 weeks. Significant increase in leg press 1-RM (61 [95% CI, 44 to 78] kg vs. 79 [95% CI, 60 to 98] kg; p < 0.001) after 4 weeks and significant further increase (39 [95% CI, 19 to 60] % (p < 0.05) at 6 months after home program. No difference between groups. Significant increase in HGF (10.6% above baseline in the group doing high volume (p < 0.05) after 4 weeks with a further increase at 6 months after home program by 23 [95% CI, 4 to 41] % (p < 0.05). Exercise capacity: Significant increase in 6MWD (172 m: p < 0.01) after 4 weeks. No difference between groups.
Stiebellehner (94)	1998	Prospective cohort	2 SLT 7 BLT	Aerobic ex	VO_{2peak} W_{peak}	Exercise capacity: Significant increase in VO_{2peak} (1.13 ± 0.26 L/min vs. 1.26 ± 0.27 L/min; p < 0.05) and W_{peak} (66 ± 22 W vs. 81 ± 22 W, p < 0.05).

Table 2.1 Summary of studies of exercise training in lung and heart-lung transplant (continued)

Author	Year	Study design	Transplant type	Interventions	Outcome measures	Findings
Ross (95)	1993	Prospective cohort	7 SLT 1 BLT	Aerobic ex	VO_{2max} Haemodynamic responses	Exercise capacity: Significant increase in VO_{2max} (9.2 ± 0.8 mL/kg/min vs. 13.4 ± 0.8 mL/kg/min; $p < 0.05$) and W_{max} (21 ± 3 W vs. 52 ± 6 W; $p < 0.05$).
Vivodtzev (14)	2011	Controlled trial	2 SLT 9 BLT 1 HLT	Home based aerobic ex	QF max torque on magnetic stimulation VO_{2peak} HRQL Fibre type changes	Muscle strength: Significant increase in Twq (+4.6 ± 2.6 kg; $p = 0.001$). Exercise capacity: Significantly reduced $VE_{isowatt}$ when expressed as % of peak value in TG (94 ± 5% vs. 81 ± 15% VE_{peak}; $p = 0.02$) VE_{CET} (41.2 ± 7.1 L/min vs. 35.7 ± 4.6 L/min; $p = 0.04$). HRQL: Significant decrease in CRQ Dyspnoea score (3.6 ± 1.5 vs 4.2 ± 1.2; $p = 0.03$). Other: Significant increase in endurance time (+9 ± 12 min; $P < 0.05$). No difference between groups.

Adapted from Wickerson et al (96).

Definition of abbreviations: ^{o} (degree), 1-RM (one repetition maximum); 6MWD (six-minute walk distance); AT (anaerobic threshold); BF (biceps femoris); BLT (bilateral lung transplant); BMD (bone mineral density); CI (confidence interval); CRQ (Chronic Respiratory Disease Questionnaire); ex: exercise; FEV_1 (forced expiratory volume in 1 second); FVC (forced vital capacity); HGF (handgrip force); HLT (heart-lung transplant); HRQL (health-related quality of life); K_m (Michaelis constant for the enzyme being investigated); LT (lung transplant i.e. procedure not specified); MEP (maximal expiratory pressure); MIP (maximal inspiratory pressure); MVPA (moderate or vigorous intensity physical activity); O_{2AT} (oxygen update at anaerobic threshold); PA (physical activity); pred (predicted), QF (quadriceps femoris), RCT (randomised controlled trial); ROM (range of motion); SF36 (Short-Form 36 questionnaire); SLT (single lung transplant); ST (sedentary time); TG (transplant group); Twq (quadriceps femoris twitch tension); VE_{CET} (minute ventilation during constant-workload exercise test); $VE_{isowatt}$ (minute ventilation at the same workload); VO_{2peak} (peak oxygen consumption); VO_{2max} (maximal oxygen consumption); W_{max} (maximal workload); W_{peak} (peak workload).

2.2.3 Effect of lung and heart-lung transplant on health-related quality of life

Research focussing on the effect on LT on HRQL is limited with an earlier review locating only 73 articles related to HRQL in LT recipients compared to 1,131, 1,291 and 1,689 articles in cardiac, liver and renal transplant recipients, respectively (97). Nevertheless, these earlier studies show that LT confers benefit (50) with several studies reporting improvements in both physical and mental domains of HRQL (34, 98-103). Compared to pre-LT ratings, data from 28 LT recipients (25 BLT, 3 SLT) followed up until at least 55 months after LT showed significant improvement in domains of mobility, energy, sleep, social isolation, and emotional reaction (98). The improvement in these domains of HRQL were maintained for several years following LT. Similarly, using the Short-Form 36 questionnaire (SF36) to measure HRQL, 88 LT recipients (12 SLT, 76 BLT) showed significant improvements in both physical and mental health domains in the first 12 months after LT, which then remained stable for five years (101). Nevertheless, whilst HRQL improves following LT, in long term survivors it has been shown to remain below that of other people in the community. Specifically, a German study which compared 27 BLT recipients and 30 controls matched for age, gender and body mass index 208 ± 67 days after LT, found no differences in HRQL as measured by the Quality of Life Profile for Chronic Disease self-rated questionnaire (104). Likewise an evaluation of 28 LT recipients (11 SLT, 6 BLT, 11 HLT) who survived to ten years or more following LT at an English hospital (from a cohort of 96 recipients) showed that on the SF36 the scores for domains of physical function, role-physical, role emotional and general health were significantly lower than normative data (99).

Although there appears to be initial improvement in HRQL, which has been shown to then remain stable in some studies, it is also clear that following LT there is a decline in some aspects that contribute to HRQL. Specifically, in a study of 66 LT recipients (41 SLT, 25 BLT) who were surveyed before and at least six months after LT using a Transplant Symptom Frequency Questionnaire, recipients reported significantly more frequent neurocognitive and gastrointestinal symptoms, and more changes in their physical appearance (102). Lanuza et al (105) reported that over the first six months following LT, recipients reported a significant improvement in shortness of breath (at rest and with activity), less sadness, fatigue and feelings of helplessness and lack of control. However, they also reported the onset of new, frequent and distressing symptoms over this time period that include nausea, changes in taste, tremors, vomiting, stomach pain and burning or numbness of hands and/or feet. These undesirable symptoms negatively impact on HRQL. In 287

LT recipients (208 BLT, 46 SLT and 33 HLT) tremor and hirsutism, induced by immunosuppressant medications, were reported as the most frequent symptoms in 70% and 68% of recipients, respectively. Comorbid conditions, such as developing a moon face and adiposity were reported as the most distressing symptoms in 39% and 32% of cases, with subsequent negative impact on recipients' perceptions of HRQL (106).

Participation in exercise training may confer benefit to LT recipients in terms of HRQL (see Table 2.1). Specifically, significant improvements in SF36 physical and mental health summary scores have been demonstrated at the end of seven and 14 weeks of supervised exercise training (88, 92). Without a control group it is not clear whether the improvement shown in these studies would have occurred regardless of the exercise training. However, one randomised controlled trial has explored the impact of three months of thrice weekly supervised exercise training started immediately following hospital discharge after SLT and BLT, and demonstrated exercise training resulted in superior outcomes in terms of HRQL (37). Specifically, the physical function and role physical domain scores of the SF36 were significantly higher one year after LT procedure in the intervention group compared to the control group (i.e. 77 ± 11 vs. 65 ± 17; $p = 0.039$ [physical function] and 83 ± 28 vs. 52 ± 32, $p = 0.011$ [role physical], respectively).

2.2.4 Effect of lung and heart-lung transplant on sedentary time and physical activity

Few studies have explored the effect of LT on accumulation of ST and participation in PA. One study has reported 82% of LT candidates as either sedentary or extremely sedentary (107) with little change in ST from pre-transplant levels through to 12 months after discharge. In another study that used a Dynaport activity monitor, ST recorded in 16 LT recipients (2 SLT, 14 BLT) prior to LT, at hospital discharge, three and 12 months following discharge was essentially unchanged; 504 ± 113 min/day, 525 ± 106 min/day and 495 ± 99 min/day and 459 ± 108 min/day, respectively (37). Further, LT recipients have been shown to spend more time in sedentary behaviour than healthy people. Specifically, when measured 15.5 months post-procedure, 22 LT recipients spent 30% more time in sedentary behaviour (i.e. lying or sitting) when compared to an aged and gender matched healthy control group (i.e. 447 ± 76 min/day vs. 358 ± 112 min/day; $p = 0.002$) (6).

As seen with the change in exercise capacity, the few studies that measure PA in terms of time spent in different levels of intensity of PA or average daily steps also

tend to demonstrate an improvement following LT. Specifically, a group of LT recipients (8 SLT, 39 BLT) who were approximately five years post-procedure, were reported to take significantly more daily steps when compared to LT candidates (i.e. 6,642 ± 2,886 average daily steps vs. 1,407 ± 1,166 average daily steps; $p < 0.001$) (108). Earlier work has shown that, when compared with pre-LT values, time spent undertaking moderate intensity PA, measured using a SenseWear Armband (SWA) activity monitor, did not significantly change at the time of hospital discharge (i.e. 7.2 min/day per day [95% confidence interval (CI), 4.5 to 9.9] min/day pre-LT vs. 7.8 min/day [95% CI, 4.7 to 10.9] at time of hospital discharge). However, significant improvements in the time spent undertaking moderate intensity PA were evident three months after LT compared to the time of hospital discharge (i.e. 7.8 min per day [95% CI, 4.7 to 10.9] at hospital discharge vs. 18.4 min/day [95% CI, 13.5 to 23.5] at three months) and this improvement was sustained at six months (34).

Despite the increase in PA levels, following LT, recipients engage in less PA than healthy people. In the study by Wickerson et al (34), although significantly improved, at three months post-LT, the time spent undertaking moderate intensity PA by LT recipient was 55% lower than the general population. These data are consistent with another study that collected measures of PA using the SWA and showed that 15.5 months post-LT, LT recipients spent 66% less time undertaking moderate or vigorous intensity physical activity (MVPA) (i.e. 67 ± 61 min/day vs. 154 ± 96 min/day; $p = 0.001$) than a control group (6). With respect to average daily steps, when measured using a Dynaport activity monitor, 15 months after LT, 22 LT recipients (7 SLT, 15 BLT) undertook significantly less steps than a control group (i.e. 4,977 ± 2,332 steps vs. 8,645 ± 3,491 steps; $p = 0.000$) and also spent significantly less time walking (i.e. 55 ± 25 min/day vs. 81 ± 26 min/day; $p = 0.002$) and standing (i.e. 201 ± 76 min/day vs. 283 ± 99 min/day; $p = 0.004$) (6). Of note, both of these studies exploring PA did not differentiate results by transplant type, so it is difficult to determine with certainty changes in PA in BLT recipients alone. Measures of PA specifically in HLT recipients are not reported in the literature though case examples of recipients with an active lifestyle ten years after procedure are reported (109).

Participation in exercise training following LT has been show to benefit recipients in terms of ST and time spent participating in PA (see Table 2.1) (37). Specifically, compared with a control group that received only counselling to participate in PA after hospital discharge, LT recipients who undertook an additional three month rehabilitation program following hospital discharge spent significantly more time

undertaking MVPA one year after discharge (i.e. 98 ± 67 min/day vs. 58 ± 70 min/day; p = 0.047). This was consistent with data showing LT recipients also spent significantly more time walking on completion of the intervention period (i.e. 56 ± 24 min/day vs. 38 ± 23 min/day; p = 0.008). This improvement in walking time was maintained at one year following hospital discharge, with the intervention group spending more time walking when compared with the control group (i.e. 85 ± 27 min/day vs. 54 ± 30 min/day; p = 0.006). Differences in time walking between the intervention and control group are also reflected in average daily steps with the intervention group taking significantly more daily steps on completion of the intervention period (i.e. 5,194 ± 1,586 steps vs. 3,451 ± 2,175 steps; p = 0.004) and at 12 months after hospital discharge (i.e. 7,406 ± 2,574 steps vs. 4,462 ± 2,518 steps; p = 0.002). Notably, as most of the recipients had had a BLT i.e. 83% in the intervention group and 88% in the control group, this study provides useful comparison data for this current study. As outlined by Wickerson (110), it is important to recognise that more than 70% of LT recipients at the centre where this study was undertaken were excluded, with those included having had an uncomplicated post-operative course. Such inclusions and exclusions make extrapolating data to a fully representative population of LT recipients difficult and is reflective of the complex nature of LT.

One important factor to consider when interpreting measures of ST and PA is that there is a lack of consensus regarding the minimum numbers of days over which measures need to be sampled to obtain data that are considered representative of a 'typical' day. Matthews et al (111) studied healthy adults and found that three to four days with a minimum wear time of 12 hours was acceptable, but recommended at least seven days of monitoring to allow for day-by-day variation and reliability of measures of inactivity. Langer et al (12) recommend a wear time of four consecutive days of 12 hours or more. Other studies have used as little as two or three days of activity data (65, 112, 113) and McNamara et al (114) required data over at least three days together with ≥ 85% wear time in a study of people with COPD. Changes in PA following pulmonary rehabilitation are recommended to be measured for four weekdays, including only days with at least eight hours of wearing time during waking hours (115).

2.2.5 Summary

Lung transplant procedures result in significant improvements in lung function, exercise capacity and HRQL. Recipients also spend less time sedentary, spend more time participating in physical activities such as standing and walking and more

time undertaking MVPA. However, despite these improvements, LT recipients do not return to the same level of function as healthy people. Exercise training has been demonstrated to be beneficial in improving these measures of function.

2.3 Changes in peripheral muscles and their function following lung and heart-lung transplant

This part will describe the effect of LT and HLT on peripheral muscles, with a particular focus on QF. Specifically, the effect of LT on peripheral muscle strength, mass and endurance will be described. In addition a brief overview of the effect of exercise training and the potential causes of dysfunction of the peripheral muscles will be outlined.

2.3.1 Effect of lung and heart-lung transplant on peripheral muscle strength

Reduced peripheral muscle strength which is evident prior to LT (116-120) remains a feature following LT. Despite measuring at different time-points post-LT and the use of different methodologies, several studies have demonstrated reductions in QF strength in LT recipients (4-7, 13, 93). Values of QF force generated following LT have been compared with those derived from published prediction equations (5, 6, 93) or from a reference population (6, 7, 13) with LT recipients being able to generate approximately 60% of the torque predicted. Most studies used a robust dynamometer to measure QF strength, with only one study describing the use of a hand-held dynamometer (5), which has been shown to underestimate measures strength, particularly in QF (121). However, whilst using prediction equations or comparing to data collected in reference populations is likely to account for age and gender-related differences in muscle function, this method does not account for differences in assessment protocol such as the opportunity to practice, encouragement given or equipment used or differences in fat free mass (FFM) of the QF i.e. the size of the muscle. Only Mathur et al (13) considered the impact of the size of the QF on QF strength when comparing LT recipients to a group of people with COPD. The COPD group was chosen to assist in determining if changes in skeletal muscle are due to pre-transplant condition or factors related to post-transplant care. They found that LT recipients had greater impairments in skeletal muscle and concluded that both the size and strength of muscle were similarly reduced.

Regarding the time course of change in QF strength, in the first few weeks following LT, earlier work in 36 LT recipients (15 SLT, 21 BLT) demonstrated a reduction in

strength of 32 ± 21% from pre-transplant values, with QF strength measured using a Cybex Norm dynamometer (7). Even though rehabilitation resulted in improvement, QF force remained below pre-LT values at three months post-LT (7). A different study showed that one year post-LT, maximum QF force measured using a hand-held dynamometer was 67 ± 19% predicted, which was similar to that recorded in the same group pre-LT (i.e. 62 ± 19%) (5). Of note, wait time to LT was a predictor of QF strength post-LT, with those with a long wait time to LT having less QF strength than those with a short wait time (5).

It is not clear if impairments in muscle strength are evenly distributed following LT. Pinet et al (15) compared diaphragmatic, abdominal and QF strength between a group of 12 people with CF 48 months after LT (5 HLT, 7BLT) and a group of healthy controls matched for age, height and gender and demonstrated that, whilst the diaphragmatic and abdominal muscles had preserved strength, QF maximum torque was 33% lower in the LT recipients. This preservation of strength in the diaphragm and abdominal muscles and reductions in strength of QF was accompanied by preservation of muscle size in the diaphragm and abdominal muscles, measured by muscle thickness of the diaphragm and abdominals and a 31% reduction in QF cross-sectional area (see Section 2.3.2). Whilst QF strength remained correlated with cross-sectional area in both groups, the cross-sectional area of the QF per unit of lean body mass, as measured by bio-electrical impedance analysis, was 21% lower in the LT recipients. Studies exploring the strength of other peripheral muscles such as BB are not reported in the literature.

Participation in exercise training following LT appears to be of benefit in terms of muscle strength (see Table 2.1). Specifically, a recent pilot study has demonstrated that, when prescribed as part of inpatient rehabilitation commenced early after LT, resistance training resulted in a 22.5% increase in peak torque generated by QF (i.e.1.20 [95% CI: 0.99 to 1.41] Nm/kg prior to training vs. 1.46 [95% CI: 1.8 to 1.74] Nm/kg after training; $p < 0.05$) and that this improvement occurred similarly between groups who performed different numbers of repetitions (93). In addition, an earlier study that explored the effect of a seven or 14 week program of aerobic and resistance exercises in SLT and BLT recipients commenced after hospital discharge, an increase was demonstrated in the peak torque generated by QF of approximately 34 Nm (88). This is consistent with earlier work suggesting that thrice weekly exercise training started approximately one month after LT can improve QF strength from 51 ± 28% to 59 ± 26% of predicted values ($p < 0.05$) (7). Similarly, in 11 HLT recipients, QF maximum isokinetic torque improved significantly from 48 ±

16 Nm to 82 ± 18 Nm ($p < 0.001$) following an intensive inpatient exercise training program that included aerobic exercise, inspiratory muscle training and resistance exercises (4). Like QF, improvements in biceps femoris torques were also seen in these studies (4, 88). However, as these studies did not include a control group, it is not known if these improvements in muscle strength were a result of normal recovery after LT. One randomised controlled trial has been conducted in which the intervention group completed a program of aerobic exercise, QF resistance exercises and counselling to participate in exercise and a control group received only counselling. This study demonstrated greater gains in QF torque in the intervention group compared with the control group (i.e. on completion of training, QF torque expressed as a percent of predicted values was 17% greater in the intervention group [95% (CI), 9 to 25], which was maintained after one year) (37). What is not clear though is which components of the exercise training programs, that is aerobic exercises vs. resistance training were needed to produce these improvements in QF strength.

2.3.2 Effect of lung and heart-lung transplant on peripheral muscle mass

Smaller muscles, that is those with less muscle mass compared to healthy people, are a feature of disease groups that go on to have a LT. Specifically, when compared to matched healthy people, the cross-sectional area of the thigh muscles derived from computerised tomography (CT) scan or dual-energy X-ray absorptiometry (DEXA) scan is approximately 25 to 35% less in people with COPD (120, 122) and approximately 30% less in people with CF (116).

Following LT there are only a few studies that have examined the time course of change in FFM. Lung transplant recipients have been reported to show a decline in FFM initially following LT, measured using bio-electrical impedance analysis, but then these measures increase and are higher at one year post-procedure when compared with pre-LT values, though in men this difference did not reach statistical significance (i.e. in men 17.5 ± 2.0 kg/m^2 before LT vs. 18.3 ± 1.9 kg/m^2 one year after LT; in women 13.7 ± 2.0 kg/m^2 before LT vs. 15.3 ± 2.0 kg/m^2 one year after LT; $p < 0.05$) (123). Despite this improvement, values of FFM remain lower than that measured in a control group and after two years following LT one-third of recipients do not appear to have reached their age- and height-expected quantities of FFM (123). That is, compared with data collected in seven healthy controls, whole body FFM measured using bio-electrical impedance analysis in 12 LT recipients (9 BLT, 2 SLT and 1 HLT) three years post-LT was significantly less being 46 ± 6 kg vs. 56 ± 6 kg ($p = 0.005$) (14). The gains in FFM seen initially post-LT may decline thereafter

with one study showing that five years post-procedure, LT recipients had similar FFM to that seen in LT recipients (i.e. FFM index 17 ± 2.9 kg/m^2 in recipients vs. 15 ± 1.7 kg/m^2 in candidates) (108).

A disadvantage of using bio-electrical impedance analysis to measure FFM is that this technique provides only whole of body data, rather than data about specific muscle groups. In contrast, other methods such as CT scan, magnetic resonance imaging, ultrasound and DEXA allow for the assessment of both regional and whole body FFM. This is an important consideration since earlier work has suggested regional differences in the distribution of FFM. That is, SLT recipients have been shown on magnetic resonance imaging to have smaller thigh muscle volume than people with COPD (i.e. between group difference -84 cm^3 [95% CI, -594 to 427] in QF and -88 cm^3 [95% CI, -375 to 199] in the hip adductors) (13). Data obtained via CT scanning 12 LT recipients (7 BLT, 5 HLT) with CF showed a 31% reduction in mid-thigh cross-sectional area (median [range]) 48 [8 to 95] months after LT, but preserved diaphragm and abdominal muscles mass (15).

The impact of exercise training on muscle mass in LT recipients has not been explored, with much of the focus on improvements in muscle strength, which was described in section 2.3.1. However a 12 week program involving aerobic and resistance training in heart transplant recipients resulted in increased leg lean muscle mass (i.e. 0.78 kg [95% CI, 0.31 to 1.3] more than a group that did not undertake training) (124) suggesting that there may be benefit in exploring exercise training to improve muscle mass in LT recipients.

2.3.3 Effect of lung and heart-lung transplant on peripheral muscle endurance

Muscle endurance is the ability to sustain a specific task (25, 125) and is most often reported as the time to task failure. Following LT, endurance of QF has been demonstrated to be reduced. Specifically, an early study of nine LT recipients (7 SLT, 2 BLT) explored the endurance of the QF in LT recipients using a protocol that required participants to perform bilateral QF contractions from 90 degrees of flexion to full extension at 0.5Hz with a duty cycle of 0.5. The resistance applied to QF was increased by 0.4 kg at one minute intervals from zero to 2.8 kg. Time to task failure, defined as the inability to maintain either the 0.5Hz cadence or full leg extension for three consecutive efforts, was reached significantly earlier in the LT recipients, compared with a healthy control group (i.e. 5.4 ± 0.4 min vs. 7.8 ± 0.7 min; $p = 0.009$) (125). After adjusting for differences in age and lean body mass earlier task failure was found to be still evident in the LT group. This shorter time to task failure

was associated with a lower VO_{2max} and exaggerated acidosis in the QF. Likewise, Mathur et al (13) showed that a group of six SLT recipients tended to have lower QF endurance when compared to a group of six stable patients with COPD who were similar in terms of age gender and body mass index. Specifically, to assess endurance, the maximum torque of the QF (MT_{QF}) achieved during a maximal voluntary isometric contraction (MVIC) for each participant was determined using a dynamometer. The MT_{QF} was then used to determine a target torque in an endurance protocol in which participants performed a single sustained contraction at 80% of their MT_{QF} with task failure defined as the point where the torque generated fell to below 20% of the target force. Whilst the MT_{QF} generated was similar in both groups (i.e. 75 ± 27 Nm in the transplant group vs. 71 ± 18 Nm in the COPD group), the LT group tended to have lower endurance as evidenced by a shorter time to task failure (i.e. between-group difference -13 s [95% CI, -29 to 2]). However it is important to note that this study lacked power to detect this difference as it had small participant numbers. Further these data were collected in SLT recipients and further work is needed to explore differences in QF endurance in BLT and HLT recipients.

Performance of muscle endurance tasks involve “a complex interplay between the availability and extraction of oxygen and the incorporation of substrate into mitochondria. Adequate muscle oxygen supply is determined by cardiac output, local muscle perfusion, and blood oxygen content. In turn, muscle capillarity, mitochondrial density, and muscle enzyme concentration influence oxygen extraction” (25). The studies conducted by Evans et al (125) and Mathur et al (13) are just two examples of the variety of methods undertaken to measure muscle endurance. However, whilst the protocols used in these two studies measure muscle endurance, they do not quantify the rate of muscle fatigue that occurred, with fatigue defined as “an exercise-induced reduction in the ability of muscle to produce force or power, whether or not the task can be sustained” (126). Muscle fatigue develops gradually soon after the onset of sustained PA resulting in a decrease in the force or power that a muscle can generate and may be caused by central and/or peripheral mechanisms (127). The rate of muscle fatigue has been shown to be a function of the force-time product. That is, when undertaking repeated submaximal QF contractions interspersed with maximal contractions, the rate of decline in maximum force measured will be faster when the contractions are performed at higher torques and/or performed at higher frequencies. However, it has been shown that where the force-time product is the same, endurance time varies.

For example, contracting at 70%MT_{QF} for 3 s followed by a 7 s rest and contraction at 30%MT_{QF} for 7 s followed by a 3 s rest results in the same force-time product. However, despite the same force-time product, the time to task failure was faster when the contractions were performed at the higher of the two target torques (i.e. 7.9 minutes and 15.4 minutes, respectively) (128).

As shown in the study by Dolmage et al (128), a common protocol used to quantify the development of muscle fatigue is to interrupt fatiguing exercise with brief maximal contractions and assess the rate of decline in peak torque generated during these contractions. These maximal contractions may be performed voluntarily or by superimposing a twitch force by stimulating the femoral nerve using electrical stimulation (129) or more comfortable magnetic stimulation (130). Stimulating the femoral nerve during a MVIC (i.e. twitch interpolation) is a useful way to explore muscle fatigue as it allows the fatigue that occurs to be differentiated into central or peripheral components. Central fatigue refers to the decrease in muscle force being attributable to a decline in motoneuronal output (131). When central fatigue occurs, twitch interpolation results in extra force being evoked, indicating that fatigue results from processes proximal to the site of motor axon stimulation (132). Peripheral fatigue refers to the decrease in muscle force being attributable to a process within the muscle itself, occurring at or distal to the neuromuscular junction (133). When peripheral fatigue occurs twitch interpolation does not result in any extra muscle being evoked, indicating that fatigue results distal to the site of motor axon stimulation. Twitch interpolation using magnetic stimulation has been used to measure changes in QF strength in LT recipients (14), but as yet has not been reported as being used to measure fatigue during assessment of QF endurance. One earlier study did explore fatigue of the tibialis anterior muscle using electrically induced tetanic contractions in a group of six LT recipients and compared findings with a control group (134). This study found that the tetanic contractions resulted in a progressive decline in contraction force in both groups. However the rate and magnitude of the decline did not differ between groups, even though the initial torques generated by the LT group were 39% lower than the forces generated in the control group.

The scarcity of studies that have used stimulation to explore fatigue, particularly in LT recipients, is likely to reflect barriers such as: (i) the pain associated with electrical stimulation and (ii) the need for expensive equipment to perform magnetic stimulation.

In addition to measures such as time to task failure and rates of fatigue with voluntary or stimulated muscle contraction, muscle fatigue can be explored by examining changes in neural activation derived from electromyography (EMG) i.e. overall number of signals, firing fate and synchronisation of the active motor units (135-137).

Few studies have explored QF endurance in LT recipients and those that have done so have relied on only one measurement of endurance. Further, no study has reported both effort-dependent and effort-independent measures associated with QF endurance in this patient population nor the effect of exercise training on QF endurance.

2.3.4 Causes of muscle dysfunction in lung and heart-lung transplant

As previously discussed (see Section 2.3.1, 2.3.2 and 2.3.3) it is well established that LT recipients have evidence of peripheral muscle dysfunction prior to their transplant. However, as the study described in this Masters of Philosophy thesis only reports on measures of muscle function that were collected following LT, the scope of this next section has been limited to a brief description of the main factors that occur during the post-LT period, that are likely to contribute to muscle dysfunction.

2.3.4.1 Physical inactivity

One factor that has been postulated to contribute to peripheral muscle dysfunction following LT is their ongoing reduced participation in MVPA (see Section 2.2.4). Work in populations known to experience marked reduction in PA, and even weightlessness (e.g. space medicine and studies of limb immobilisation), have shown that inactivity produces a number of unfavourable skeletal muscle changes. These changes include a loss of muscle mass, reduced oxidative (mitochondrial) enzyme activity and loss in the cross-sectional area of muscle fibre types (19). The reduction in Type 1 fibres appears to be greater than seen in other fibres types, both in studies that have explored the effects of limb immobilisation and following a period of detraining in athletes (20, 21). Using magnetic resonance imaging, a study of the effect of 17 weeks of bed rest in healthy males demonstrated a significant loss of total body lean tissue of (mean ± SD) 3.9 ± 2.1 kg; $p < 0.05$) with the loss of muscle volume being greater in the lower limbs relative to the back muscles. Specifically, a 16 to 18% reduction in the volume of QF was measured compared to a 9% reduction in the intrinsic lower back muscles (138). This loss in muscle volume in QF was accompanied by a rapid reduction in slow-speed isokinetic muscle

strength (i.e. measured at 60^0/s). Specifically, after only one week of bed rest slow-speed isokinetic torque of QF was reduced by 14.7 ± 6.3 Nm/s (p = 0.003). At the same time-point slow-speed isokinetic torque of BB was not significantly reduced (i.e. -2.6 ± 14.6 Nm/s; p = 0.769). After 16 weeks of bed rest, QF slow-speed isokinetic torque was demonstrated to continue to decline whilst BB remained unaffected (i.e. -30.7 ± 7.3 Nm/s [p = 0.0001] in QF compared to -2.5 ± 14.0 Nm/s; p = 0.612] in BB). This difference between lower and upper limbs is likely due to the lack of use of lower limbs during bed rest whilst the upper limbs are able to still be used for usual activity. Interestingly, the decline in QF isokinetic torque when tested at higher speeds (i.e. 120 or 180^o/s) did not occur until after nine weeks (i.e. -6.2 ± 8.6 Nm/s [p = 0.134] after one week compared to -17.0 ± 9.4 Nm/s [p = 0.002] after nine weeks). Performance of QF resistance exercises performed every third day (i.e. supine squats) during a period of bed rest has been demonstrated to reduce the impact of bed rest on both QF volume and QF strength (139, 140).

Although there are few data that have explored the changes in the histology and biochemistry of the peripheral muscle in LT recipients, data collected via biopsy of vastus lateralis of seven LT recipients demonstrated a lower quantity of Type 1 fibres when compared to seven healthy people of similar age and gender (141). Similarly, this study demonstrated lower activity of mitochondrial enzymes, such as citrate synthase and 3-hydroxyacyl-CoA-dehydrogenase, without noting differences in the activities of anaerobic enzymes. These changes, which are suggestive of peripheral muscle deconditioning resulting at least in part from reduced participation in PA, will reduce the oxidative capacity of the muscles and produce metabolic changes which result in the early accumulation of lactate during activity and muscle fatigue.

2.3.4.2 Medication use

In the period following LT, recipients are required to take a large number of medications, many of which may negatively impact peripheral muscle function.

Corticosteroid medication used both before and after LT is well recognised as a medication that contributes to impairment in muscle function (1, 142, 143). In a group of 12 LT recipients (7 BLT, 5 HLT), the dose of corticosteroids, specifically methylprednisolone, has been demonstrated to be an independent predictor of reduction in the size of QF ($R^2 = 0.83$; p = 0.002) (15). This suggests that periods during which this medication use is increased, such as during episodes of acute rejection, may be particularly detrimental to the size of QF, and in turn QF strength.

Glucocorticoids, a subgroup of corticosteroids, cause a reduction in muscle protein synthesis and enhanced proteolysis through increased myostatin levels and reduced insulin-like growth factor-1 levels (29). The effect of these medications in reducing lean muscle mass is also reported in other groups such as renal transplant (123, 144).

Immunosuppressive agents that are used following LT, such as cyclosporine, are also recognised as factors that may contribute to impairment in muscle function (145). In six LT recipients, cyclosporine induced mitochondrial myopathy was proposed as the potential cause of low peripheral muscle oxygen uptake in the vastus lateralis muscle during a cardiopulmonary cycle exercise test (26). Cyclosporine inhibits release of calcineurin and has been found in animal studies to cause muscle atrophy with a reduction in overall muscle size and cross-sectional fibre area (27). Case reports of tacrolimus, also a calcineurin inhibitor, causing inflammatory myopathy ten months following renal transplant (146) and two years after liver transplant (147) are cited in the literature, though this rare side effect has not been reported in LT recipients.

2.3.4.3 Other

Although a feature of many of the conditions that may progress to LT, it is currently unknown whether systemic inflammation plays a role in peripheral muscle dysfunction following LT.

Muscle biopsy of vastus lateralis in eight LT recipients (2 SLT, 4 BLT, 2 HLT) taken within seven days of performing an incremental exercise test demonstrated subnormal muscle calcium regulation and impaired potassium regulation, when compared to a group of healthy controls (28). These impairments were identified as contributing to poor muscle performance.

2.3.5 Summary

Peripheral muscle dysfunction is proposed as an important contributor to the ongoing impairments in function in LT recipients. The function and size of the peripheral muscles, specifically QF, has been explored by a number of studies with the muscles shown to be smaller and to have impaired strength. A small number of studies having explored endurance of this muscle. It is not yet known if impairment is greater in skeletal muscle strength or endurance in this population or what relationships exist between these muscle strength and endurance with measures of function such as exercise capacity, ST or time spent undertaking different levels of intensity of PA.

CHAPTER 3 METHODS

This chapter describes the methodology used for the study undertaken for this Masters of Philosophy degree. Study design and approvals from the relevant Human Research Ethics Committees are described along with inclusion and exclusion criteria and the strategies used to recruit participants. Details pertaining to the collection of variables used to describe the characteristics of the two groups are described, such as demographic and anthropometric data, spirometric lung function and health-related quality of life (HRQL). Thereafter, methods used to measure quadriceps femoris (QF) and biceps brachii (BB) strength, QF endurance, body composition, exercise capacity, sedentary time (ST) and physical activity (PA) are described.

3.1. Study design

The study was cross-sectional and observational in design. Data collection took place between May 2011 and October 2013 at Royal Perth Hospital (RPH) and Curtin University. Data were collected on two sessions, nine to 14 days apart, and each session was approximately 2.5 hours in duration (see Figure 3.1). The assessment protocol and description of measurements are outlined in Sections 3.4 and 3.5.

3.2 Approval from Human Research Ethics Committees

Prior to commencement of data collection, approval was sought and granted by the Human Research Ethics Committee at RPH (EC2009/120) with reciprocal approval from the Human Research Ethics Committee at Curtin University (HR 57/2010).

3.3 Participant recruitment

Two groups of participants were recruited. These groups were labelled as the transplant group (TG) and the control group (CG).

Recruitment to the TG was undertaken at the Advanced Lung Disease clinic at RPH. That is, lung transplant (LT) recipients who met the inclusion criteria were given written information about the study by clinic staff during their routine appointments for post-transplant review. Participants in the CG were recruited via posters at RPH and Curtin University and via word of mouth.

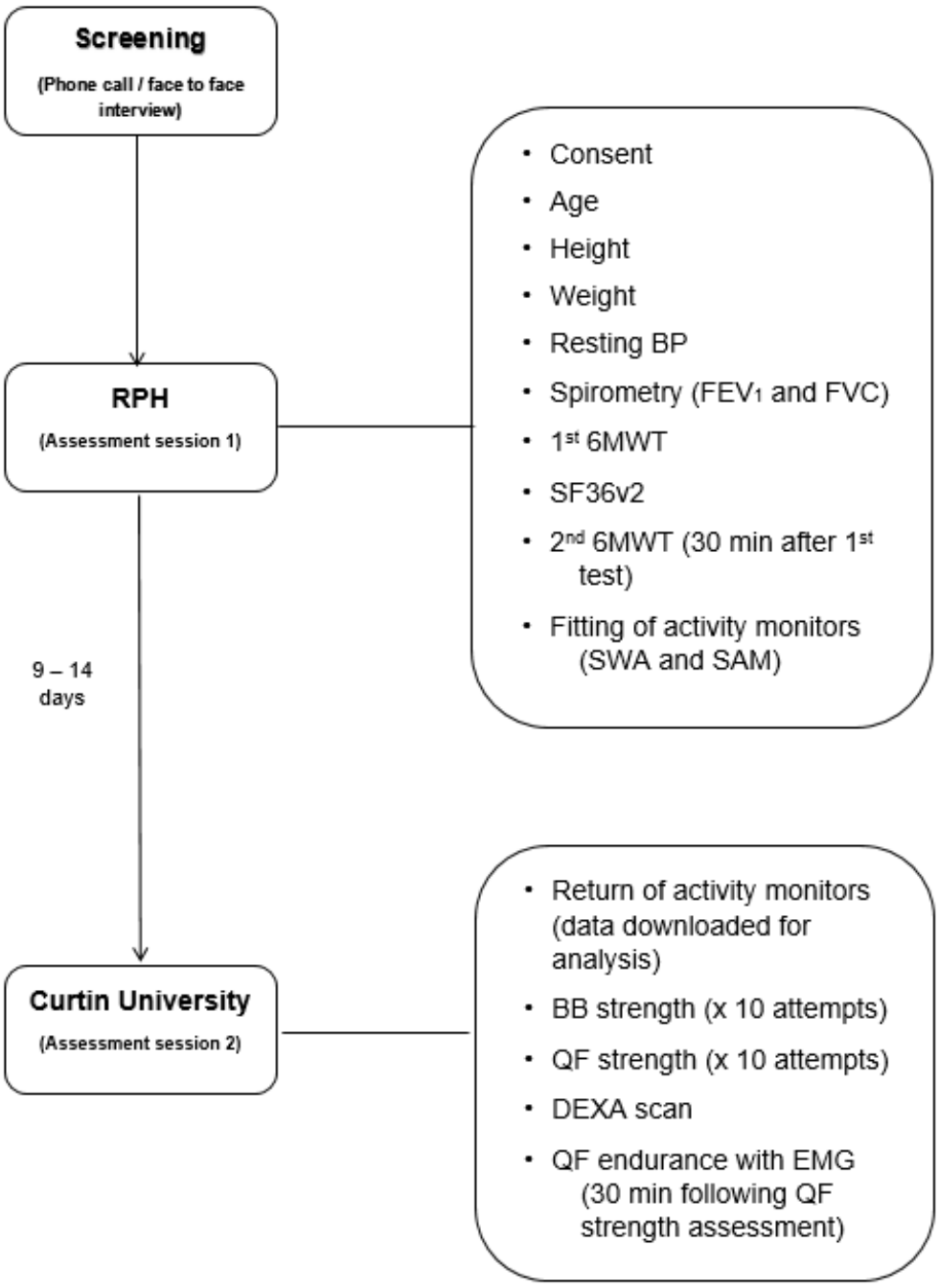


Figure 3.1 Study protocol.

Definition of abbreviations: biceps brachii (BB); blood pressure (BP); dual-energy X-ray absorptiometry (DEXA); EMG (electromyography); FEV_1 (forced expiratory volume in one second); FVC (force vital capacity); quadriceps femoris (QF); Quality Metric Incorporated Short Form 36 version 2 (SF36v2); Royal Perth Hospital (RPH); SAM (StepWatch™ Activity Monitor); six-minute walk test (6MWT); SWA (SenseWear Pro 3 Armband).

Potential participants in either the TG or CG, who expressed an interest in participating in the study, were asked to contact the candidate for more information. During the initial conversation with each potential participant, the candidate administered a screening questionnaire to ascertain whether or not the person met the study criteria. This screening questionnaire sought information regarding age, weight, smoking history, pre-existing medical conditions including current medication use, mobility restrictions, history of recent upper respiratory tract infection or illness, current pregnancy and existence of any metal implants (see Appendix 1). This initial conversation was also used to determine the persons' capacity to understand English.

Those participants who met the study criteria and agreed to participate were invited to attend two assessment sessions. At the beginning of the first assessment session, written informed consent was obtained (see Appendix 2).

In order to attempt and balance the two groups in terms of age and gender (i.e. factors known to influence muscle strength) (148) recruitment of participants to the TG was commenced first. Once the age and gender of the TG were known (n = 10; 43 [20] yr; 5 females), recruitment of participants to the CG was initiated with participant characteristics balanced between the TG and CG for age and gender.

3.3.1 Transplant group: inclusion, exclusion criteria and brief rationale for these criteria

3.3.1.1 Inclusion criteria

Participants were eligible for inclusion to the TG if they were; (i) aged 18 years or over, (ii) had undergone a bilateral lung transplant (BLT) or heart-lung transplant (HLT) at RPH and (iii) were at least six months post-transplant.

3.3.1.2 Rationale for inclusion criteria

Regarding the age criterion, participants were excluded if they were under 18 years to avoid issues of assent vs. consent in minors, which is a concern for approvals from the Human Research Ethics Committee at RPH. This criterion did not result in any potential participant being excluded from the study as the RPH transplant program is for adults and people under the age of 18 years are very rarely transplanted at this centre.

The other two criteria (i.e. had undergone a BLT or HLT at RPH and were at least six months post-transplant) related predominantly to ensuring that the TG were characterised by minimal, if any, impairment in spirometric measures of lung

function (see Section 3.5.1.1). Earlier work has shown that, almost three years following single lung transplant (SLT) there was persistent impairment in spirometric measures of lung function with forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) being 50% and 65% of that predicted in a healthy population, respectively (17, 79). In contrast, over the same time period following BLT, minimal impairment in spirometric measures of lung function has been reported, with FEV_1 and FVC being 80% and 90% of that predicted in a healthy population, respectively (17). Additionally, in contrast to SLT, the improvements in FEV_1 and FVC seen following BLT show minimal decline over the first five years post-transplant (17). Therefore, to optimise the likelihood that participants in the TG were not characterised by impairment in spirometric measures of lung function, recruitment to this study excluded those who had undergone SLT. The six month time point for inclusion to the study is also supported by data showing that at six months following transplant, spirometric measures of lung function are nearing maximal post-transplant values (79). It ensured that those in the TG had completed their post-transplant rehabilitation at RPH.

3.3.1.3 Exclusion criteria

Exclusion criteria applied to the TG comprised; (i) inability to understand English, (ii) impaired lung function, defined as a FEV_1 to FVC ratio of ≥ 0.7 (149) (or for people > 60 yr a FEV_1 to FVC ratio between 0.65 and 0.7 (150)) or evidence of bronchiolitis obliterans syndrome, (iii) clinically unstable defined as any reports of feeling unwell or periods of organ rejection requiring an increase in immunosuppressant medications in the previous 30 days, a resting heart rate of > 100 bpm and/or a resting blood pressure of > 150/100 mmHg, (iv) a history of a musculoskeletal, neurological or other condition that precluded them from participating in exercise testing and (v) any factor which limited their capacity to undergo a dual-energy X-ray absorptiometry (DEXA) scan such as current pregnancy, weight > 120 kg, presence of metal implants other than sternal wires or radiological examinations using contrast media in the previous seven days.

3.3.1.4 Rationale for exclusion criteria

Potential participants who were unable to understand English were excluded as the assessment of QF endurance required adherence to instructions in real-time which was unlikely to be achieved, even with use of an interpreter.

Participants were excluded if they had impaired lung function, as this study required those in the TG to be characterised by minimal, if any, impairment in spirometric measures.

Exclusion criteria related to clinical instability and conditions that compromised the capacity to perform optimally during exercise testing or represented contraindications to DEXA scans to ensure that participants were able to complete all assessments related to participation in this study.

3.3.2 Control group: inclusion, exclusion criteria and brief rationale for these criteria

3.3.2.1 Inclusion criteria

Participants were eligible for inclusion to the CG if they were aged between 18 and 70 years.

3.3.2.2 Exclusion criteria

Exclusion criteria applied to the TG were also applied to the CG. Specifically, these comprised; (i) inability to understand English, (ii) impaired lung function, defined as a FEV_1 to FVC ratio of ≥ 0.7 (149) (or for people > 60 yr a FEV_1 to FVC ratio between 0.65 and 0.7 (150)), (iii) clinically unstable defined as any reports of feeling unwell in the previous 30 days, a resting heart rate of > 100 bpm and/or a resting blood pressure of > 150/100 mmHg, (iv) a history of a musculoskeletal, neurological or other condition that precluded them from participating in exercise testing and (v) any factor which limited their capacity to undergo a DEXA scan such as current pregnancy, weight > 120 kg, presence of metal implants other than sternal wires or radiological examinations using contrast media in the previous seven days.

One additional exclusion criteria applied to the CG was a current use of inhaled or oral corticosteroid medication.

3.3.2.3 Rationale for the exclusion criteria

The rationale for exclusion criteria applied to the CG is consistent with those described earlier in section 3.3.1.4. Participants who were currently taking inhaled or oral corticosteroid medication were excluded as a result of the recognised deleterious effect of corticosteroid medications on muscle strength (143). This ensured that measures of muscle strength in the CG were not compromised by the use of these medications.

3.4 Assessment protocol

For both assessment sessions, participants were instructed to wear clothing suitable for exercise testing as well as to abstain from exercise on the day of assessment and to avoid consuming caffeine or a heavy meal for at least two hours prior to the session. For the second assessment session, an additional instruction was given to avoid stair climbing on the day of assessment (see Appendix 3).

The first assessment session was conducted at RPH. During this session, demographic, anthropometric and spirometric data were collected. Thereafter, measurements were made of six-minute walk distance (6MWD) and HRQL. At the end of this assessment session, participants were fitted with two PA monitors. They were instructed to wear both monitors during the waking hours for eight consecutive days, only removing them for activities conducted in water (e.g. showering, swimming).

The second assessment session was conducted at Curtin University. At the beginning of this session, participants returned the PA monitors. Thereafter, measures were made of QF strength, QF endurance, BB strength and body composition. Participants were required to rest for a minimum of one hour between the assessments of QF strength and endurance.

3.5 Measurements

3.5.1 Participant characteristics

For participants in both the TG and the CG, age and gender were recorded. Measures were collected of height (m) and weight (kg) using a stadiometer and calibrated scales (AND, Model: UC321), respectively. Spirometric measures of lung function, HRQL and body composition were also collected (see Sections 3.5.1.1, 3.5.1.2 and 3.5.1.3, respectively for more detail). For participants in the TG, information was recorded pertaining to the reason for transplantation, type of surgery, length of stay in intensive care after surgery, length of stay in hospital after surgery and months since surgery.

3.5.1.1 Spirometric measures of lung function

Spirometric measures of lung function were collected using a standardised protocol (151) with a calibrated portable spirometer (Microlab Viasys® Healthcare, CA, USA). Participants were seated, wearing a nose clip and asked to perform a minimum of three forced expiratory manoeuvres from total lung capacity to residual volume.

Forced expiratory manoeuvres in which the participant failed to maximally inhale prior to the test, failed to achieve a blast of exhalation or did not continue with a forced exhalation to the end of the test, were excluded and the test was repeated. The greatest FEV_1 and FVC achieved across the three forced expiratory manoeuvres were recorded as the test result. Data were expressed in litres and as a percentage of the value predicted in a healthy individual using reference values derived from NHANES III data (152).

3.5.1.2 Health-related quality of life

Health-related quality of life was measured using the Quality Metric Incorporated Short Form 36 version 2 (SF36v2). The SF36v2 is a health status measure comprising 36 items which are organised into eight domains i.e. physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. For each domain, scores range from 0 to 100 and higher scores indicate better HRQL. The physical functioning, role physical, bodily pain and general health domains are combined to give an overall summary score of physical health i.e. physical health summary score, and the vitality, social functioning, role emotional and mental health domains are combined to give a summary score of mental health i.e. mental health summary score (153). Participants self-completed a written version of the questionnaire. Data were taken from written responses and entered into the proprietary software to calculate results for each domain and the summary scores. The SF36v2 has been used widely to measure HRQL in the LT population (34, 37, 53, 91, 92, 101).

3.5.1.3 Body composition

Body composition was measured via whole body DEXA scan using a GE Medical Systems Lunar Prodigy scanner (GE Healthcare Ltd, WI, USA). Prior to every data collection session, output from the DEXA scanner was calibrated, according to the manufacturer's protocol.

Participants were assessed in supine, with their legs together and arms by their side with forearms pronated. Reports were generated from the DEXA software for total lean body mass (kg), total fat mass (kg), bone mineral content (kg), lean lower limb mass (kg) and lean upper limb mass (kg).

3.5.2 Muscle strength and endurance

Muscle strength (QF and BB) and endurance (QF only) were assessed using standardised protocols via the HUMAC Norm (HUMAC Norm CSMi 2009, Stoughton, MA, USA). This device is a mechanical dynamometer that records

torque values that range between 0.1 Nm and 678 Nm. Testing for both QF and BB was performed on the side of hand dominance, defined as the hand that the participant used for writing. Biceps brachii was chosen as a comparison muscle to QF as; (i) it is a large proximal muscle that works against gravity, (ii) it is comprised of a similar proportion of Type I and Type II muscle fibres as QF (32), (iii) it is used in many activities of daily living and (iv) its strength can be measured using the same equipment and approach as QF.

The measurement of QF strength and endurance was separated by a minimum of one hour.

The HUMAC Norm was chosen over a hand-held dynamometer as the latter has been shown to underestimate measures of QF torque (121).

In order to obtain measures of physiological activity of the QF during the endurance protocol, electromyography (EMG) of the vastus medialis and vastus lateralis muscles was undertaken (see Section 3.5.2.7 for more detail).

3.5.2.1 Calibration procedures

Prior to every data collection session, output from the HUMAC Norm was calibrated. To do this, known weights of 0 kg, 25 kg and 50 kg were applied to the HUMAC Norm lever arm whilst it was in the horizontal position. Torque measured by the HUMAC Norm were compared with the HUMAC Norm expected values (see Appendix 4). In the event of any disparity between expected and measured results, the configuration of the HUMAC Norm was reviewed and errors corrected where necessary. Calibration procedures were then repeated until the expected and measured results were consistent and the HUMAC Norm software confirmed that the devices internal calibration process had been successful.

Measures of muscle torque obtained using the HUMAC Norm were recorded on a custom-written LabVIEW program (LabVIEW SP12014, National Instruments Corp, Austin TX, USA) using a sampling frequency of 1,000 Hz. In addition to the process used to calibrate the output from the HUMAC Norm software, agreement was also ensured between measures of torque displayed on the HUMAC Norm and those recorded by the LabVIEW system. That is, the torque generated using three known weights (0 kg, 25 kg and 50 kg) were compared between the HUMAC Norm and LabVIEW system. Where necessary, the configuration of the HUMAC Norm and LabVIEW were reviewed until 100% agreement was obtained in the measures of torque.

3.5.2.2 Starting position for participants

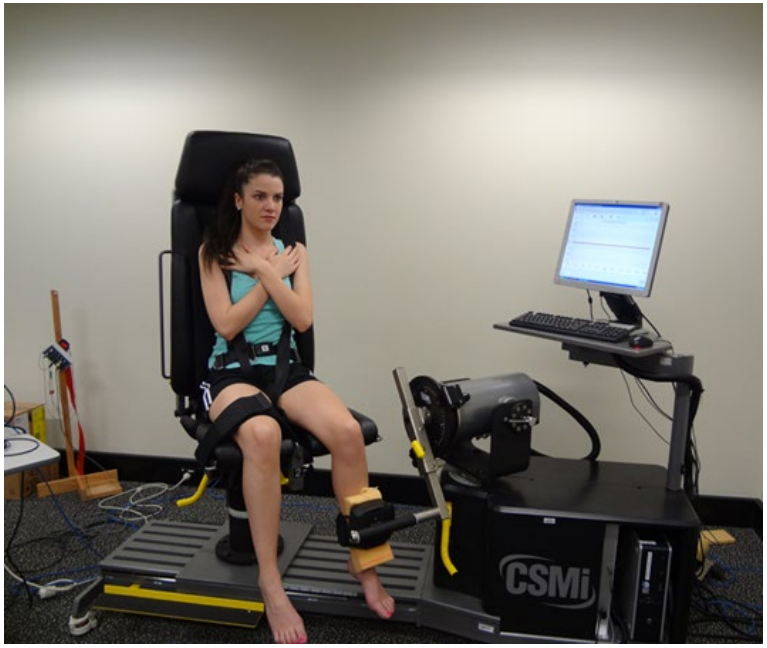
Participants were seated in an upright position, with their back supported on the HUMAC Norm chair. A harness was used to stabilise the trunk. The position of the chair and the dynamometer was then adjusted according to the muscle group to be tested and to suit each participant's body shape and size.

Specifically, to standardise measures of QF strength and endurance, the participants' knee was placed in 60 degrees of flexion. This position has been used in a range of studies using a computerised dynamometer (6, 7, 12, 34, 37, 64, 119, 154, 155) and has been shown to result in the maximum torque for this muscle group (156). The axis of the HUMAC Norm lever arm was aligned with the lateral epicondyle of the knee and the pressure pad on the lever arm was placed 2 cm proximal to the ankle. Padding was placed over the tibia for the participant's comfort (see Figure 3.2 [i]).

For measures of BB strength, the participants' shoulder of their dominant arm was placed in the neutral position, the elbow flexed to 90 degrees and the forearm supinated. A starting position of 90 degrees of elbow flexion was chosen as previous studies have used this position (154) and it has been shown that maximum torque is generated at this angle (157). The axis of the HUMAC Norm lever arm was aligned with the elbow joint (lateral epicondyle) and the pressure pad of the lever arm was placed 2 cm proximal to the wrist. Padding was placed on the anterior aspect of the wrist to optimise participant comfort (see Figure 3.2 [ii]).

Once the participant was in the correct position, both the chair and dynamometer were locked into position.

(i)



(ii)

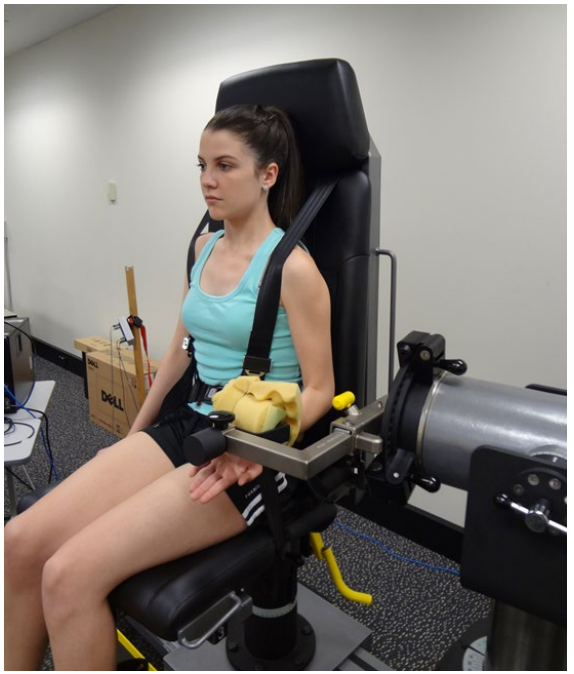


Figure 3.2 Starting position and equipment used to assess the strength of (i) quadriceps femoris and (ii) biceps brachii.

3.5.2.3 Protocol used to measure the strength of quadriceps femoris and biceps brachii

Prior to data collection, the torque required to hold the weight of the limb against gravity was measured. That is, immediately prior to measuring QF strength, with the knee at 60 degrees of flexion, the ankle was suspended from the lever arm using the HUMAC Norm ankle strap, the participant was instructed to relax and the torque measured by the HUMAC Norm was recorded. Similarly, immediately prior to measuring BB strength, the forearm with the elbow in 90 degrees of flexion was placed on top of the pressure pad, the participant was instructed to relax and the torque measured by the HUMAC Norm was recorded. For both muscle groups, the (158) torques required to hold the weight of the limb against gravity were used in the calculation of maximum torques (see Section 3.5.2.4).

Prior to measuring the strength of the QF and BB, each participant was given the opportunity to warm up. That is, they were instructed to perform five isometric contractions at approximately 50% of their perceived maximum effort. Each contraction was sustained for three to five seconds. Thereafter, measures were made of the maximum torque generated during ten maximal voluntary isometric contractions (MVICs). Maximal voluntary isometric contractions were chosen as other measures of muscle strength such as isokinetic tests are impacted by the velocity of contraction performed, with higher velocity contractions having been shown to elicit lower peak torques than isometric contractions (158). Additionally, one test of muscle strength testing allowed for determination of QF and BB strength without significant burden being placed on participants. Each participant was instructed to extend their knee (for QF) or to flex their elbow (for BB) against the HUMAC Norm lever arm and to generate as much torque as possible. During each contraction, the candidate provided standardised, strong encouragement to optimise effort and participants received real-time visual feedback of the torque generated on the HUMAC Norm screen (see Figure 3.3). A minimum of 30 seconds rest was provided between contractions. On completion of ten MVICs for each muscle group, participants rated their perception of limb tiredness of QF ($tiredness_{QF}$) and of BB ($tiredness_{BB}$) using the 0 to 10 point Borg scale (159). Participants were also asked to rate their overall perceived exertion (RPE) using the 6 to 20 point RPE scale (159) at the end of the ten MVICs and this was recorded as RPE_{QF} and RPE_{BB}, respectively.

Figure 3.3 HUMAC Norm screen viewed by participant during three to five second maximal voluntary isometric contraction during the strength test.

Data are torque (Nm) on the y-axis plotted against time (s) on the x-axis. The vertical line (depicted by A), indicates the bar that moves across the screen as the participant generates torque. The curved line (depicted by B) indicates the torque generated by the participant that was observed in real-time during a contraction.

3.5.2.4 Definition of maximum torque

Data pertaining to the torque generated by QF and BB during each MVIC were exported from LabVIEW to Excel 2010^{TM} (Microsoft, WA, USA). For each MVIC, torque data were sorted and the single greatest torque generated during each contraction were extracted. Maximum torque of the QF (MT_{QF}) was defined as the average of the three greatest torques generated during the MVICs of the QF (see Figure 3.4), which was then added to the torque required to hold the leg against gravity (see Section 3.5.2.3). Likewise, maximum torque of the BB (MT_{BB}) was defined as the average of the three greatest torques generated during the MVICs of the BB, which was then added to the torque required to hold the forearm against gravity (see Section 3.5.2.3).

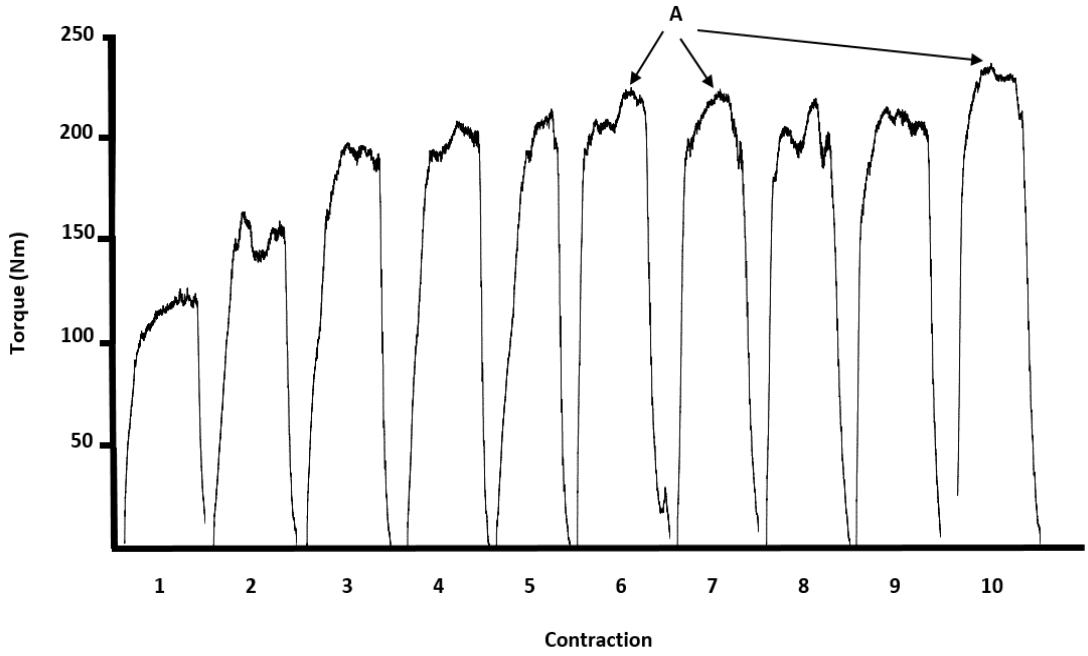


Figure 3.4 Schematic of ten contractions produced during assessment of maximum torque of quadriceps femoris for one participant.

Data are torque (Nm) on the y-axis plotted against ten repetitions of three to five second maximal voluntary isometric contractions (MVICs) on the x-axis. The single greatest torque generated during each MVIC were extracted. Thereafter, the maximum torque of quadriceps femoris (MT_{QF}) was calculated as the average of the three greatest torques (depicted by A), summed together with the torque required to hold the leg against gravity.

3.5.2.5 Protocol used to measure the endurance of quadriceps femoris

The starting position for the assessment of QF endurance was the same as that outlined in Section 3.5.1.2. Prior to commencing the assessment of QF endurance, surface EMG electrodes were applied (see Section 3.5.2.6). The protocol used to assess QF endurance was adapted from that described by Bigland-Ritchie et al (129, 160) and involved a series of work periods (six seconds duration), interspersed with rest periods (four seconds duration), which resulted in a contraction duty cycle of 0.6. Throughout each of the work periods, participants were instructed to contract their QF to meet or exceed a target equivalent to 60% of the previously measured maximum torque of the QF (60%MT_{QF}). This target torque was visible to the participant on the HUMAC Norm screen (see Figure 3.5). All participants were strongly encouraged to continue with this protocol until they were unable to reach their target of 60%MTQF over three consecutive work periods (see Section 3.5.2.7 for definition of task failure). In addition to defining QF endurance as the time to task failure, QF endurance was also quantified as the rate of decline in MT_{QF} during the protocol (see Section 3.5.2.7). To collect these measures, during the first work period at the start of each minute, participants were instructed to contract their QF for the first three seconds at 60%MT_{QF} and then, for the next three seconds, to contract their QF maximally i.e. perform a MVIC. Data generated during the MVICs performed at the start of each minute during the assessment of QF endurance were labelled MT_{QF_end}.

Figure 3.6 shows the torque generated by the QF during the endurance protocol for a representative participant. On completion of the protocol, participants were asked to rate their perception of lower limb muscle tiredness on the 0 to 10 point Borg scale (159) and to rate their perceived overall exertion 6 to 20 point RPE scale (159).

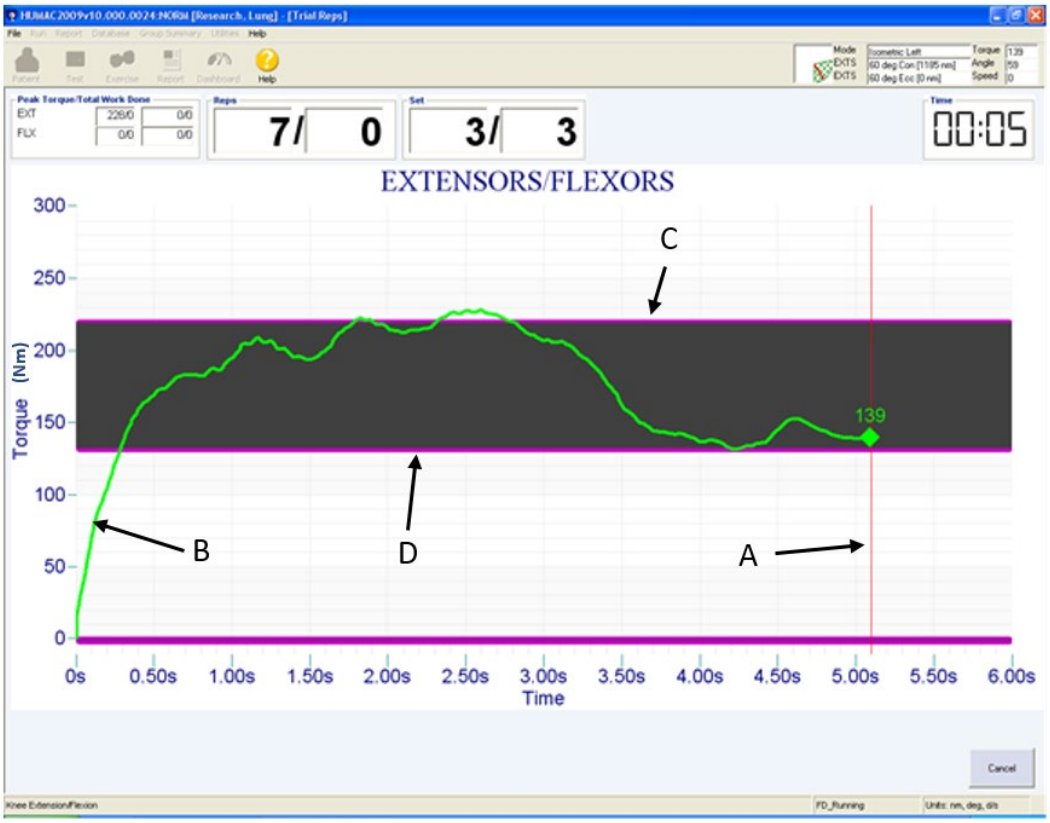


Figure 3.5 HUMAC Norm screen viewed by participants during the six second work intervals of the endurance test.

Data are torque (Nm) on the y-axis plotted against time (s) on the x-axis. The vertical line (depicted by A), indicates the bar that moved across the screen as the participant generated torque. The curved line (depicted by B) indicates the torque generated by the participant seen in real-time during a contraction. The horizontal line (depicted by C) shows the target torque for the MVIC determined during QF strength testing. The horizontal line (depicted by D) shows the target torque to be attained during each six second work period of the endurance protocol i.e. 60%MT_{QF}.

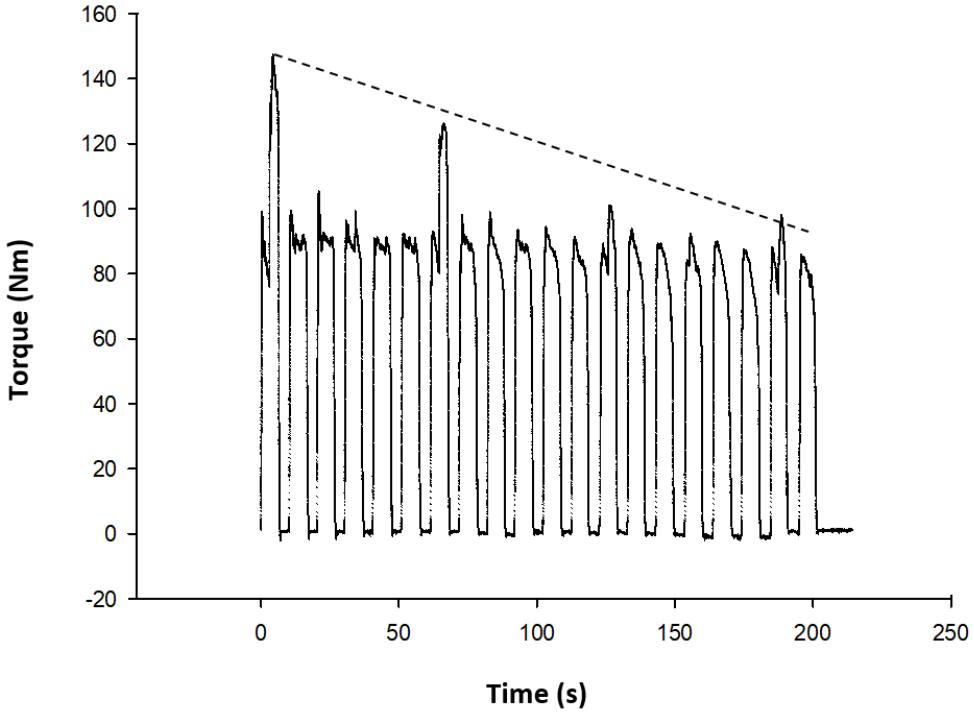


Figure 3.6 Torque generated for each contraction during quadriceps femoris endurance protocol by a participant.

Data are torque (Nm) on the y-axis plotted against time (s) on the x-axis. The dashed line shows the rate of decline of MT_{QF_end}.

3.5.2.6 Electromyography

Muscle activity was assessed using surface EMG and recorded via bipolar surface electrodes where the signals were single differential amplified (Common mode rejection 115 dB at 60 Hz; bandwidth filter 10 to 1000 Hz; Bortec AMT-8, Bortec [GA1] Biomedical Ltd, Calgary, Alberta Canada). The configuration is shown in Figure 3.7. These signals were then transferred to hard drive at 1 kHz using a 32 bit A-D card.

Skin preparation prior to the application of the surface electrodes was done according to standard protocols with the goal of reducing impedance. Specifically, each electrode site was prepared by shaving to remove hair, light skin abrasion with an abrasive cloth and cleaned using alcohol wipes. Once dry, electrodes (Ag/AgCl, 3M™ Red Dot™, Germany) were placed with a centre to centre distance of 25 mm on the vastus medialis and vastus lateralis muscles. The electrode configurations were aligned parallel with the muscle fibres according to SENIAM guidelines (www.seniam.org accessed 13/05/2010). Specifically, for vastus medialis the electrodes were placed on a line between the anterior superior iliac spine and the joint space of the knee in front of the anterior border of the medial ligament, at a point that was 80% of the distance from the anterior superior iliac spine between the two points. For vastus lateralis the electrodes were placed on a line between the anterior superior iliac spine and the lateral aspect of the patella, at a point that was 66% of the distance from the anterior superior iliac spine between the two points. An earth electrode was placed on the tibial tuberosity of the same leg. Pairwise comparisons of electrodes were assessed using an Ohmmeter (Curtin University, Australia) to measure skin impedance. If the inter-electrode impedance was greater than 10 kΩ, preparation of the skin for these surface electrodes was repeated.

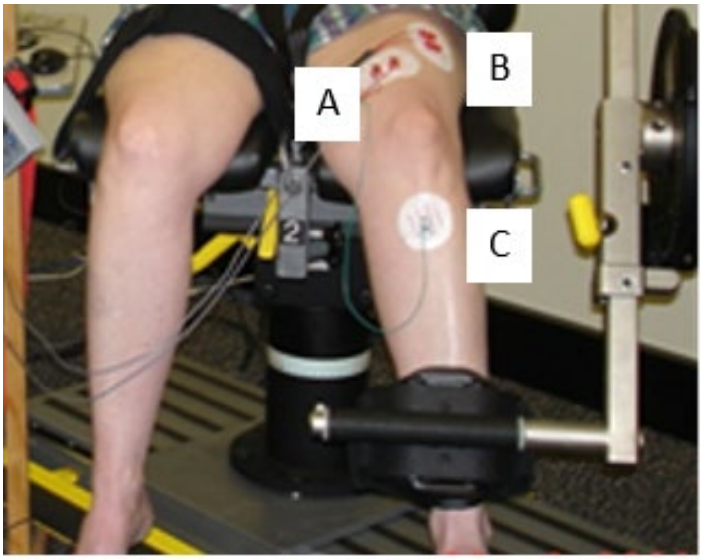


Figure 3.7 Configuration of electromyography electrodes during the assessment of quadriceps femoris endurance.

Placement of electrodes for recording EMG signals are shown for vastus medialis (A), vastus lateralis (B) and the tibial tuberosity (C).

The EMG cables were taped down to minimise movement artefacts and the signal from each channel was sent to and displayed on the LabVIEW screen. This allowed for real-time inspection of display of the EMG signal. Prior to commencing the assessment of QF endurance, participants were asked to perform a single maximal contraction of QF. During this, the EMG signal was displayed on the LabVIEW screen. The fixed and variable gain (i.e. amplitude factor of the signal) was adjusted to improve the signal display without clipping the signal. Figure 3.8 shows a screenshot of LabVIEW during QF contraction.

3.5.2.7 Determining quadriceps femoris endurance

The endurance of the participant's QF was determined during data analysis and defined in two ways; the time to task failure (T_{lim}) and the rate of decline of maximum torque. Final measures of endurance for both T_{lim} and rate of decline of maximum torque used in statistical analysis were determined during inspection of electronic data.

Time to task failure was defined as the time (s) to the first six second work period during which a participant was unable to sustain at least 90% of the torque–time integral (i.e. area subtended by the torque-time curve) which was equivalent to their target 60%MT_{QF} × 6 s.

This was determined using a two-step process. First, using SigmaPlot (SigmaPlot 12.0, Systat Software Inc, CA, USA), a threshold value to define task failure was calculated. To do this, for each participant, SigmaPlot was used to calculate the torque-time integral (i.e. area subtended by the torque-time curve, expressed as Nm·s) equivalent to 60%MT_{QF} × 6 s. Thereafter, a value equivalent to 90% of this integral was calculated and used as the criteria to define task failure. Once this value had been determined, data pertaining to the torque generated by the QF during each contraction of the endurance protocol were exported to SigmaPlot and the torque-time integral for each work period was calculated using the 'integrate' function. For each participant, T_{lim} was defined as the first work period during which they met the criteria for task failure (i.e. achieved a torque-time integral of < 90% of that equivalent to 60%MT_{QF} × 6 seconds). The calculations undertaken to determine if a contraction met the task failure criteria are illustrated in Figure 3.9. A value of 90% was chosen to reflect that the rise time to the target torque cannot be achieved by a participant instantaneously and that the torque generated during the contraction fluctuates slightly (i.e. a perfect steady state of muscle torque during a muscle contraction will not be achieved).

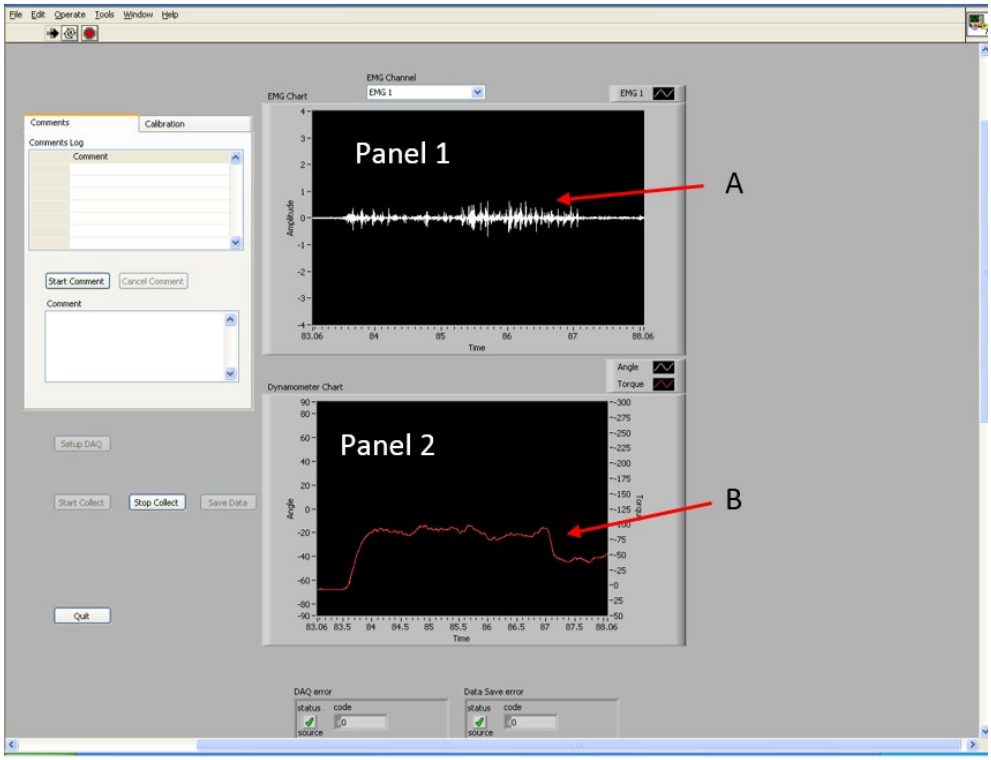


Figure 3.8 Screenshot of electromyography signal and torque generated by participant during a quadriceps femoris contraction at 60% of their previously determined maximum torque.

Panel 1 shows the amplitude of the electromyography (EMG) signal (Hz) on the y-axis against time (s) on the x-axis. The EMG signal (depicted by A) is from vastus medialis.

Panel 2 shows torque (Nm) on the right y-axis against time (s) on the x-axis. The line (depicted by B) shows the torque generated during the quadriceps femoris contraction.

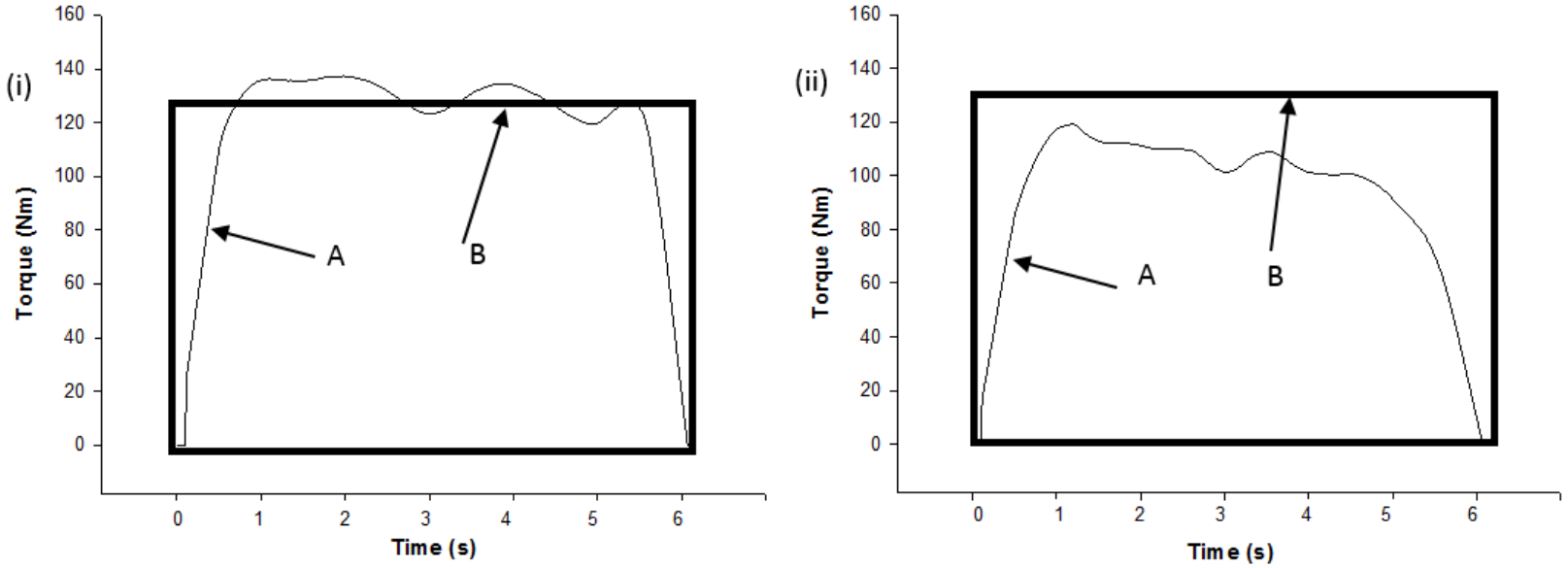


Figure 3.9 An illustration of the torque generated (against time) during two work periods (in the endurance protocol) for the same participant in which (i) did not meet the criteria for task failure and (ii) met the criteria for task failure.

Data shown are torque (Nm) on the y-axes plotted against time (s) on the x-axes. In both (i) and (ii), the bold line (depicted by B) shows the area subtended by the torque-time curve (for a contraction equivalent to 60%MT_{QF} for six seconds), in which for this participant was 798 Nm.s. The torque-time integral that was used to determine task failure for this participant was 718 Nm.s (i.e. calculated at 90% of 798 Nm.s). Figure 3.9 (i) shows a contraction in which the torque-time integral was 832 Nm.s (above the threshold for task failure) and (ii) shows a contraction in which the torque-time integral was 632 Nm.s (below the threshold for task failure.)

The rate of decline in maximum torque was also determined during the process of data analyses. To do this, the maximum torque generated during the MVICs performed during the six second work period at the start of each minute (MT_{QF_end}) were extracted. The change in MT_{QF_end} over the course of the assessment was calculated.

3.5.2.8 Use of electromyography data to support the assessment of quadriceps femoris endurance

The EMG data from vastus medialis and vastus lateralis were integrated in LabVIEW (see Section 3.5.2.7) and exported to Excel™. Given that the middle three second period of the contraction performed at the start of each minute of the protocol was not of steady state i.e. participants performed a three second contraction at 60%MT_{QF} followed by a three second MVIC, data from these contractions were excluded from EMG analyses. For all other contractions performed during assessment, an algorithm selected the middle three seconds of each six second work period performed. This three second epoch was chosen as it was a period of steady state of isometric hold, minimising large variations of amplitude and maximising the possibility of the waveform being stationary. This waveform where the level of activation was relatively stable provided optimal data for assessment of the median frequency using a Fast Fourier Transformation (161).

For each participant, these data were used to investigate changes in the frequency and power of the EMG signal from both vastus medialis and vastus lateralis. The power was determined using the mean root mean square. The frequency content was assessed using the median frequency band (45 to 95 Hz) derived from the Fast Fourier Transformation and the high/low frequency band ratio. The latter is a root mean square power ratio of the root mean square power of the signal within the high frequency band (above 95 Hz) and the low frequency band (15 to 45 Hz). The high/low frequency band ratio was derived from the amplitude assessments of the high and low frequency band amplitudes. This method of analyses was chosen as a decrease in median frequency from surface EMG profiles is a recognised method of determining (high frequency) fatigue in an isometric muscle contraction (162). As is the case in this current studies analyses, the methods employed to generate median frequency data rely on stationary waveforms and high sampling rates. Relative changes in the amplitude of specific frequency bands have been shown to be highly correlated to changes in median frequency (161). Frequency banding techniques, like median frequency changes, are sensitive to elements of fatigue that have a shorter recovery time than those associated with muscle performance or perception

of local muscle fatigue. The high/low ratio is a method that controls for a lack of stationarity of the EMG waveform should this be present (161).

3.5.3 Exercise capacity

Exercise capacity was measured using the six-minute walk test (6MWT). The testing protocol was adapted from the European Respiratory Society/American Thoracic Society guidelines (163). Specifically, the test was performed on an indoor flat 45 m walking track. Participants were instructed to walk as far as they could in six minutes. Standardised instructions at the start of the test and encouragement each minute during the test were provided. In accordance with clinical practice, during the test the candidate walked behind the participant, without affecting the participants' walking pace. This allowed the candidate to observe the participant and to record physiological measures during the test. During the test if the participant needed to, they were instructed that they could rest (in sitting, standing or leaning against a wall) but the time spent resting was included in the six minutes. Where a rest was required participants were encouraged to recommence walking as soon as they felt able. If the participant chose to rest during the test, the number of rests and total rest time were recorded. Participants were asked to report any symptoms such as dizziness or unusual pain and were told that if this should occur then the test would be stopped. To account for improvements resulting from test familiarisation, two tests were performed, with a minimum of 30 minutes between tests (163). The test with the longest distance walked i.e. the longest six-minute walk distance (6MWD) was recorded as the result. Six-minute walk distance was expressed in metres and as a percentage of the predicted value using reference equations derived in a sample with a similar age range to the age criteria used in this study (see Appendix 5) (164).

During the 6MWT, arterial oxygenation saturation (SpO_2) and heart rate (HR) were continuously monitored using a handheld pulse oximeter with finger sensor (Dixtal Novametrix Model 512) and a heart rate monitor (Polar Monitor FS3C ™), respectively. The SpO_2 and HR were recorded immediately prior to commencing the test, at the end of each minute and on test completion. Participant rating of perceived shortness of breath and leg tiredness was recorded immediately prior to commencing the test and on test completion using the 0 to 10 point Borg scale (165).

The 6MWT has been used extensively in LT as a measure to determine the need for and timing of this procedure (39, 166, 167) and to evaluate its impact on exercise capacity (5, 12, 34, 37, 64, 88, 91, 92, 168).

3.5.4 Sedentary time and physical activity

Physical activity was measured using two PA monitors; the SenseWear Pro3 Armband (SWA) (BodyMedia, Inc. Pittsburgh, PA, USA) and the Stepwatch™ Activity Monitor (SAM) (Modus Health, Washington, DC, USA). These two monitors were selected as the SWA, whilst providing information on intensity of movement, and can be used to extract information on possible sedentary time, does not yield accurate measures of step count (169-175). In contrast, SAM does record step count very accurately (176-178), which is a measure that is easily understood by clinicians, but step count alone is of limited value when attempting to isolate sedentary time. Participants were asked to wear these monitors during the waking hours of eight consecutive days, removing them only for water-based activities (e.g. immersion in water during showering and swimming). Specifically, participants were instructed to start using the devices on rising in the morning and to remove them on retiring to bed at night. All participants were instructed on the correct fitting of each monitor and provided with a contact number to call if they thought the devices were malfunctioning. Once the devices were returned, data were downloaded and exported to Excel™ for analyses.

3.5.4.1 Defining the minimal wear time for inclusion in the analyses of sedentary time and physical activity

There is a lack of consensus regarding the minimum number of days over which measures of ST and PA need to be sampled to obtain data that are representative of a typical day (see Section 2.2.4). Criteria for inclusion of data in these analyses have been adapted from a previous study in people with chronic obstructive pulmonary disease (COPD) (114). To be included a participant had to contribute SWA data over minimum of ten hours per day for a minimum of three days. Further, the SWA needed to be in contact with the participant's arm and collecting data for a minimum of 90% of the time between when they first put the device on in the morning to when they took the device off in the evening (i.e. 90% wear time). For participants who met these inclusion criteria, SWA data were averaged over every day that contributed a minimum of ten hours of data with at least 90% wear time. The SAM data were averaged over the same days as the SWA.

3.5.4.2 The SenseWear™ Armband

The SWA was attached to right upper arm over the triceps brachii muscle using an armband (see Figure 3.10). The SWA utilises a multisensory array including a bi-axial accelerometer, heat flux sensor, galvanic skin response sensor, skin temperature sensor, and a near-body ambient temperature sensor to estimate energy expenditure. Energy is estimated as metabolic equivalent tasks (METS), by integrating sensor inputs, via a proprietary algorithm. The SWA has been shown to yield accurate measures of energy expenditure in healthy adults (169, 170), in those with a chronic disease such as COPD (171-173) and cystic fibrosis (174) and has more recently been used in studies of LT candidates (107). Whilst the device also reports step count the accuracy of this measure, used in isolation of other inputs, is unclear (175).

Once the SWA data were exported to Excel™, using the energy expenditure output, each minute of wear time was grouped into the following categories; ST (< 1.5 METS), light intensity PA (1.5 to 2.9 METS), moderate intensity PA (3.0 to 5.9 METS) and vigorous intensity PA (6.0 METS and over). For each day included in the analyses, time in each category was expressed as a percentage of total wear time.

3.5.4.3 The StepWatch™ Activity Monitor

The SAM was attached to the right ankle using the proprietary ankle strap (see Figure 3.11). The device consists of a sensor, electronics and battery inside a polycarbonate case. It measures 75 x 50 x 20 mm and weighs approximately 38 g. The SAM was programmed via its Universal Serial Bus (USB) docking station to the StepWatch™ Analysis Software. Programming required entering data on the participant's height and normal walking pace. The SAM has been shown to accurately count steps in adults, including those characterised by very slow gait cadences (176-178). As the SAM records the number of steps taken by the right leg only, this value was doubled to calculate the total number of steps taken.

Figure 3.10 Sensewear Pro3 Armband attached to the right upper arm.

Figure 3.11 StepWatch™ attached to the right.

3.6 Sample size calculations

In order to detect a reduction in the MT_{QF} in the TG equal to 30 ± 30% of values achieved by the CG ($\alpha = 0.05$; $1-\beta = 0.8$), a sample size of 17 LT recipients and 17 healthy controls was sought. However, given the problems with recruitment of participants to the TG (see Section 4.1), a decision was made to recruit a larger sample to the CG. This approach served to reduce the standard error of measurements made in the CG and optimise statistical power.

3.7 Data analysis and calculations

Data were analysed using the Statistical Package for Social Sciences (SPSS version 20; IBM, NY, USA), unless otherwise specified. Due to the modest sample size, variables were reported as median [interquartile range]. Where appropriate minimum and maximum values are also shown. For all inferential statistics, a p-value of < 0.05 was considered significant.

Participant characterises including age, height, weight, measures of lung function, functional exercise capacity and HRQL are compared between the TG and CG using independent Mann-Whitney U tests.

Mann-Whitney U tests were used to compare the following variables between the TG and CG; (i) MT_{QF} and MT_{BB}, expressed as Nm, and measures of limb tiredness and overall effort during strength testing (i.e. research question 1), (ii) MT_{QF} and MT_{BB}, expressed as Nm per kilogram of limb lean muscle mass (i.e. research question 2), (iii) the ratio of MT_{BB} to MT_{QF} (i.e. research question 3) and (iv) T_{lim} and measures of limb tiredness and overall effort during endurance testing (i.e. research question 4).

Further analyses of the data collected during the assessment of QF endurance (i.e. research question 4) comprised; (i) Kaplan-Meier Kaplan-Meier analysis to explore differences in proportion of participants who had not met task failure at the end of each minute during the test and (ii) a Lowess smoother and a mixed model analyses (using Stata; Statacorp, USA) of data to compare the rate of decline of MT_{QF_end} in both groups.

For sub-analyses of within group differences in muscle strength and muscle mass in the TG see Appendix 6.

Regarding the EMG data, for each contraction performed during the assessment of QF endurance, the median frequency values for vastus medialis and vastus lateralis were plotted and smoothed using a Lowess smoother. Thereafter, a mixed model (random intercept and slope) (using Stata; Statacorp, USA) was applied to analyse the rate of change of median frequency for each muscle over time.

Regarding research question 5, in both groups, relationships between variables were explored using a 2-tailed Pearson's correlation coefficients. Specifically, relationships were explored between MT_{QF} and 6MWD, ST and time spent undertaking different intensities of PA and average daily step count. Likewise, relations were explored between T_{lim} and 6MWD, ST and time spent undertaking different intensities of PA and average daily step count. In the TG, relationships were also explored between measures of muscle function i.e. (MT_{QF}, MT_{BB} and T_{lim}) and mass (i.e. lean lower limb mass and lean upper limb mass) and the LT recipients' intensive care length of stay, hospital length of stay and the time following surgery.

CHAPTER 4 RESULTS

This chapter describes the results of the study undertaken for this Masters of Philosophy degree and answers the research questions stated in Chapter 1. The results presented include information related to outcome of the recruitment process and characteristics of participants in the transplant group (TG) and control group (CG). Thereafter, results pertaining to the measures of muscle strength of the quadriceps femoris (QF) and biceps brachii (BB) muscles are reported. These measures are expressed as torque as well as being normalised for differences in muscle mass of the lower and upper limb. Measures of QF endurance are presented as time to task failure (T_{lim}) and rate of decline in the maximum torque generated by the QF. Data pertaining to measures of fatigue using electromyography (EMG) are also presented. In addition, data are summarised on measures of exercise capacity using the six minute walk test (6MWT), sedentary time (ST) and time spent in different levels of intensity of physical activity (PA), measured using two activity monitors, and associations are presented between these variables and measures of QF strength and endurance.

4.1 Participant recruitment

Figure 1 shows recruitment of participants to the TG. Over the period of data collection, a total of 69 people were at least six months, but no more than five years, following a single, bilateral or heart-lung transplant procedure. Of these 54 had undergone a bilateral lung transplant (BLT) or heart-lung transplant (HLT) and were screened further to determine eligibility to participate in this study. Data collection was completed on ten participants (five females) following BLT or HLT.

Indications for BLT were cystic fibrosis (n = 6; 60%), emphysema (n = 2; 20%) and interstitial pulmonary fibrosis (n = 1; 10%). The indication for HLT was pulmonary hypertension and right heart failure in adulthood, complicating a Modified Mustard procedure performed on diagnosis of truncus arteriosus and ventricular septal defect at birth. Participants were (median [interquartile range]) 37 [39] months post-transplant. Details of their intensive care and overall length of stay in hospital post-transplant are shown in Table 4.1.

Lung transplant immunosuppressive medication maintenance regimes at the RPH LT program for longer term recipients include a calcineurin inhibitor (i.e. cyclosporine), prednisolone and mycophenolate, with a change to tacrolimus if recipients develop any adverse effects or features of rejection (49).

All participants in the TG had completed an inpatient (i.e. during their admission post-transplant) and an outpatient rehabilitation program. The three month long outpatient rehabilitation program commenced following hospital discharge and consisted of one hour of supervised exercise training undertaken two to three times per week with encouragement to complete a home program. Following this, participants were offered a maintenance program of one supervised exercise training session per week and encouraged to continue their home program. Participation in the supervised maintenance sessions was voluntary.

Regarding recruitment to the healthy control group, 20 people expressed an interest in participating in this study. Of those all appeared to meet the study criteria and therefore data collection was completed on these 20 participants (nine females) who constituted the CG.

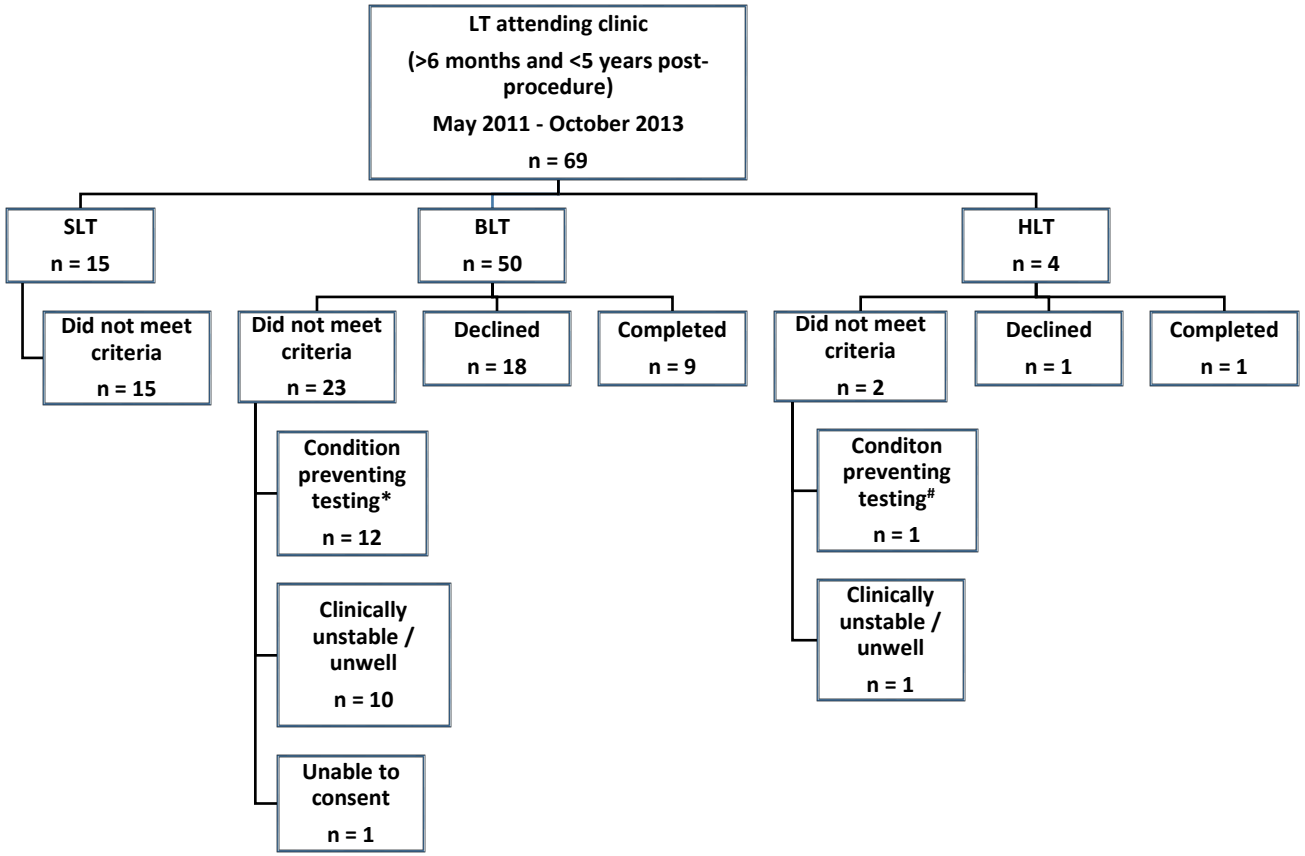


Figure 4.1 Recruitment of participants.

Definition of abbreviations: Bilateral lung transplant (BLT); heart-lung transplant (HLT); lung transplant (LT); single lung transplant (SLT);
** conditions preventing testing in BLT included brachial plexus injury, ruptured biceps brachii, sternal instability, hip pain/necrosis, paraplegia;*
 # condition preventing testing in HLT was stroke.

4.2 Participant characteristics

4.2.1 Demographic and anthropometric data

Characteristics of the participants recruited to the TG and CG are presented in Table 4.1. Although, when compared with the CG, the TG were somewhat older (median [IQR]) (43 [20] yr vs. 39 [25] yr) and weighed less (62.5 [22.6] kg vs. 71.0 [20.6] kg), these differences were not statistically significant.

4.2.2 Spirometric lung function

All participants in both groups completed the spirometric measures of lung function and these data are presented in Table 4.2. Compared with the CG, the TG were characterised by lower forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), expressed in litres (L) and as a percentage of the predicted value in healthy adults. Nevertheless, no participant in the TG had a $FEV_1/FVC < 0.7$.

4.2.3 Health-related quality of life

All participants in both groups completed the Quality Metric Incorporated Short Form 36 v.2 (SF36v2) questionnaire as a measure of health-related quality of life (HRQL) and these data are presented in Table 4.3. Compared with the CG, the TG were characterised by lower scores for physical functioning, general health and role emotional domains, and a lower physical health summary score.

4.2.4 Body composition

All participants in both groups underwent a dual-energy X-ray absorptiometry (DEXA) scan to measure body composition and these data are presented in Table 4.4. Compared with the CG, the TG were characterised by a lower total lean body mass, lower bone mineral content, and lower lean lower and upper limb muscle mass.

Table 4.1 Demographic and anthropometric data in the transplant and control groups.

	Transplant group (n = 10)		**Control group** (n = 20)		**p-value***
	median [IQR]	min to max	median [IQR]	min to max	
Age (yr)	43 [20]	25 to 58	39 [25]	21 to 67	0.91
Height (m)	1.72 [0.14]	1.56 to 1.82	1.74 [0.25]	1.65 to 1.90	0.17
Weight (kg)	62.5 [22.6]	48 to 83	71.0 [20.6]	56 to 110	0.11
Body mass index (kg/m^2)	22.1 [5.9]	18.2 to 26.6	23.8 [2.8]	17.9 to 32.1	0.25
Intensive care length of stay (day)	6.5 [23]	3 to 40	-	-	
Total hospital length of stay (day)	24 [33]	15 to 65	-	-	
Length of time after surgery (month)	37 [39]	9 to 62	-	-	

*Definition of abbreviations: Interquartile range (IQR); maximum (max); minimum (min). *Differences between groups assessed using Mann-Whitney U tests.*

Table 4.2 Spirometric lung function in the transplant and control groups.

	Transplant group (n = 10)		**Control group** (n = 20)		**p-value***
	median [IQR]	min to max	median [IQR]	min to max	
FEV_1 (L)	2.98 [0.83]	2.02 to 3.88	3.80 [1.00]	2.21 to 4.94	0.013
FVC (L)	3.55 [1.12]	2.50 to 5.40	4.78 [1.64]	3.11 to 7.08	0.019
FEV_1/FVC (%)	78 [20]	70 to 95	81 [11]	66 to 91	0.81
FEV_1 (%pred)	83 [30]	65 to 112	99 [17]	78 to 117	0.022
FVC (%pred)	88 [21]	71 to 101	107 [14]	87 to 121	<0.001

*Definition of abbreviations: Forced expiratory volume in one second (FEV_1); forced vital capacity (FVC); interquartile range (IQR); maximum (max); minimum (min); percentage of predicted (%pred). * Differences between groups explored using Mann-Whitney U tests.*

Table 4.3 Health-related quality of life scores in the transplant and control groups.

	Transplant group (n = 10)		**Control group** (n = 20)		**p-value***
	median [IQR]	min to max	median [IQR]	min to max	
Physical functioning	90 [8]	80 to 95	100 [5]	90 to100	<0.001
Role physical	94 [11]	62 to 100	100 [0]	69 to 100	0.15
Bodily pain	79 [14]	51 to 100	84 [28]	62 to 100	0.17
General health	71 [18]	55 to 80	82 [20]	57 to 100	0.017
Vitality	72 [20]	62 to 100	75 [17]	44 to 94	0.98
Social functioning	100 [16]	75 to 100	100 [0]	75 to 100	0.14
Role emotional	92 [19]	58 to 100	100 [0]	83 to 100	0.049
Mental health	82 [21]	65 to 100	90 [10]	75 to 100	0.16
Physical health summary	52 [2]	49 to 52	55 [5]	48 to 59	<0.001
Mental health summary	55 [9]	44 to 64	57 [5]	50 to 62	0.25

*Definition of abbreviations: Interquartile range (IQR); maximum (max); minimum (min). Scores are raw values derived from SF36v2 questionnaire.*Differences between groups explored using Mann-Whitney U tests.*

Table 4.4 Body composition in the transplant and control groups.

	Transplant group (n = 10)		**Control group** (n = 20)		**p-value***
	median [IQR]	min to max	median [IQR]	min to max	
Total lean body mass (kg)	42.4 [12.2]	34.7 to 50.8	54.2 [23.6]	38.8 to 79.3	0.031
Total fat mass (kg)	18.2 [19.5]	4.4 to 32.8	17.7 [13.3]	8.4 to 38.9	0.98
Bone mineral content (kg)	2.4 [0.70]	1.6 to 3.2	3.8 [1.0]	2.1 to 4.5	0.017
Lean lower limb mass (kg)	7.0 [2.2]	5.4 to 8.1	8.8 [4.1]	5.5 to 13.5	0.011
Lean upper limb mass (kg)	2.1 [0.0]	1.4 to 2.8	3.0 [0.2]	1.8 to 6.2	0.035

*Definition of abbreviations: Interquartile range (IQR); maximum (max); minimum (min). Lean lower limb mass and lean upper limb mass is reported for the side of hand dominance.*Differences between groups explored using Mann-Whitney U tests.*

4.3. Muscle strength and symptoms reported during the assessment of muscle strength

All participants in both groups completed assessment of muscle strength of the QF and BB.

4.3.1 Torque generated by quadriceps femoris

Measures of torque generated by QF for both groups are presented in Table 4.5. Compared to the CG, the maximum torque of the QF (MT_{QF}) was less in the TG. The magnitude of the difference in median MT_{QT} between the groups was 73.3 Nm, which was equivalent to a reduction of 33% in the TG relative to the CG. However, when differences in muscle mass between the groups were considered by expressing the MT_{QF} per kg of lean lower limb muscle mass, no difference was observed between the groups.

4.3.2 Torque generated by biceps brachii

Measures of torque generated by BB for both groups are presented in Table 4.5. Compared to the CG, the maximal torque of BB (MT_{BB}) was less in the TG. The magnitude of the difference in median MT_{BB} between the groups was 10.8 Nm, which was equivalent to a reduction of 23% in the TG relative to the CG. However, when differences muscle mass between the groups were considered by expressing the MT_{BB} per kg of lean upper limb muscle mass, no difference was observed between the groups.

4.3.3 Measures of maximum torque generated by biceps brachii expressed relative to the maximum torque generated by quadriceps femoris

Measures of MT_{BB}, expressed as a proportion of MT_{QF}, in the TG and CG are presented in Table 4.6. Regardless of whether these data were measured as Nm or Nm/kg of lean muscle mass, measures of MT_{BB}, expressed as a proportion of MT_{QF} were similar between the two groups.

4.3.4 Symptoms reported during the assessment of muscle strength

Symptoms reported on completion of the assessments of muscle strength for both groups are shown in Table 4.7. For both QF and BB, no differences were seen between the groups in the ratings of muscle tiredness or overall perceived exertion.

Table 4.5 Maximum torque generated by quadriceps femoris and biceps brachii in the transplant and control groups.

	Transplant Group (n = 10)		**Control Group** (n = 20)		**p value***
	median [IQR]	min to max	median [IQR]	min to max	
MT_{QF} (Nm)	148 [87]	107 to 239	221 [140]	120 to 390	0.022
Torque normalised for lean muscle mass of the lower limb (Nm/kg)	25 [8]	17 to 30	27 [8]	16 to 37	0.37
MT_{BB} (Nm)	34 [22]	21 to 59	45 [45]	29 to 106	0.044
Torque normalised for lean muscle mass of the upper limb (Nm/kg)	17 [5]	11 to 29	19 [4]	8 to 25	0.48

*Definition of abbreviations: Interquartile range (IQR); maximum (max); maximum torque of biceps brachii (MT_{BB}); maximum torque of quadriceps femoris (MT_{QF}); minimum (min). *Differences between groups explored using Mann-Whitney U tests. Lean muscle mass for lower and upper limbs is reported for the side of hand dominance.*

Table 4.6 Maximum torque generated by biceps brachii relative to maximum torque generated by quadriceps femoris in the transplant and control groups.

	Transplant Group (n = 10)		**Control Group** (n = 20)		**p-value***
	median [IQR]	min to max	median [IQR]	min to max	
MT_{BB} : MT_{QF} (torque)	0.22 [0.07]	0.16 to 0.29	0.24 [0.07]	0.16 to 0.33	0.56
MT_{BB}: MT_{QF} (torque per kilogram of lean muscle mass)	0.67 [0.11]	0.52 to 1.04	0.70 [0.24]	0.48 to 0.90	0.35

*Definition of abbreviations: Interquartile range (IQR); maximum (max); maximum torque of biceps brachii (MT_{BB}); maximum torque of quadriceps femoris (MT_{QF}); minimum (min). *Differences between groups explored using Mann-Whitney U test.*

Table 4.7 Symptoms reported on completion of the assessment of muscle strength in the transplant and control groups.

	Transplant group (n = 10)		**Control group** (n = 20)		**p-value***
Symptoms	median [IQR]	min to max	median [IQR]	min to max	
$tiredness_{QF}$ (0 to 10)	4 [3]	0 to 9	3 [2]	0 to 9	0.18
RPE_{QF} (6 to 20)	19 [5]	13 to 20	18 [2]	7 to 20	0.45
$tiredness_{BB}$ (0 to 10)	4 [2]	0 to 9	3 [2]	0 to 7	0.18
RPE_{BB} (6 to 20)	18 [6]	13 to 20	17 [1]	6 to 20	0.53

*Definition of abbreviations: Interquartile range (IQR); maximum (max); minimum (min); rating of perceived exertion during biceps brachii testing (RPE_{BB}); rating of perceived exertion during quadriceps femoris testing (RPE_{QF}); tiredness following assessment of bicep brachii strength ($tiredness_{BB}$); tiredness following assessment of quadriceps femoris strength ($tiredness_{QF}$). *Differences between groups explored using Mann-Whitney U test.*

4.4 Quadriceps femoris muscle endurance

All participants in both groups completed the assessment of QF endurance. However due to data corruption, data from nine (90%) participants in the TG and 19 (95%) in the CG were available for analyses.

4.4.1 Time to task failure as a measure of quadriceps femoris muscle endurance

The T_{lim} measured during the assessment of QF endurance for the TG and CG was (median [IQR]) 90 [100] s and 300 [200] s, respectively. A wide range in T_{lim} was seen in the TG of 50 s to 480 s and in the CG of 150 s to 920 s. Compared with the CG, the TG had a median T_{lim} that was 210 s less than the CG ($p < 0.001$).

The Kaplan-Meier analysis (Figure 4.2) demonstrated a difference in the proportion of participants in the TG and CG who had not met task failure at the end of each minute during the assessment of QF endurance. That is, a T_{lim} of greater than three minutes was achieved in 55% of the TG compared with 90% of the CG ($p < 0.001$).

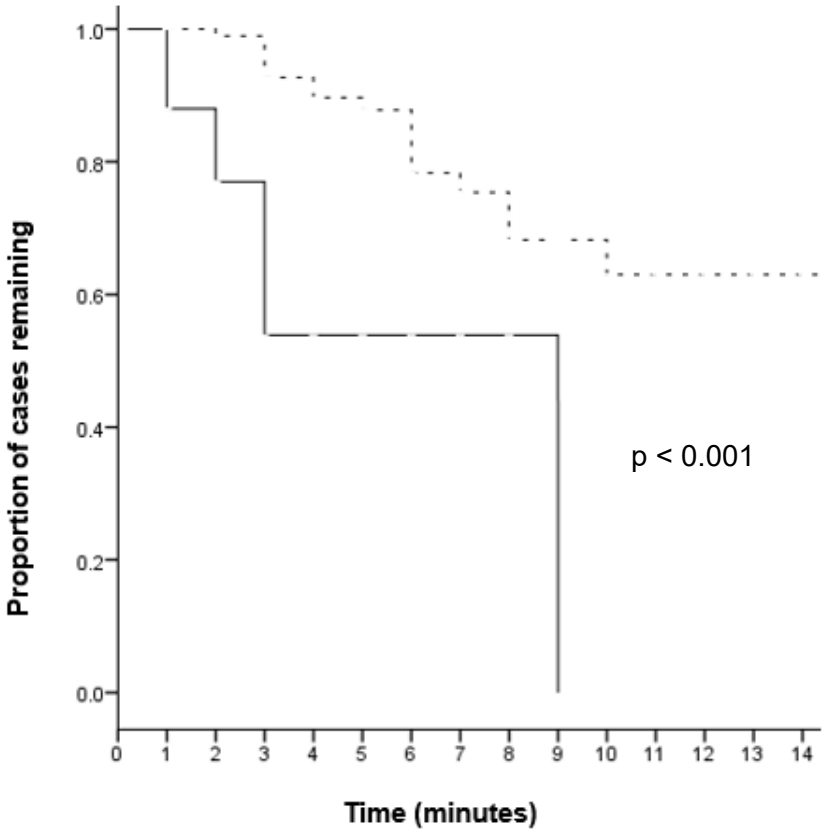


Figure 4.2 Kaplan-Meier analysis of time to task failure for the transplant and control groups.

Figure 4.2 shows the proportion of cases who had not reached task failure on they-axis plotted at the end of each minute on the x-axis during the assessment of quadriceps femoris endurance in the transplant and control groups.

Legend: ----- ----- ----- represents the transplant group and - - - - - - - - represents the control group

4.4.2 Rate of decline in maximum torque of quadriceps femoris generated during endurance protocol

For each participant in both groups, the maximum torque generated by the QF during the maximal voluntary isometric contraction (MVIC) at the start of each minute during the assessment of QF endurance (MT_{QF_end}) is plotted in Figure 4.3 (i). These same data are shown following the application of a lowess smoother in Figure 4.3 (ii).

A mixed model analysis demonstrated a significant difference in the rate of decline in MT_{QF_end} between the groups. Compared with the CG, the rate of decline in MT_{QF_end} in the TG was 60 Nm greater per contraction (95% confidence interval [CI] 6 to 114; $p = 0.031$).

Given that only one participant in the TG contributed MT_{QF_end} data to these analyses after 25 contractions (i.e. four minutes into the assessment), these analyses were repeated using only the first four measures of MT_{QF_end} in both groups (see Figure 4.4). This meant that all participants from both groups contributed the same amount of data for this analysis. Compared with the CG, the rate of decline in MT_{QF_end} in the TG was 75 Nm greater per contraction (95% CI 34 to 117; $p < 0.001$).

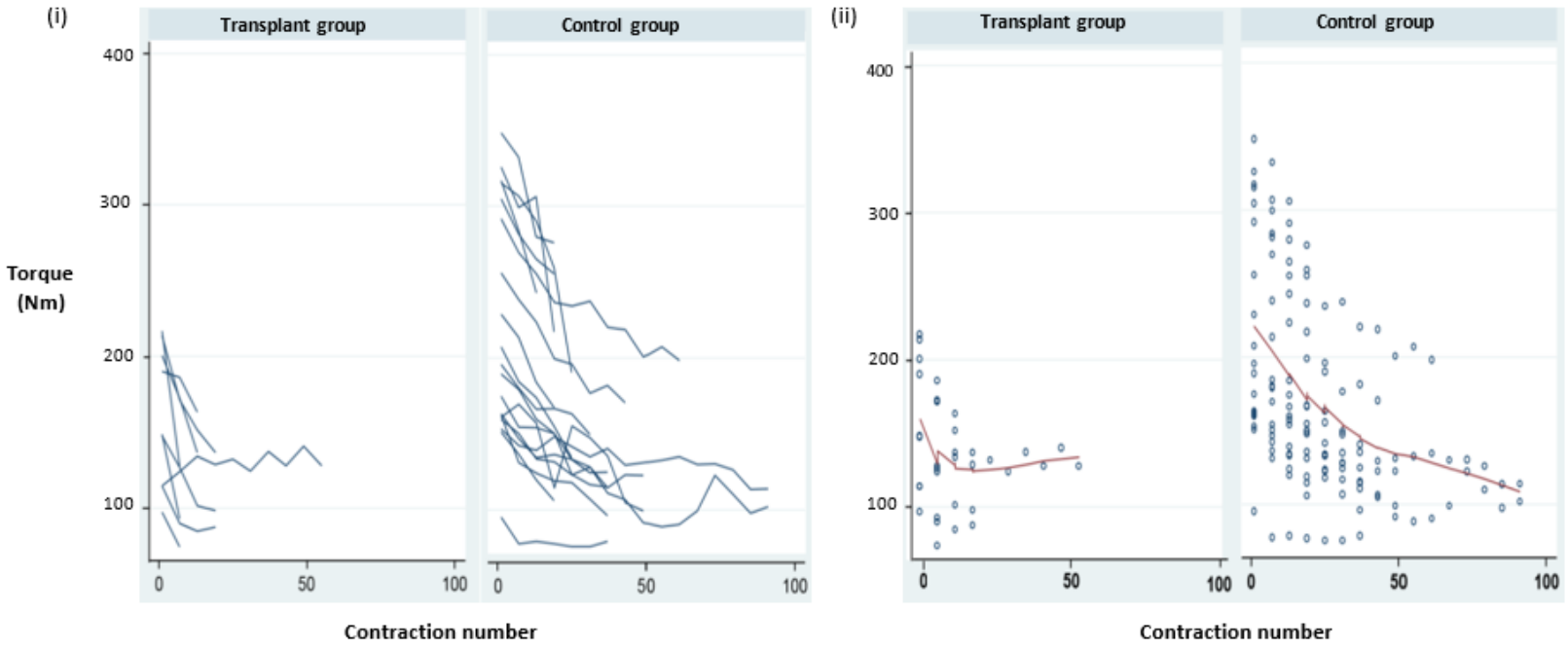


Figure 4.3 Maximum torque generated by the quadriceps femoris at the start of each minute during the assessment of quadriceps femoris endurance in the transplant and control groups.

Figure 4.3 (i) shows the MT_{QF_end} (Nm) during the assessment of QF endurance on the y-axes plotted against the MVIC for each participant on the x-axes in the transplant group (left panel) and the control group (right panel). Figure 4.3 (ii) shows the same data smoothed with a lowess smoother. N.B. the x-axes represent the total number of contractions performed by the QF during the assessment of endurance, not the number of MVICs. During the assessment of QF endurance, participants performed a MVIC at the start of each minutes only (see Section 3.5.2.5). Definition of abbreviations: maximal voluntary isometric contraction (MVIC); maximum torque generated at the start of each minute during assessment of QF endurance (MT_{QF_end}); quadriceps femoris (QF).

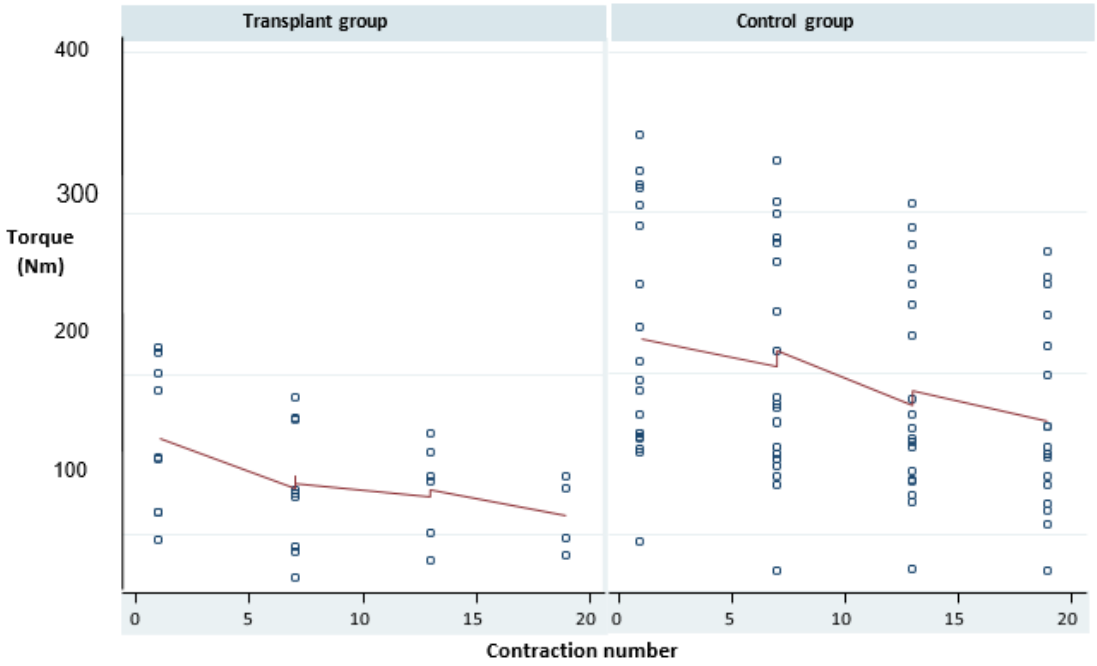


Figure 4.4 Maximum torque generated by the quadriceps femoris at the start of each minute during the assessment of quadriceps femoris endurance in the transplant and control groups (four contractions).
Data shows MT_{QF_end} (Nm) during the assessment of QF endurance on the y-axis plotted against the first four MVICs for each participant during the assessment of QF endurance on the x-axes in the transplant group (left panel) and the control group (right panel). N.B. the x-axes represent the total number of contractions performed by the QF during the assessment of endurance, not the number of MVICs. Figure shows data smoothed with a lowess smoother. Definition of abbreviations: maximal voluntary isometric contraction (MVIC); maximum torque generated by the quadriceps femoris at the start of each minute (MT_{QF_end}); quadriceps femoris (QF).

4.4.3 Symptoms reported on completion of the assessment of quadriceps femoris endurance

Symptoms reported on completion of the assessment of QF endurance for both groups are shown in Table 4.8. There were no differences in the rating of limb tiredness or overall perceived exertion between the groups.

Table 4.8 Symptoms reported on completion of the assessment of quadriceps femoris endurance.

	Transplant group (n = 9)		**Control group (n = 19)**		**p-value***
	median [IQR]	min to max	median [IQR]	min to max	
tiredness$_{QF}$ (0 to 10)	7 [4]	3 to 10	7 [4]	0.5 to 10	1.00
RPE (6 to 20)	19 [2]	17 to 20	19 [3]	17 to 20	1.00

*Definition of abbreviations: Interquartile range (IQR); maximum (max); minimum (min); rating of perceived exertion (RPE); tiredness following assessment of quadriceps femoris endurance (tiredness$_{QF}$). * Differences between groups explored using Mann-Whitney U tests.*

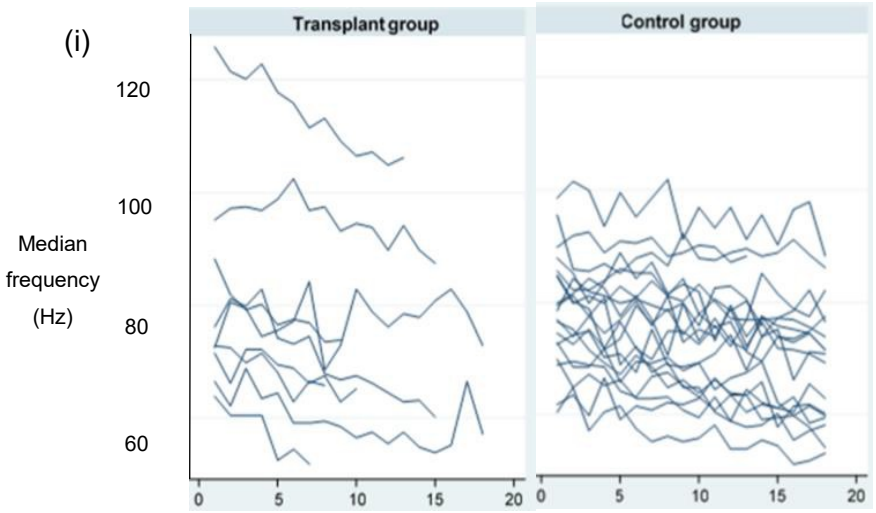
4.4.4 Analysis of electromyography

Only one participant was able to maintain QF contractions for longer than four minutes during the assessment of QF endurance. Therefore EMG data were analysed for only the first four minutes for all participants. This resulted in 18 data points being available for analyses.

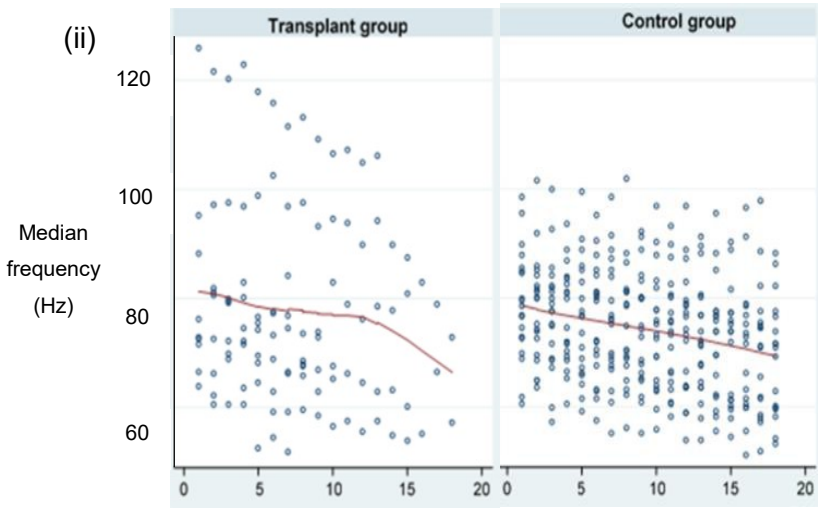
Values for EMG median frequency and smoothed values (lowess smoother) for each contraction performed during the assessment of QF endurance are shown for vastus medialis in Figure 4.5 (i) and 4.5 (ii) for vastus lateralis in Figure 4.5 (iii) and 4.5 (iv), respectively.

A mixed model analysis demonstrated no difference between groups in the median frequencies of vastus medialis during muscle contractions (between group difference in frequency of 0.34 Hz [95% CI -9.80 to 10.49] more per contraction). In contrast, when compared with the CG, the median frequencies of vastus lateralis during the muscle contractions, were less in the TG (between group difference in frequency of -7.29 Hz [95% CI -13.97 to -0.61] less per contraction).

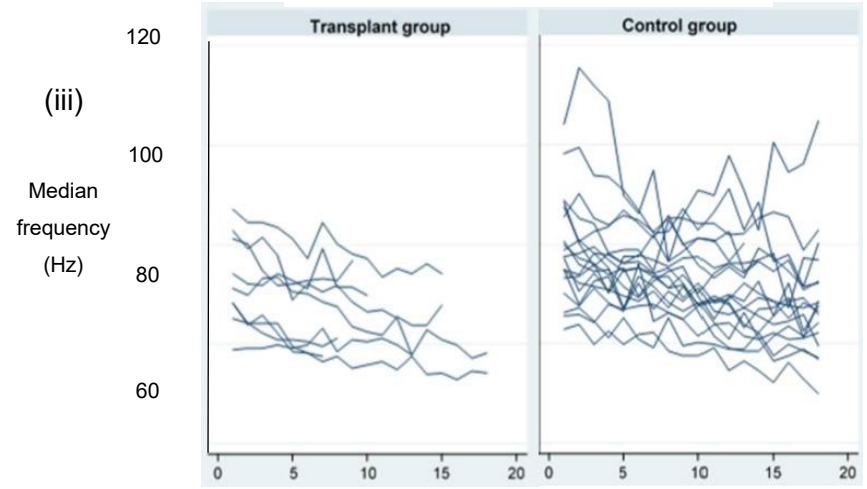
(i)


Transplant group
Control group
Median frequency (Hz)
120
100
80
60
0
5
10
15
20
EMG signal for each contraction

(ii)


Transplant group
Control group
Median frequency (Hz)
120
100
80
60
0
5
10
15
20
EMG signal for each contraction

(iii)


Transplant group
Control group
Median frequency (Hz)
120
100
80
60
0
5
10
15
20
EMG signal for each contraction

(iv)

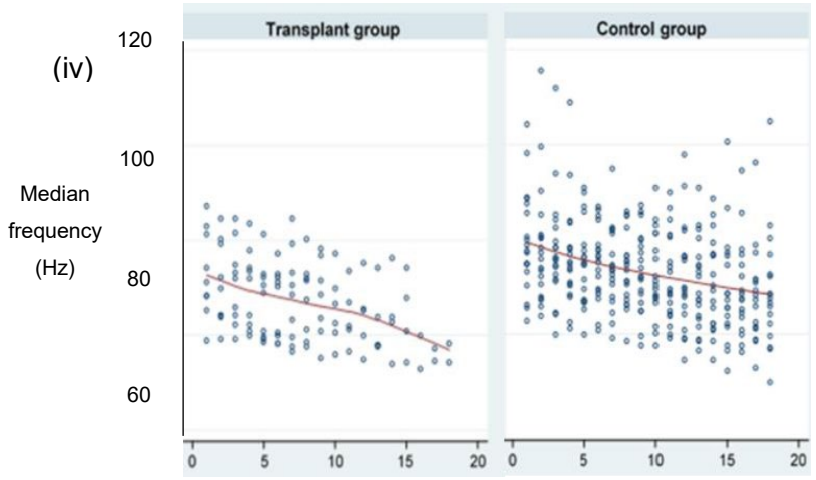

Transplant group
Control group
Median frequency (Hz)
120
100
80
60
0
5
10
15
20
EMG signal for each contraction

Figure 4.5 Median frequency of electromyography signals during assessment of quadriceps femoris endurance.

Data shows EMG; (i) median frequency (Hz) and, (ii) smoothed median frequency (Hz) from vastus medialis (on the y-axes) plotted over the first 18 muscle contractions undertaken at 60%MT_{QF} (on the x-axes) during the assessment of quadriceps femoris endurance. The same data for vastus lateralis are shown at (iii) and (iv), respectively.

4.5 Exercise capacity

All participants in both groups completed the 6MWT. Measures of six-minute walk distance (6MWD), resting heart rate, peak heart rate recorded during the test, nadir arterial oxygen saturation measured by pulse oximetry and symptoms of leg tiredness and shortness of breath before and after the test in both groups are presented in Table 4.9. Compared with the CG, the TG had a lower 6MWD, a higher resting HR and reported a greater severity of shortness of breath on test completion (all $p < 0.05$).

Table 4.9 Data collected during the six-minute walk tests.

	Transplant group (n = 10)		**Control group** (n = 20)		**p-value***
	median [IQR]	min to max	median [IQR]	Min to max	
6MWD (m)	671 [107]	527 to 795	797 [68]	651 to 845	< 0.001
6MWD (%pred)	94 [16]	73 to 102	104 [9]	92 to 116	< 0.001
HR at rest (bpm)	99 [19]	88 to 126	81[17]	59 to 103	< 0.001
HR at end-test (bpm)	142 [29]	125 to 161	142 [24]	90 to 174	0.75
SOB at rest (0 to 10)	0 [0.5]	0.5 to 1	0 [0.5]	0 to 0.5	0.37
SOB at end-test (0 to 10)	3 [0.8]	2 to 7	2 [1.8]	0.5 to 3	0.028
Leg tiredness at rest (0 to 10)	0.5 [1.3]	0 to 2	0.0 [1.8]	0 to 2	0.75
Leg tiredness at end-test (0 to 10)	3 [1.5]	2 to 4	2.5 [2]	0 to 12	0.20
SpO_2 nadir (%)	96 [1]	95 to 97	96 [3]	89 to 97	0.18

*Definition of abbreviations: Heart rate (HR); interquartile range (IQR); maximum (max); minimum (min); percentage of predicted (%pred); shortness of breath (SOB); arterial oxygen saturation measured via pulse oximetry (SpO_2). * Differences between groups explored using Mann-Whitney U tests. Values for 6MWD (%pred) are calculated from the reference equation developed by Gibbons et al (164).*

4.6 Sedentary time and physical activity

Data were available from the SenseWear Pro 3 Armband (SWA) for all participants in both groups. Due to data corruption issues, data from the StepWatch Activity Monitor (SAM) were available in 19 (95%) participants in the CG.

4.6.1 Monitor wear time

Data pertaining to wear time for the SWA in both groups are shown in Table 4.10. There were no differences in measures related to wear time between the groups.

4.6.2 Sedentary time and time spent undertaking physical activity

4.6.2.1 Sedentary time and physical activity measured by the SenseWear Pro3 Armband

Waking hours, divided into ST, and time spent in light, moderate and vigorous intensity PA, obtained using the SWA in both groups are presented in Table 4.11. Given the small amount of time spent in vigorous intensity PA by both groups, values for time spent in moderate or vigorous intensity activity (MVPA) combined are also presented. Whilst the TG spent 9% less of their waking hours undertaking MVPA when compared with those in the CG, this difference did not reach statistical significance. No differences in measures of ST or time spent in light intensity PA between the groups were found.

4.6.2.2 Daily step count measured by the StepWatch Activity Monitor

The average number of daily steps taken, measured using the SAM in the TG and CG, were median [IQR]) 9,582 [3,620] steps and 13,283 [4,514] steps, respectively. Compared with the CG, the TG had a median number of daily steps that was 3,701 less than the CG. This difference between the groups approached statistical significance ($p = 0.05$)

Table 4.10 SenseWear Pro 3 Armband wear time.

	Transplant group (n = 10)		**Control group** (n = 20)		**p-value***
	median [IQR]	min to max	median [IQR]	min to max	
Days included in analyses†	6 [5]	3 to 9	6 [2]	5 to 8	0.75
On body time (min)	863 [136]	718 to 910	853 [128]	776 to 1005	0.59
% on body time	98 [1]	98 to 100	98 [2]	96 to 100	0.08

*Definition of abbreviations: Interquartile range (IQR); maximum (max); minimum (min). * Differences between groups explored using Mann-Whitney U tests. † for a description of the criteria used to determine whether or not a day was eligible for inclusion in these analyses, refer to section 3.5.4.1.*

Table 4.11 Sedentary time and time spent undertaking physical activity at different intensities, expressed as a percentage of total waking hours.

	Transplant group (n = 10)		**Control group** (n = 20)		**p-value***
	median [IQR]	min to max	median [IQR	min to max	
Sedentary time	60 [20]	41 to 82	60 [15]	44 to 82	0.56
Light intensity physical activity	27 [15]	6 to 33	23 [13]	10 to 33	0.50
Moderate intensity physical activity	10 [20]	7 to 56	18 [11]	4 to 35	0.59
Vigorous intensity physical activity	0 [1]	0 to 6	1 [2]	0 to 6	0.14
Moderate or vigorous intensity physical activity	10 [21]	7 to 58	19 [13]	4 to 40	0.45

*Definitions: Sedentary time (< 1.5 METS), light intensity physical activity (1.5 to 2.9 METS), moderate intensity physical activity (3.0 to 5.9 METS), vigorous intensity physical activity (≥ 6.0 METS) and moderate or vigorous intensity physical activity (≥ 3.0METS). Definition of abbreviations: Interquartile range (IQR); maximum (max); minimum (min). * Differences between groups explored using Mann-Whitney U tests.*

4.7 Associations between measures of quadriceps femoris function, exercise capacity, sedentary time and physical activity during daily life

Data were explored to determine if relationships existed between measures of muscle function (i.e. MT_{QF} and T_{lim}) and 6MWD, ST, time spent undertaking PA at different intensities and average daily step count. In the TG, data were explored to determine if relationships existed between measures of muscle function (i.e. MT_{QF} and T_{lim}) and the intensive care length of stay after surgery, hospital length of stay after surgery and the length of time after surgery when participants were assessed for the study.

4.7.1 Muscle strength

4.7.1.1 Quadriceps femoris strength and functional exercise capacity

Figure 4.6 (i) presents MT_{QF} for all participants in the TG, plotted against 6MWD. There was a significant positive correlation between MT_{QF} and 6MWD in the TG. No correlation was seen between these variables in the CG (see Figure 4.6 [ii]).

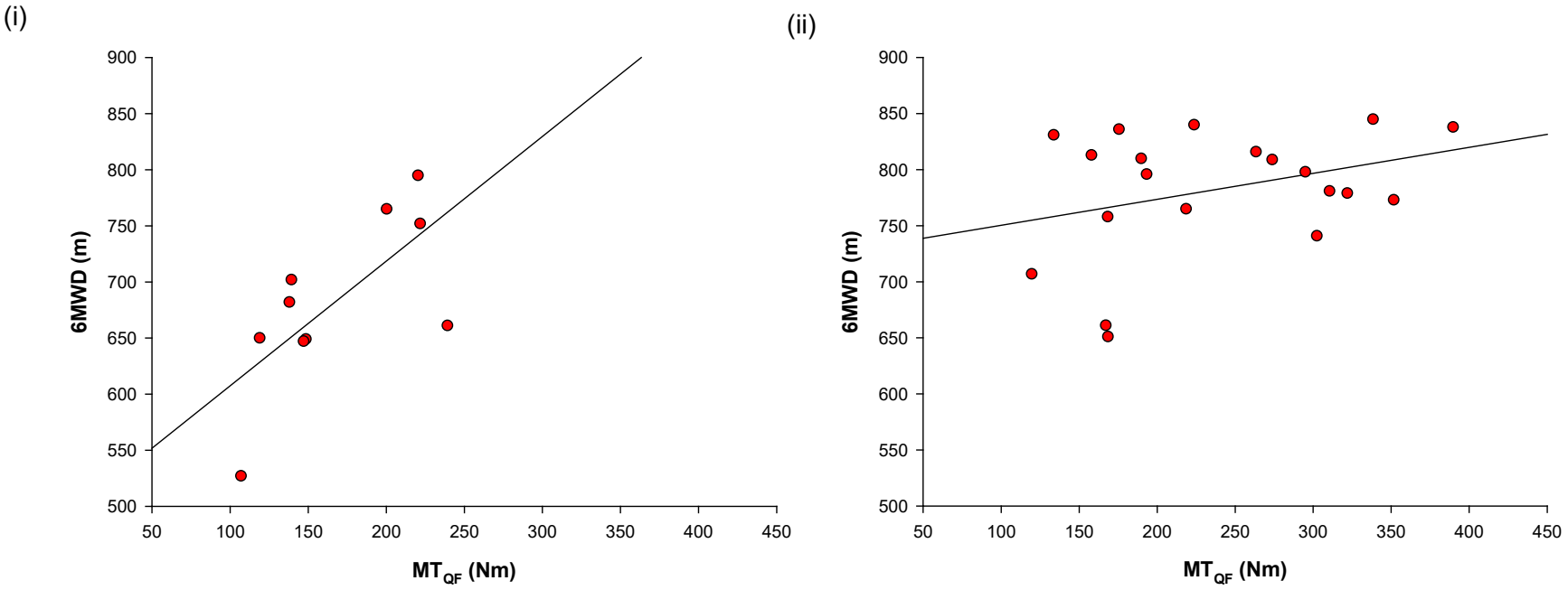


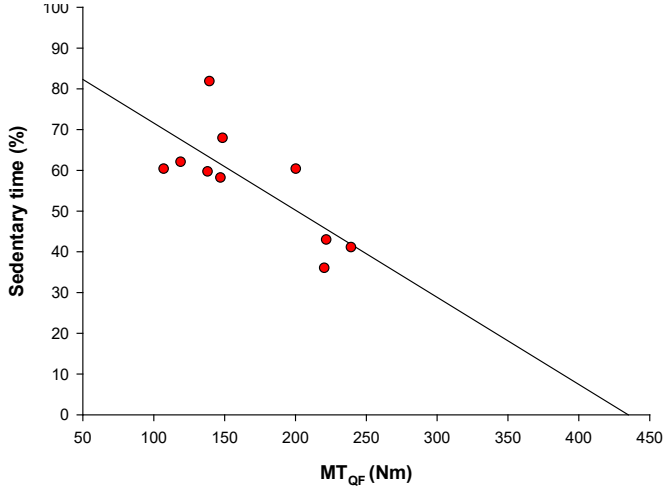
Figure 4.6 Scatterplot of the maximum torque generated by quadriceps femoris and six-minute walk distance in the (i) transplant group and (ii) control group.

Data are MT_{QF} (Nm) on the x-axis plotted against 6MWD (m) on the y-axis. The line of best fit is shown. Correlations explored using Pearson's correlation coefficient were as follows: Figure 4.6(i): r = 0.691; p = 0.021; Figure 4.6(ii): r = 0.311; p = 0.154. Definition of abbreviations: Six-minute walk distance (6MWD); maximum torque generated by quadriceps femoris (MT_{QF}).

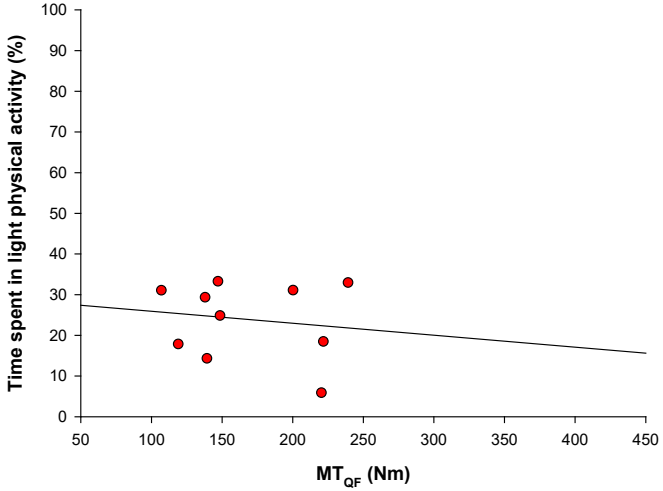
4.7.1.2 Quadriceps femoris strength and measures of sedentary time, physical activity and daily steps

Figure 4.7 presents MT_{QF} for all participant in the TG, plotted against; (i) the percentage waking hours spent in ST, (ii) the percentage of waking hours spent undertaking light intensity PA, (iii) the percentage of waking hours spent undertaking MVPA and (iv) average daily step count. There was a significant negative correlation between MT_{QF} and the percentage of waking hours spent in ST, and a significant positive correlation between MT_{QF} and the percentage of waking hours spent undertaking MVPA. In the CG, no relationships were seen between MT_{QF} and any measure of ST or PA (see Figure 4.8).

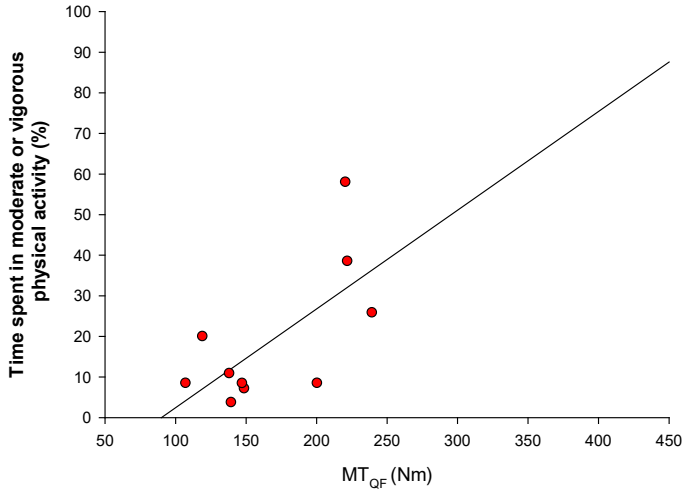
(i)


Sedentary time (%)
MT$_{QF}$ (Nm)

(ii)


Time spent in light physical activity (%)
MT$_{QF}$ (Nm)

(iii)


Time spent in moderate or vigorous physical activity (%)
MT$_{QF}$ (Nm)

(iv)

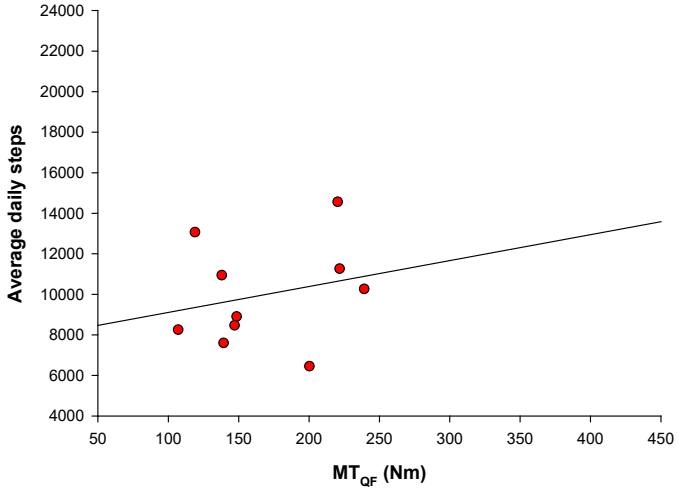
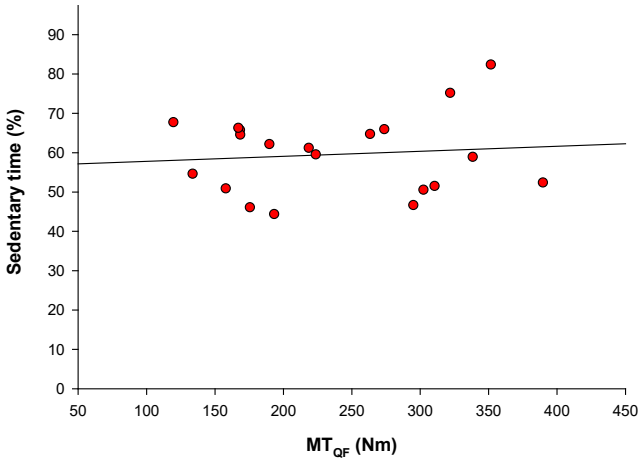

Average daily steps
MT$_{QF}$ (Nm)

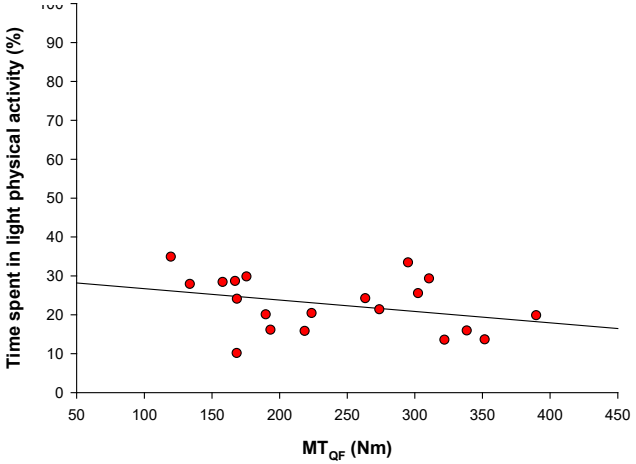
Figure 4.7 Scatterplot of maximum torque generated by quadriceps femoris and sedentary time, time spent undertaking physical activity of different intensities and average daily steps in the transplant group.

Data are MT_{QF} (Nm) on the x axis plotted against; (i) sedentary time, expressed as a % of waking hours, (ii) time undertaking light physical activity, expressed as a % of waking hours, (iii) time undertaking moderate or vigorous physical activity, expressed as a % of waking hours and, (iv) average daily steps on the y-axes. The line of best fit is shown. Correlations explored using Pearson's correlation coefficient were as follows: Figure 4.7(i): r = -0.744; p = 0.014. Figure 4.7(ii): r = -0.150; p = 0.679. Figure 4.7(iii): r = 0.738; p = 0.023 and Figure 4.7(iv): r = 0.241; p = 0.503. Definition of abbreviations: Maximum torque of the quadriceps femoris (MT_{QF}).

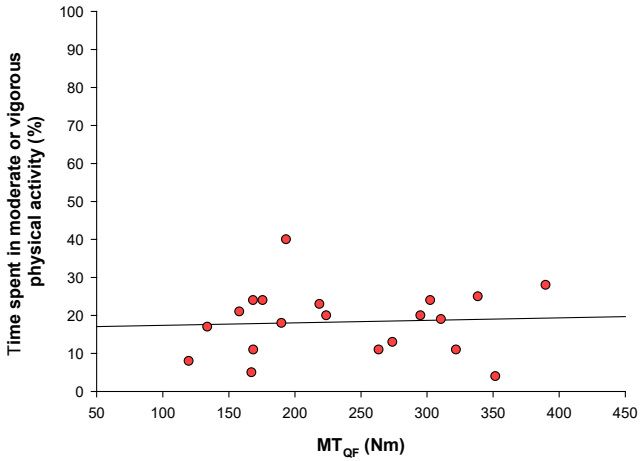
(i)


Sedentary time (%)
MT$_{QF}$ (Nm)

(ii)


Time spent in light physical activity (%)
MT$_{QF}$ (Nm)

(iii)


Time spent in moderate or vigorous physical activity (%)
MT$_{QF}$ (Nm)

(iv)

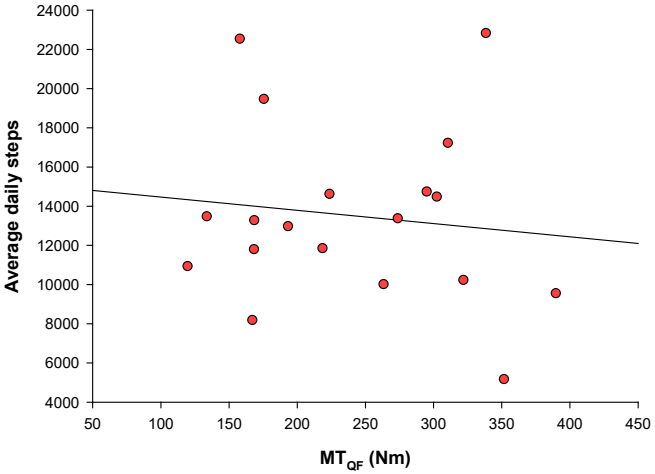

Average daily steps
MT$_{QF}$ (Nm)

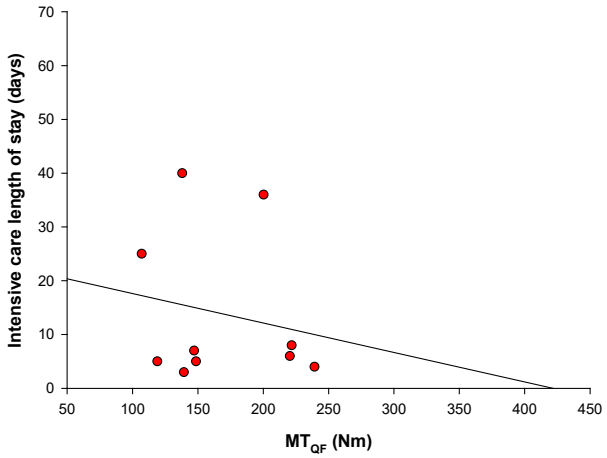
Figure 4.8 Scatterplot of maximum torque generated by quadriceps femoris and sedentary time, time spent undertaking physical activity of different intensities and average daily steps and in the control group.

Data are MT_{QF} (Nm) on the x-axis plotted against; (i) sedentary time, expressed as a % of waking hours, (ii) time undertaking light physical activity, expressed as a % of waking hours, (iii) time undertaking moderate or vigorous physical activity, expressed as a % of waking hours and, (iv) average daily steps on the y-axes. The line of best fit is shown. Correlations explored using Pearson's correlation coefficient were as follows: Figure 4.8(i): r = 0.103; p = 0.666. Figure 4.8(ii): r = -0.333; p = 0.151. Figure 4.8(iii): r = 0.062; p = 0.795; Figure 4.8(iv): r = -0.122; p = 0.619. Definition of abbreviations: Maximum torque of the quadriceps femoris (MT_{QF}).

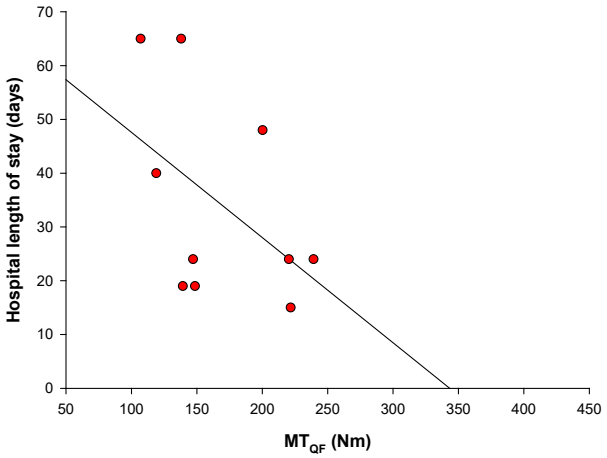
4.7.1.3 Quadriceps femoris strength and time since lung transplant

Figure 4.9 presents MT_{QF} for ten participants in the TG plotted against, (i) the participants post-surgery intensive care length of stay, (ii) the post-surgery overall hospital length of stay and, (iii) the length of time post-transplant that assessment for the study was undertaken. Figure 4.9 (iv) presents MT_{QF} expressed as a percentage of predicted strength derived from published equations (see Appendix 7). No clear or consistent correlations were seen between these variables.

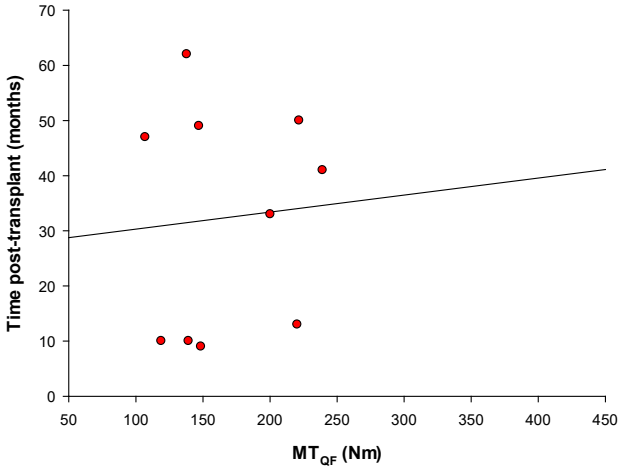
(i)


Intensive care length of stay (days)
MT$_{QF}$ (Nm)

(ii)


Hospital length of stay (days)
MT$_{QF}$ (Nm)

(iii)


Time post-transplant (months)
MT$_{QF}$ (Nm)

(iv)

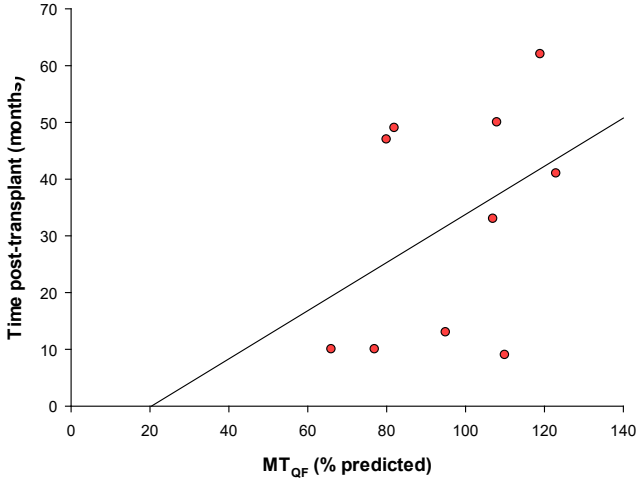

Time post-transplant (months)
MT$_{QF}$ (% predicted)

Figure 4.9 Scatterplot of maximum torque generated by quadriceps femoris plotted against time factors after lung transplant in the transplant group.

Data are MT_{QF} expressed in Nm on the x-axes plotted against (i) intensive care length of stay after lung transplant (days), ii) overall hospital length of stay after lung transplant (days), time post-transplant that the participant was assessed for the study (months) and (iv) MT_{QF} expressed as a percentage of predicted torque on the x-axis plotted against length of time (months) post-transplant on the y-axis. The line of best fit is shown. Correlations explored using Pearson's correlation coefficient were as follows: Figure 4.9(i): r = -0.184; p = 0.612. Figure 4.9(ii): r = -0.489; p = 0.152. Figure 4.9(iii): r = 0.073; p = 0.841. Figure 4.9(iv): r = 0.410; p = 0.240. Definition of abbreviations: Maximum torque of the quadriceps femoris (MT_{QF}).

4.7.2 Quadriceps femoris endurance

4.7.2.1 Quadriceps endurance and exercise capacity

Figure 4.10 (i) presents T_{lim} for the nine participants in the TG who completed the QF endurance testing, plotted against 6MWD. No correlation was seen between these variables. Likewise, no correlation was seen between these variables in the CG (see Figure 4.10 [ii]).

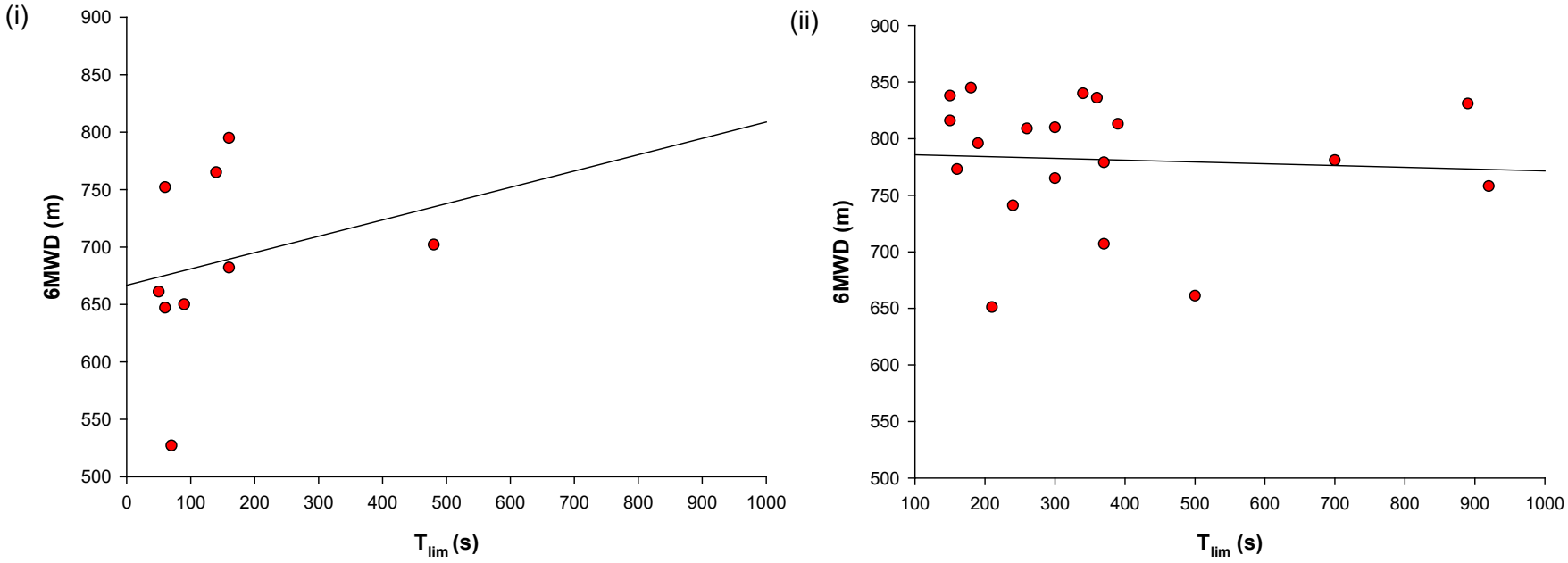


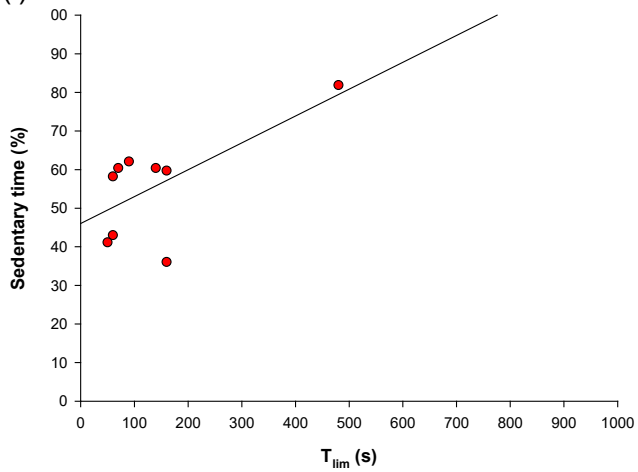
Figure 4.10 Scatterplot of time to task failure during assessment of endurance of quadriceps femoris and six-minute walk distance and in the (i) transplant group and (ii) control group.

Data are T_{lim} (s) on the x-axes plotted against 6MWD (m) on the y-axes. The line of best fit is shown. Correlations are explored using Pearson's correlation coefficient were as follows: Figure 4.10(i): r = 0.462; p = 0.21; Figure 4.10(ii): r = -0.064; p = 0.796. Definition of abbreviations: Six-minute walk distance (6MWD); time to task failure during assessment of quadriceps femoris endurance (T_{lim}).

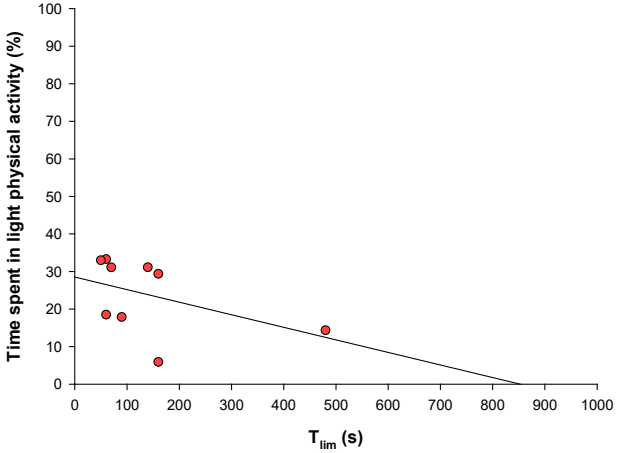
4.7.2.2 Quadriceps femoris endurance and sedentary time, physical activity and daily steps

Figures 4.11 and 4.12 present T_{lim} for all participants in the TG and CG, respectively, plotted against; (i) the percentage of waking hours spent in ST, (ii) the of percentage of waking hours spent undertaking light intensity PA, (iii) the of percentage of waking hours spent undertaking MVPA and (iv) average daily step count. A positive correlation was evident in the TG between T_{lim} and the percentage of waking hours spent in ST. However one participant achieved a T_{lim} of 480 s which was 320 s longer than any other participant in this group. Given that this outlier may have influenced this relationship the analyses were repeated omitting this participants' data (see Figure 4.13). In doing so no correlation between T_{lim} and percentage of waking hours spent in ST was evident. No correlation was seen between the variables explored in the CG (see Figure 4.12).

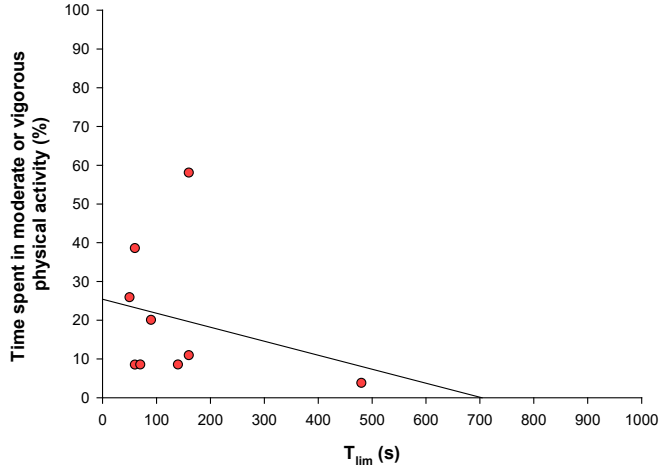
(i)


Sedentary time (%)
00
90
80
70
60
50
40
30
20
10
0
0
100
200
300
400
500
600
700
800
900
1000
T lim (s)

(ii)


Time spent in light physical activity (%)
100
90
80
70
60
50
40
30
20
10
0
0
100
200
300
400
500
600
700
800
900
1000
T lim (s)

(iii)


Time spent in moderate or vigorous physical activity (%)
100
90
80
70
60
50
40
30
20
10
0
0
100
200
300
400
500
600
700
800
900
1000
T lim (s)

(iv)

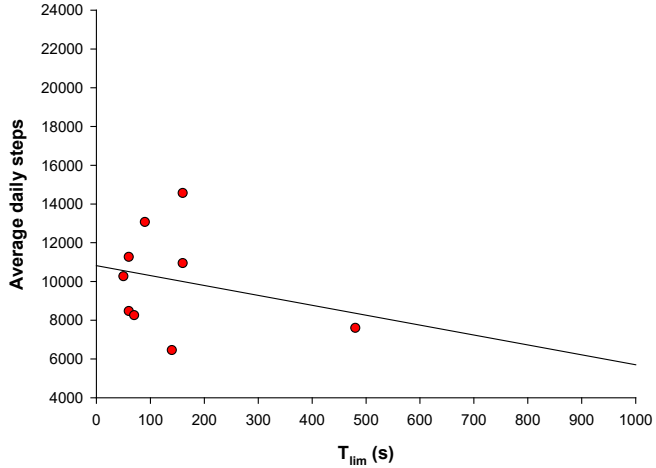
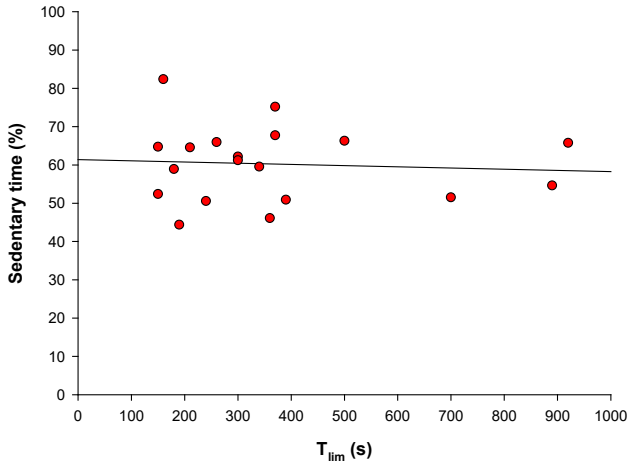

Average daily steps
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
0
100
200
300
400
500
600
700
800
900
1000
T lim (s)

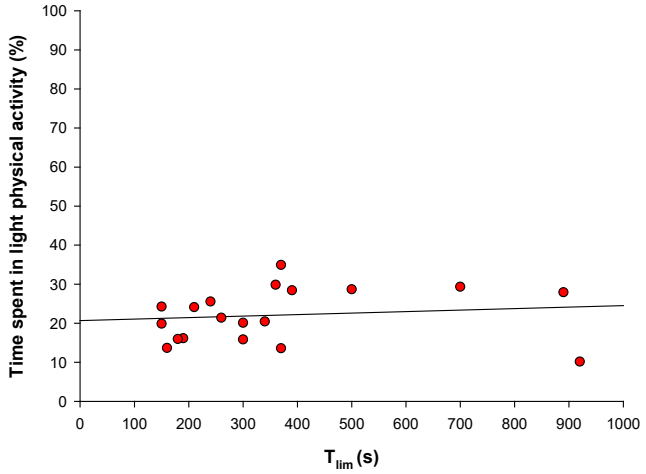
Figure 4.11 Scatterplot of time to task failure during the assessment of quadriceps femoris endurance and sedentary time, time spent, undertaking physical activity of different levels of intensity and average daily steps in the transplant group.

Data are T_{lim} (s) (n = 9) on the x-axes is plotted against; (i) sedentary time, expressed as a % of waking hours, (ii) time undertaking light physical activity, expressed as a % of waking hours, (iii) time spent undertaking moderate or vigorous physical activity, expressed as a % of waking hours and, (iv) average daily steps y-axes. The line of best fit is shown. Correlations explored using Pearson's correlation coefficient were as follows: Figure 4.11(i): r = 0.671; p = 0.048. Figure 11(ii): r = -0.454; p = 0.220. Figure 11(iii): r = -0.271; p = 0.480. Figure 4.11(iv): r = -0.251; p = 0.501. Definition of abbreviation: Time to task failure (T_{lim}).

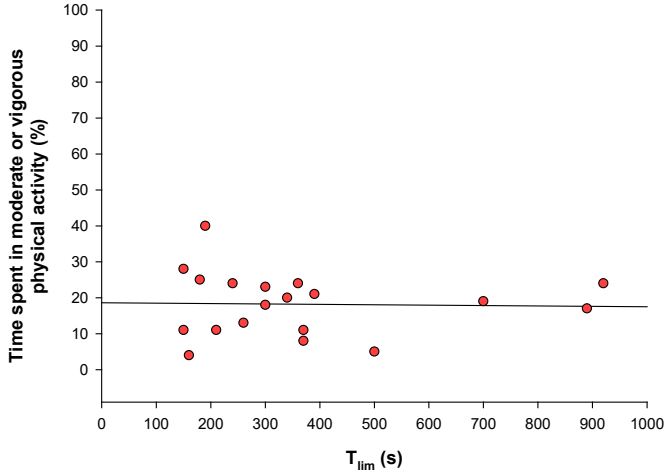
(i)


Sedentary time (%)
T_{lim} (s)

(ii)


Time spent in light physical activity (%)
T_{lim} (s)

(iii)


Time spent in moderate or vigorous physical activity (%)
T_{lim} (s)

(iv)

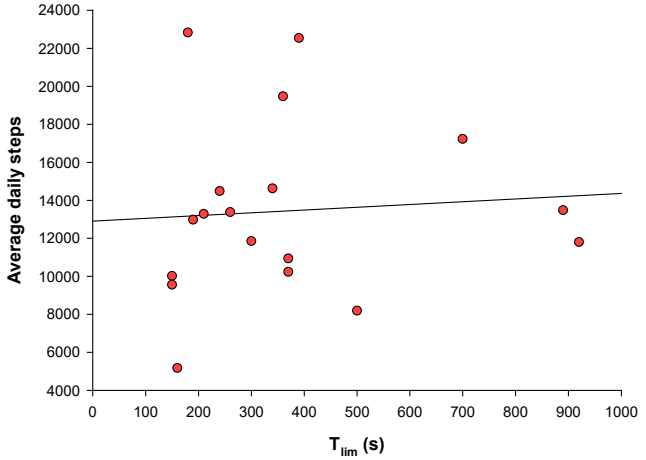
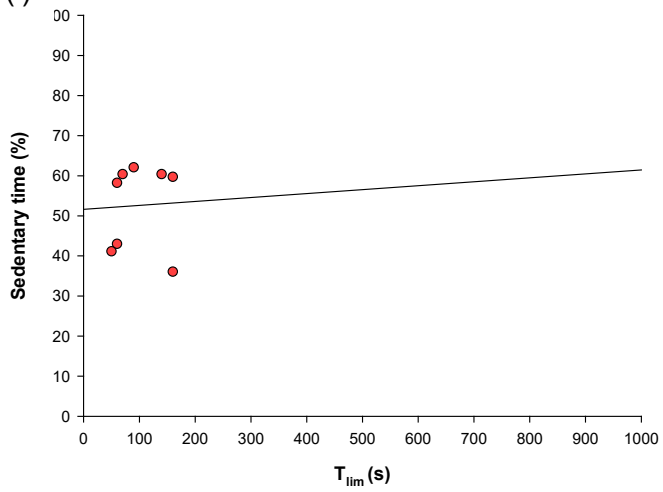

Average daily steps
T_{lim} (s)

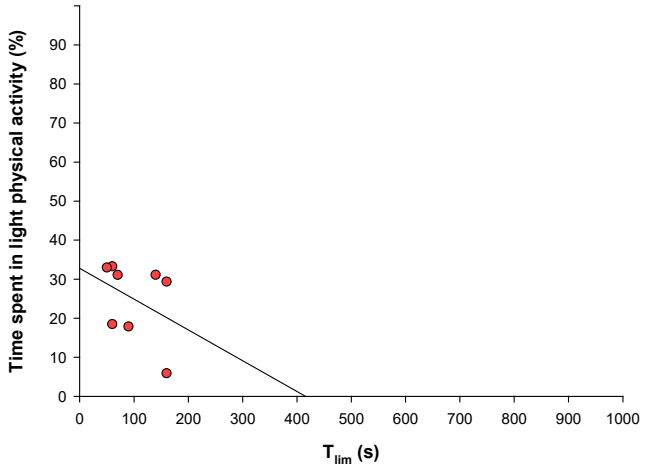
Figure 4.12: Scatterplot of time to task failure during the assessment of quadriceps femoris endurance and sedentary time,time spent, undertaking physical activity of different levels of intensity and average daily steps in the control group.

Data are T_{lim} (s) on the x axes plotted against; (i) sedentary time, expressed as a % of waking hours (n = 19), (ii) time undertaking light physical activity, expressed as a % of waking hours (n = 19), (iii) time spent undertaking moderate or vigorous physical activity, expressed as a% of waking hours (n = 19) and, (iv) average daily steps (n = 18) y-axes. The line of best fit is shown. Correlations are explored using Pearson's correlation coefficient were as follows: Figure 4.12(i): r = -0.075; p = 0.761. Figure 4.12(ii): r = 0.132; p = 0.591. Figure 4.12(iii): r = -0.017; p = 0.944. Figure 4.12(iv): r = 0.075; p = 0.767. Definition of abbreviation: Time to task failure (T_{lim}).

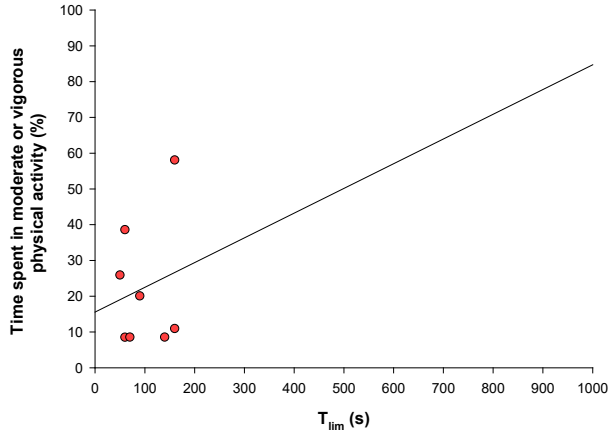
(i)


Sedentary time (%)
0
10
20
30
40
50
60
70
80
90
00
0
100
200
300
400
500
600
700
800
900
1000
T lim (s)

(ii)


Time spent in light physical activity (%)
0
10
20
30
40
50
60
70
80
90
0
100
200
300
400
500
600
700
800
900
1000
T lim (s)

(iii)


Time spent in moderate or vigorous physical activity (%)
0
10
20
30
40
50
60
70
80
90
100
0
100
200
300
400
500
600
700
800
900
1000
T lim (s)

(iv)

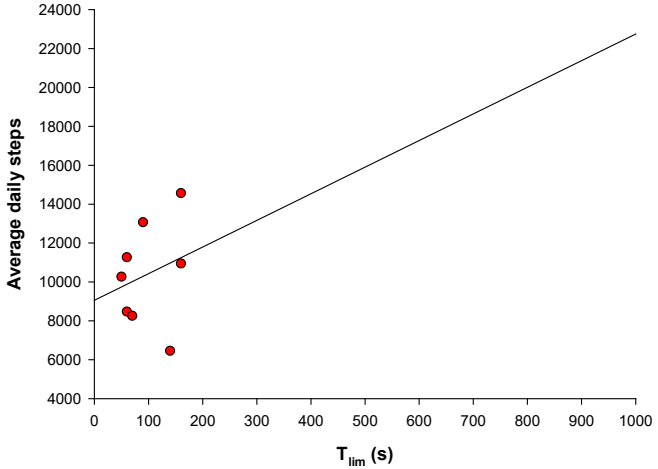

Average daily steps
4000
6000
8000
10000
12000
14000
16000
18000
20000
22000
24000
0
100
200
300
400
500
600
700
800
900
1000
T lim (s)

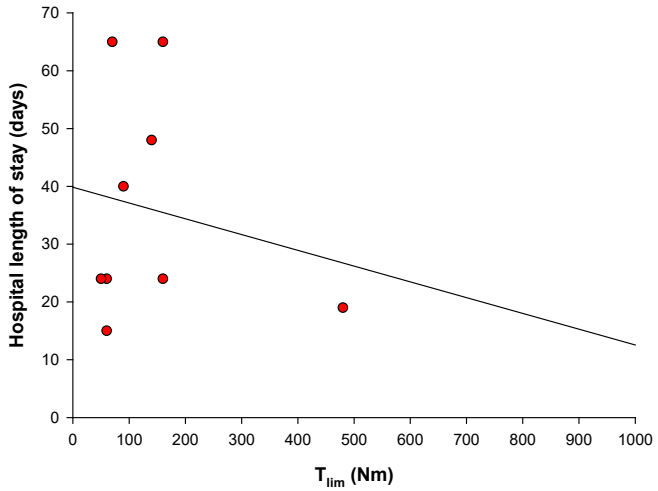
Figure 4.13 Scatterplot of time to task failure during the assessment of quadriceps femoris endurance and sedentary time, time spent, undertaking physical activity of different levels of intensity and average daily steps in the transplant group, after exclusion of the outlier.

Data are T_{lim} (s) (n = 8) on the x-axes plotted against; (i) sedentary time, expressed as a % of waking hours, (ii) time undertaking light physical activity, expressed as a % of waking hours, (iii) time spent undertaking moderate or vigorous physical activity, expressed as a % of waking hours and, (iv) average daily steps y-axes. The line of best fit is shown. Correlations are explored using Pearson's correlation coefficient were as follows: Figure 4.13(i): r = 0.043; p = 0.919. Figure 13(ii): r = -0.375; p = 0.360. Figure 13(iii): r = 0.181; p = 0.668. Figure 4.13(iv): r = 0.242; p = 0.563. Definition of abbreviation: Time to task failure (T_{lim}).

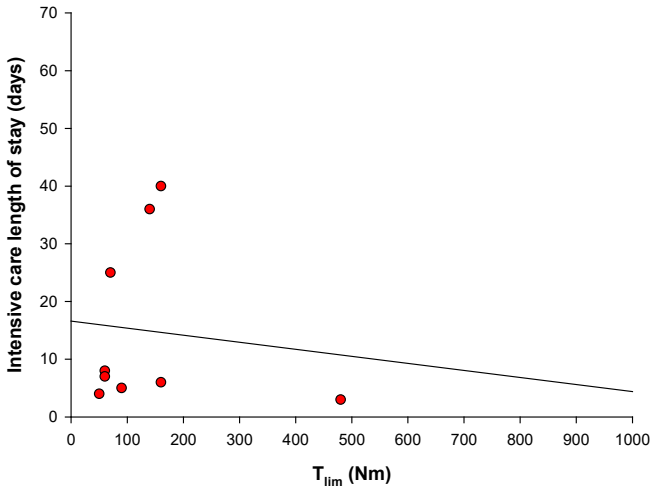
4.7.2.3 Quadriceps femoris endurance and time since lung transplant

Figure 4.14 presents T_{lim} for the nine participants in the TG who completed the QF endurance testing plotted against, (i) the participants post-surgery intensive care length of stay, (ii) the post-surgery overall hospital length of stay and, (iii) the length of time post-transplant that assessment for the study was undertaken. No clear or consistent correlations were seen between these variables.

(i)


Hospital length of stay (days)
0
10
20
30
40
50
60
70
0
100
200
300
400
500
600
700
800
900
1000
T lim (Nm)

(ii)


Intensive care length of stay (days)
0
10
20
30
40
50
60
70
0
100
200
300
400
500
600
700
800
900
1000
T lim (Nm)

(iii)

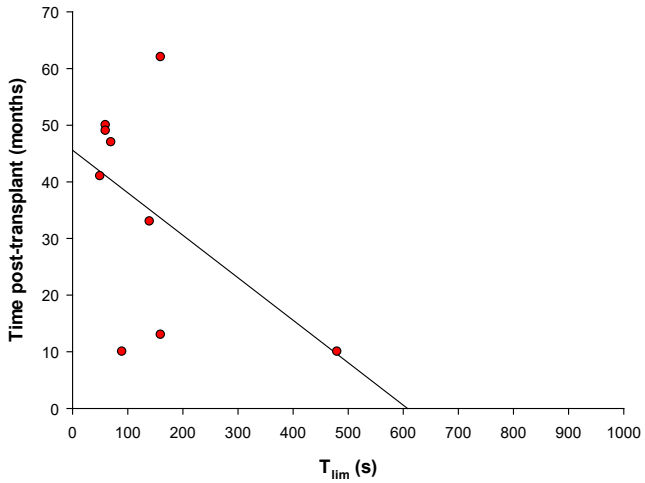

Time post-transplant (months)
0
10
20
30
40
50
60
70
0
100
200
300
400
500
600
700
800
900
1000
T lim (s)

Figure 4.13 Scatterplot of time to task failure during the assessment of quadriceps femoris endurance and time factors after lung transplant in the transplant group.

Data are T_{lim} (s) on the x-axes plotted against (i) intensive care length of stay after lung transplant (days), (ii) overall length of stay in hospital after transplant (days) and, (iii) length of time after transplant that participants were assessed (months) on the y-axes. The line of best fit is shown. Correlations are explored using Pearson's correlation coefficient were as follows: Figure 4.13(i): r = -0.112; p = 0.774. Figure 4.13(ii) r = -0.189; p = 0.625. Figure 4.13(iii) r = -0.515; p = 0.156. Definition of abbreviation: Time to task failure (T_{lim}).

CHAPTER 5 DISCUSSION

The primary goal of this study was to determine whether or not people following bilateral lung transplant (BLT) and heart-lung transplant (HLT) had impaired strength and endurance of quadriceps femoris (QF), relative to healthy peers of similar age and gender proportion. To do this, a cross-sectional, observational design was used whereby data were compared between a transplant group (TG) and a control group (CG). A robust computerised dynamometer was used to measure maximum torque generated by QF. Lean muscle mass was measured using gold standard dual energy X-ray absorptiometry (DEXA) to explore differences in QF strength, after accounting for any between-group differences in muscle mass. Further, to provide some insight into the causes of impairments in strength, the distribution of impairment was compared between QF and the biceps brachii (BB) muscle. In addition to the assessment of strength, endurance of QF was also measured using a standardised assessment adapted from the protocol of Bigland-Ritchie et al (129). The assessment of QF endurance was supplemented with the use of electromyography (EMG) to provide effort-independent data to explore physiological fatigue. Finally, measures were collected of functional exercise capacity, sedentary time (ST) and levels of intensity of physical activity (PA). Relationships were explored between QF strength and endurance and measures of exercise capacity, specifically six-minute walk distance (6MWD), ST and time spent participating in daily PA.

The key findings of this study were:

First, when compared to the CG, those in the TG had impaired strength of the QF and BB muscles, when expressed in terms of torque generated during a maximal voluntary isometric contraction. This impairment in QF and BB strength appeared to be, at least in part, the result of a smaller muscle mass in the TG, as there was no evidence of a difference in strength between groups when differences in muscle mass were considered in the analyses. The impairment in strength was similar between the QF and BB suggesting that there may be a systemic cause to the muscle weakness, such as a side-effect of immunosuppressant medications.

Second, when compared to the CG, those in the TG had reduced endurance of the QF, as measured using two effort-dependent measures of muscle endurance and one effort independent measure of fatigue.

Third, when compared to the CG, those in the TG had a reduction in exercise capacity and showed a tendency to take less steps during daily life.

Finally, in the TG, QF strength rather than QF endurance was associated with functional measures of 6MWD, ST and participation in moderate or vigorous intensity physical activity (MVPA). No association was demonstrated between these measures in the CG.

5.1 Impairments in peripheral muscle strength and muscle mass

This study demonstrated that, in a sample who had undergone BLT or HLT, the maximum torque generated by QF (MT_{QF}) was equivalent to 67% of that generated by healthy people of similar age and gender proportion. A primary assumption of this study was that the lung transplant (LT) recipients had normal or near normal lung function. If this was the case then comparisons of exercise capacity and muscle function can be made without attributing any differences to the impact of poor lung function. Whilst the TG were found to have significantly lower measures of lung function compared to the CG, all participants in the TG had a forced expiratory volume in one second to forced vital capacity ratio ≥ 70%. Indeed the TG in this study were unlikely to have a ventilatory impairment to exercise, and were on average, three years post-transplant and so had ample time to recover their activity levels and condition their peripheral muscles. Although this study recruited adults between 6 months and 5 years post-transplant, this extended time frame is unlikely to have influenced the results as no clear correlation was seen between MT_{QF} and intensive care length of stay after transplant, hospital length of stay after transplant and length of time post-transplant that the participants were assessed for this study (see Section 4.7.1.3). Although the finding of reduced QF strength is consistent with other studies of LT recipients (4-7, 34, 37) this is one of the few studies to confirm this reduction exists by comparing data collected in a control group of healthy people, using identical equipment and assessment protocols, rather than by expressing QF torque as a percentage of that predicted using previously published equations.

The magnitude of impairment measured in the current study is similar to some, but not all, previous reports of the strength of QF following LT. Specifically, consistent with the data reported in this study, earlier work has reported that measures of QF strength following LT often range between 66 and 78% of that predicted in healthy

controls (5, 6, 15, 34, 168). However, the magnitude of impairment reported in this study was less than that reported in one study (7) which also collected measures of MT_{QF} in adults following LT. In this study, the MT_{QF} was equivalent to (mean ± SD) 59 ± 26% of that measured in a healthy population, which is considerably less than observed in the current study. This disparity in the reduction in MT_{QF} between this study and the data presented in the current study does not appear to be related to differences in the equipment or protocols used to assess this outcome. That is, both studies assessed QF using a computerised dynamometer and used the same starting position of 60 degrees of knee flexion. However, in contrast with the current study in which measures of QF were collected, on average, three years following LT, in this earlier study by Maury et al (7), measurements of QF were collected three months after transplant. Given that recovery of QF strength has been demonstrated to occur up to one year following LT (37) it may be expected that the participants in the current study had shown greater natural recovery of QF strength as the measurements were taken closer to three years post-procedure. Further, the disparity between the impairment in maximum torque generated by QF in the current study and this earlier study may also relate to differences in opportunity that the participants were provided to learn the assessment technique. That is, in the current study, participants were provided with ten attempts to produce their maximum QF torque whereas in the study by Maury et al, (7) participants were provided with a minimum of three contractions. Ten contractions allowed the participants more opportunity to learn the assessment requirements and may have optimised the measures of torque achieved in the current study as result. Finally, it is possible that the degree of impairment in the current study was less than that in Maury et al (7) as in this study, the torque required to support the weight of the limb was included in the measure of maximum torque, and it is not clearly described whether this was done in this earlier work.

In addition to a reduction in MT_{QF}, the data in this study also demonstrated a reduction in the maximum torque generated by BB (MT_{BB}). That is, in the TG, the MT_{BB} was equivalent to 76% of that generated by healthy controls of similar age and gender proportion. This is important as few studies have investigated the strength of peripheral muscles other than QF in LT recipients. The one earlier study that has reported on BB strength in LT recipients (n = 108) reported no impairment post-transplant (168). Specifically, BB strength was reported to be (mean ± SD) 99 ± 21% and 102 ± 22% of predicted values at six and 12 months post-transplant, respectively (168). The reasons for this disparity in demonstrating impairment in the

strength of the BB between this earlier study and the current study cannot be explained by the differences in assessment time frames or measurement technique. This is because, compared with the current study which measured MT_{BB} three years post-transplant using a chair-mounted dynamometer, the earlier study measured MT_{BB} at six and 12 months post-transplant and used a hand-held dynamometer. These differences between studies were likely to have reduced BB in the earlier study and would have resulted in greater impairment, which was not the case. Given the scarcity of data reporting on muscle strength other than the QF, further study in this area is needed.

Data in this study demonstrated that the difference in muscle strength between the TG and CG appears to be related, at least in part, to differences in muscle mass. Whilst one study has shown that two thirds of LT recipients return to normal lean muscle mass by two years post-procedure (123) this was not observed in the TG in the current study, for either the QF or BB. That is, data in this study demonstrated that lean muscle mass of the lower and upper limbs in the TG was 79% and 70% respectively of that measured in the CG. Therefore, when MT_{QF} and MT_{BB} were expressed relative to the lean muscle mass measured in the lower and upper limb, respectively, the differences between the TG and CG were negligible.

The finding that the impairment in QF strength may be explained by reductions in muscle mass is in keeping with an earlier finding in people with cystic fibrosis following LT. That is, Pinet et al (15) found maximum QF torques generated were 70% of that measured in a healthy control group matched for age, height and gender, but when expressed per unit of cross-sectional area of the muscle determined using computerised tomography scan (CT) this difference was no longer apparent. Of note however, is that the data in the current study appear to be the first to demonstrate a reduction in lower limb as well as upper limb lean muscle mass in LT recipients. Whilst earlier studies have reported impairments in strength of upper limb muscles in LT recipients (168), the current study extends these findings by showing that these impairments can be explained, at least in part, by a reduction in muscle mass. The impairment of QF and BB strength found in this current study, along with the reduction in lean muscle mass in the respective muscles suggests that systemic factors, such as immunosuppressant medications, are likely to contribute to these impairments.

Aside from muscle mass, changes in muscle quality may also have contributed to impairments of muscle strength seen in this current study. Higher levels of

intramuscular fat infiltration, as determined from CT scan for example, has been shown to be associated with decreased QF strength in the elderly (179). As LT recipients have been shown to have similar levels of intramuscular fat infiltration as people with COPD (13), who have been shown to have greater intramuscular fat infiltration than healthy controls (180, 181), it would seem reasonable that LT recipients may also have increased intramuscular fat infiltration. This study used DEXA to measure muscle mass, but did not undertake measures of muscle quality such as measures of intramuscular fat infiltration, so is unable to add further to this area of the literature.

5.2 Distribution of impairments in muscle strength

Whilst the muscle of primary interest in this current study was QF, BB was assessed to allow comparison with QF, in order to explore whether or not impairments were specific to QF or more generalisable to other peripheral muscles. The theory underpinning this approach was that dysfunction resulting from a systemic process, such as the use of anti-inflammatory or immunosuppressant medications, would produce a similar magnitude of impairment in the strength of all peripheral muscles. In contrast, dysfunction resulting from a local process such as chronic inactivity, would be more likely to produce impairments in the lower limbs, particularly the QF, with relative sparing of other upper limb muscle groups. This theory was proposed in an earlier study of people with chronic obstructive pulmonary disease (COPD) in which the loss in force-generating capacity of the QF was greater than seen in the adductor pollicis (30). The authors concluded that inactivity, rather than a systemic cause, was largely responsible for the dysfunction in the QF in people with COPD.

In the current study, BB was chosen as the muscle to compare with QF as it is characterised by similar anatomical and morphological features, but has a reduced propensity for disuse. That is, both BB and QF are large proximal muscles that work against gravity, and are comprised a similar proportion of Type I and Type II muscle fibres (32). Further, the strength of both QF and BB could be measured using the same equipment; i.e. the HUMAC Norm. However, BB is used for many activities of daily living, whereas QF is primarily used for mobility such as moving from sitting to standing and locomotion. Thus, if disuse from a sedentary lifestyle was the primary reason for impairment in QF, this should result in relative sparing of BB.

Data in this study demonstrated that there was minimal difference in distribution of impairment in muscle strength between QF and BB. Specifically, within the TG, the

difference in the impairment of muscle strength was modest with the maximum torques of QF and BB being 67% and 76% of that measured in the CG, respectively. The ratio of BB to QF strength was similar in both groups (see Chapter 4, Table 4.6). These findings suggest that systemic factors are contributing to muscle dysfunction seen following LT. This conclusion is consistent with data showing that the impairment of QF and BB strength was, at least in part, due to the reductions in muscle mass shown in both muscle groups.

Studies examining the distribution of impairments of muscle strength following LT are scarce. Only one other study has reported measures of QF and BB strength in LT recipients. This study demonstrated that twelve months after LT, there was no impairment in BB strength, which was 101 ± 22% of predicted values, but considerable impairment in QF strength, which was 72 ± 17% of predicted values (168). This finding is in contrast with this current study which suggests little or no difference in the magnitude of impairment in the force generated by these muscles. The discrepancy in findings may have resulted from differences in equipment used. Participants in the former study were assessed using a hand-held dynamometer and as outlined in sections 2.3.1 and 5.5 this method has been shown to underestimate measures of strength, particularly in QF (121). Other studies that have explored differences in the distribution of muscle weakness following LT have used different muscles to BB to compare with QF. For example, one study compared QF with handgrip strength three months after LT and demonstrated greater impairment in QF (59 ± 26% vs. 73 ± 21% of predicted values) (7). Although it is possible that a sedentary lifestyle contributed to the impairment in QF, these data are also consistent with the propensity for corticosteroid medications to selectively impact on proximal rather than distal peripheral skeletal muscles (30). In the current study, both muscles assessed were proximal and the systemic influence of such medications may explain why the similar degrees of impairment in QF and BB strength were found. An earlier study explored the distribution of impairment in muscle strength in recipients between the diaphragm, the abdominals and QF (15) and found QF strength was reduced relative to the strength of the diaphragm and abdominal muscles, even after accounting for muscle size (15). These data suggest that the continuous use of the diaphragm for respiration, and abdominal muscles for postural control, may serve to protect the strength of axial muscles, in people who require long term corticosteroid use. Taken together, the data from this study and the results of earlier work suggest that the distribution of muscle weakness is

influenced by systemic factors (similar impairment in proximal muscles) and also muscle location (distal and axial muscles are less affected than peripheral).

5.3 Impairment in quadriceps femoris endurance

This study used a standardised protocol based on that developed by Bigland-Ritchie et al (129, 160) to evaluate QF endurance in a TG and CG. The intermittent contractions in the protocol are proposed to be representative of the way in which the QF contracts during activities of daily living. Nevertheless, these contractions need to be undertaken at a high force-time product to induce muscle fatigue. The protocol used a long contraction time relative to rest time (i.e. high duty cycle) which served to restrict blood flow to the muscle such that by-products of contraction (e.g. lactate) accumulate and result in muscle fatigue. This original protocol was modified to include maximal voluntary isometric contractions (MVICs) each minute, as outlined by Dolmage and Cafarelli (128). This modified protocol allowed endurance to be quantified using two measures; (i) time to task failure and, (ii) rate of decline of the maximum torque (MT_{QF_end}).

Data in this study demonstrated that the time to task failure (defined in Section 3.5.2.6) in the TG was 30% of that measured in the CG. Furthermore, the rate of decline of QF torque measured during MVICs performed each minute during the protocol was faster in the TG when compared to the CG. In summary, these two findings suggest that the endurance of the QF was reduced in the TG compared to the CG.

The assessment of muscle endurance is complicated and data exploring the endurance of QF endurance in LT recipients are limited. Nevertheless, data from this study are consistent with two previous studies of endurance following LT. That is, Evans et al (125) explored endurance using a protocol that required participants to perform bilateral QF contractions from 90 degrees of flexion to full extension at 0.5Hz with a duty cycle of 0.5 with resistance increased by 0.4 kg at one minute intervals from zero to 2.8 kg. The authors demonstrated LT recipients reached task failure, defined as the inability to maintain either the 0.5Hz cadence or full leg extension for three consecutive efforts, earlier than a healthy control group. After adjusting for difference in age and lean body mass, earlier task failure was found to be still evident. Further, the study by Mathur et al (13) explored differences in endurance between a group of LT recipients and a group of people with COPD using a protocol of sustained QF contraction at 90 degrees of knee flexion with a

target force of 80% of their maximum torque of the QF (MT_{QF}). They demonstrated that the LT group reached task failure faster than the control group suggesting that the impairment in QF endurance was greater in LT recipients than those with COPD. This may suggest that the impairment in muscle function seen in people with COPD is worsened following LT. However this hypotheses needs to be tested in a longitudinal study that takes repeated measures of QF endurance in the same group of people with COPD both before and after a LT.

Data in this current study extend these earlier findings of reduced QF endurance following LT by using EMG to demonstrate a decline in the median frequency of vastus lateralis. In contrast with a reduction in performance during tests that rely on volitional muscle contraction, a reduction in median frequency of this muscle is stronger evidence of physiological fatigue (137, 161, 182, 183). A similar finding of reduction in EMG median frequency in vastus lateralis has been reported in people with chronic heart failure and COPD during the assessment of QF endurance using a protocol that required participants to sustain an isometric contraction at 60% of the maximum torque of the QF ($60\%MT_{QF}$), with task failure defined as a decrease in torque to below $50\%MT_{QF}$ (184, 185). The rate of decline of median frequency in vastus lateralis in the current study was faster in the TG compared to the CG. These findings, together with reports of similar intensity of muscle tiredness and perceived exertion during the test, suggest that the reduction in time to task failure and greater rate of decline in MVIC were unlikely to be due solely to differences in participant effort. Nevertheless, such data do not assist in establishing the possible contribution of central vs. peripheral fatigue.

It was beyond the scope of this study to collect muscle biopsy data and explore differences in muscle structure and histology that may have served to impair muscle endurance. However, earlier work in LT recipients (28, 141) have shown that the QF are characterised by a reduction in the proportion of Type I fibres, impaired calcium and potassium regulation during exercise and a reduction in oxidative enzyme activity. These changes serve to reduce the oxidative capacity of the muscle, which in turn creates an early reliance on anaerobic pathways. The resulting accumulation in lactate impairs muscle contractility and produces premature fatigue and contractile failure.

5.4 Impairments in and relationships between exercise capacity, sedentary time and physical activity and quadriceps femoris muscle function

Data in this study showed that when compared to the CG, those in the TG had a reduction in exercise capacity. Specifically, the 6MWD, was significantly reduced in the TG, with a 6MWD of (median [IQR]) 671 [107] m. This 6MWD was 85% of that measured in the CG, with a 6MWD of 797 [68] m. A reduction in exercise capacity is consistent with other studies that have shown exercise capacity to be reduced in LT recipients, even after completion of rehabilitation programs (4, 6, 7, 16, 34, 88, 92, 168). However in these earlier studies of SLT, BLT and HLT recipients the 6MWD was considerably less (i.e. between 449 m and 590 m) than that reported in the current study. This was not likely to result from differences in ages of the study samples as the mean age of those in these earlier studies ranged from 38 years to 59 years whilst the median age of the current study was 43 years. This disparity in the magnitude of impairment in exercise capacity, as measured by the 6MWD, is likely to result from the participants in these other studies being assessed sooner following LT procedure. Specifically, participants in these earlier studies were assessed between one month and 18 months, compared to 37 months in the current study. Therefore, the participants in the current study had more opportunity for natural recovery and time to optimise their exercise capacity. Additionally, as earlier work has shown that SLT recipients, who may have had ongoing impairments in lung function (80), their inclusion in the earlier studies may have also contributed to the disparity in magnitude of reduction in exercise capacity. Another factor may be that people in Western Australia have been shown to have higher 6MWD than other populations with published regression equations from other countries underestimating the 6MWD measured in Western Australians (186).

Data in this study did not demonstrate any differences in measures of ST or PA between the TG and the CG. The TG tended to be less active than the CG, with the TG taking 3,701 (38%) steps less than the CG. Although this difference did not reach statistical significance other studies have demonstrated significant reductions in the number of steps taken and amount of time participating in moderate intensity PAboth three and 12 months following LT (6, 34). The lack of difference in data pertaining to average daily steps, ST and PA in the current study may reflect small participant numbers and large variability in these measures, factors which compromised statistical power. It is also possible that no difference was seen

between the TG and the CG because the TG were relatively active. For example, the TG were measured as taking (median [IQR]) 9,582 [3,620] average daily steps, which is similar to Western Australian population data collected in 2009 in which females took 9,094 and males took 8,235 average daily steps (187).

In the TG in this current study, measures of QF strength, but not endurance, were associated with several functional outcomes, including 6MWD, ST and time spent undertaking MVPA. Specifically, an association of moderate strength (r = 0.69) was demonstrated between MT_{QF} and 6MWD. Similar associations have been reported between these variables in LT recipients (168) and is also consistent with data in other populations characterised by impaired QF function, such as in people with COPD (119). The relationship between MT_{QF} and 6MWD in people with LT is also supported by data from an earlier study demonstrating that post-operative improvements in QF strength were strongly associated with improvements in exercise capacity up to two years following LT (16). Data in this current study also demonstrated a moderate negative association (r = -0.74) between MT_{QF} and ST (expressed as a percentage of waking hours) and a moderate positive association (r = 0.74) between MT_{QF} and time spent undertaking MVPA (expressed as a percentage of waking hours). These results are supported, at least in part, by an earlier study of LT recipients (6) which showed near normal leg muscle strength in those who participated in higher levels of daily PA. Of note, although MT_{QF} was associated with the time spent undertaking MVPA (expressed as a percentage of waking hours), no association was seen between MT_{QF} and average daily steps. This suggests that QF strength may be more influenced by intensity, rather than quantity of walking-based PA. The finding that MT_{QF} was both negatively associated with ST (expressed as a percentage of waking hours) and positively associated with time spent in MVPA (expressed as a percentage of waking hours) indicates that decreasing ST and increasing time spent in MVPA are lifestyle targets that may optimise QF strength. Nevertheless, it is important to note that coefficients of determination for the relationships between MT_{QF} and these functional outcomes were 55% and 54%, respectively. This suggests that there are factors other than MT_{QF} that contribute to increased ST and reduced participation in MVPA in people following BLT and HLT. Whilst the LT cohort in this study were well, LT recipients may spend more time sedentary and reduce their participation in MVPA for a number of reasons. Examples may include the burden of regular clinic attendance required to monitor lung allograft and general health taking away from time to participate in PA, the development of renal dysfunction and diabetes (55) and,

reported negative symptoms such as nausea and burning or numbness of the feet (105), all of which may result in a lack of ability or motivation to participate in PA, along with usual deterrents such as weather conditions.

Although this study demonstrated reductions in T_{lim} in the TG, associations were not observed between T_{lim} and 6MWD, ST (expressed as a percentage of waking hours) or participation in MVPA (expressed as a percentage of waking hours). One interpretation of these data is that strength, rather than endurance, contributes to the impairments in functional outcomes such as 6MWD, ST and participation in MVPA. However, it is also possible that the lack of relationship between T_{lim} and these outcomes reflected the high variability in T_{lim} and the small participant numbers available for these analyses, which served to compromise the power needed to detect these relationships.

In contrast to the relationships observed in the TG, in the CG, no association was demonstrated between MT_{QF} or T_{lim} with 6MWD, ST (expressed as a percentage of waking hours) or participation in MVPA (expressed as a percentage of waking hours). The 6MWD of the CG in this current study was 797 [68] m, which indicates no impairment and suggests that in people with normal exercise tolerance, the speed achieved during ground-based walking is not limited by QF strength or endurance. Additionally the amount of ST or time spent undertaking MVPA appears not to be impacted by QF strength or endurance.

5.5 Strengths and limitations of this study

This study was cross-sectional and observational in design and as such, these data cannot be used to report on causal relationships. Nevertheless, within the scope of this Masters of Philosophy research project, new information regarding muscle function following BLT and HLT has been found which adds to knowledge in this area of research.

The strengths of this study relate mainly to the methodology used. That is, this study used a rigorous protocol to measure strength of the QF and BB. Participants were provided with a warm-up followed by standardised encouragement and were given ten opportunities to optimise the maximum torque they could generate during strength testing. Similarly a standardised protocol was used during endurance of the QF testing with strong encouragement provided to continue the task as long as possible. Electromyography of vastus medialis and lateralis was used during the

endurance protocol in order to give an effort independent measure of fatigue of the QF.

Assessment of maximum torque of the QF and BB were assessed using robust equipment, the HUMAC Norm dynamometer. This device has been shown to be superior to other measures of muscle torque such as hand-held dynamometry, which has been shown to underestimate maximum torque, particularly in QF (121). An additional advantage to using the HUMAC Norm was that it allowed for the weight of the lower leg and forearm to be accounted for in maximum torques generated. Even though other studies have used such devices, this advantage is not usually specifically described. Specific calibration procedures were followed to ensure measures were accurate.

This study used DEXA, which is well recognised as an appropriate and safe way to measure lean muscle mass. It is preferred to CT scan as it emits only low doses of radiation. To ensure results were comparable all measures were taken on the same machine as it is recognised that variability in results can occur between different machines (25). The machine was calibrated prior to each use.

Two different types of monitors were used in this study to obtain measures of PA. One monitor measured the intensity of the activity undertaken and the second monitor provided an accurate measure of step count.

An important limitation of this study related to the sample size. That is, recruitment to this study did not reach the planned enrolment of 17 people to the TG and the CG. Only ten LT recipients (9 BLT and 1 HLT) and 20 healthy controls were recruited to the study. Technical issues reduced the data available for analyses of QF endurance, and measures of ST and levels of PA. Low participant numbers means that this study is likely to lack power to detect some results and therefore some non-significant findings may represent a Type II error. Small numbers required non-parametric statistics to be used and 95% confidence intervals were not often able to be reported. Therefore the precision around the estimates of the differences was not often clear. When 95% confidence intervals were reported, these were often wide. However, whilst numbers in each group were small the differences in some measures were large. Examples include, T_{lim} which was 200 s shorter in the TG compared to the CG and the rate of decline of maximum torque generated at the start of each minute (MT_{QF_end}) was 75 Nm faster, albeit with a wide confidence interval.

The small sample size may also limit the generalisability of results to the wider LT population. Generalisability of results may be further compromised by the inclusion of 60% of the TG in the current study were being recipients with cystic fibrosis (CF) with recipients with CF tending to be younger than adult LT recipients included in the international transplant registry (188) i.e. median age of the TG was 43 yr in the current study vs. 55 yr in the international transplant registry. Nevertheless, sub-analyses of the transplant group data in this study showed measures of lean muscle mass and muscle strength were similar between the CF and the non-CF LT recipients (see Appendix 6).

Although the length of time post-transplant in the TG was 37 [39] (median [interquartile range] months, three participants were less than 12 months post-transplant. It could be argued that as muscle strength remains reduced in LT recipients, even up to 12 months following LT (12), that these three participants had not had time to recover to their optimal level of strength. However, the absence of any relationship between measures of muscle function (i.e. MT_{QF} and T_{lim}) and intensive care length of stay after LT, hospital length of stay after LT and time post-transplant that participants were assessed suggests that differences in the length of time post-transplant between study participants had little influence on their recovery of muscle function.

During the assessment of QF strength and endurance, there was no attempt made to stimulate the femoral nerve to explore twitch interpolation. Some studies have used electrical (189) or magnetic stimulation (130, 190, 191), including in LT (14), to explore twitch interpolation of QF, which provides insight into the presence of central vs. peripheral fatigue and into the influence of participant effort. As the assessment of muscle strength and endurance in the current study was based on voluntary muscle contractions, it could be argued that reduced torque may simply reflect sub-maximal effort. However, early work has shown that participants can attain maximal force through voluntary effort in both QF (160) and BB (192). To overcome the potential limitations associated with relying on voluntary muscle contractions in the assessment of strength and endurance four strategies were used. First, strong standardised encouragement was given to participants throughout all tests. Second, measures of limb tiredness, shortness of breath and a rating of perceived exertion were collected in both groups. These measures did not differ between the two groups suggesting there was no differences in effort. Third, the study measured endurance in two ways i.e. time to task failure and rate of decline of maximum

torque and these results both demonstrated a reduction. Finally the study used EMG to obtain effort independent physiological measures of fatigue.

A further limitation is that, in order to account for differences in muscle mass between the TG and CG, lean lower limb and upper limb mass were used as a surrogate for muscle mass of QF and BB. It is possible that this approach was too generic and not an accurate reflection of the size of QF and BB.

It is important to acknowledge that in this study no data were collected prior to BLT or HLT. Therefore, it is not possible to comment on the extent of the impairment in muscle function or loss of muscle mass following the BLT and HLT relative to that which might have been evident prior to the LT. This study also did not report the specific details of post-operative course e.g. intensive care length of stay after LT, periods of infection or organ rejection, or rehabilitation undertaken by the LT recipients as this was not possible within the scope of this Masters of Philosophy research project. Further work to explore the impact of rehabilitation before and after LT, infection and rejection on muscle function is required, as is investigation of muscle function in LT recipients who develop bronchiolitis obliterans syndrome (BOS), a group who were excluded from this study.

5.6 Clinical implications and future directions

This study demonstrated that the strength of QF and BB were reduced and the endurance of QF was decreased in the LT recipients studied. The reduction in strength may be mediated by systemic factors and appeared to be the result of a reduction in muscle mass. This reduction in strength was also related to functional outcomes, such as 6MWD, ST and time spent undertaking MVPA. Therefore, these data highlight the importance of targeting increases in muscle mass, to facilitate muscle strength. This in turn may optimise exercise capacity and help to achieve less sedentary and more active lifestyles. It also suggests that systemic factors which compromise muscle mass, such as short courses of high dose steroids, may prompt the need for additional rehabilitation.

Given muscle strength and mass were impaired in both QF and BB, this study suggests that during rehabilitation, there may be a need to optimise muscle strength and mass of large proximal muscles in both the lower and upper limbs, rather than focussing exclusively on the quadriceps. Further, as endurance was also impaired,

exercise modalities that service to optimise both strength and endurance are likely to be of benefit.

Consideration should be given to including, along with measures of lean muscle mass, measurement of muscle strength of large muscles such as QF and BB as part of ongoing assessment of people following LT. The dynamometer used in this study was not portable so whilst it may be useful in a laboratory setting, and has the potential to be used in a gymnasium/rehabilitation environment, it has less utility in hospital ward areas. Alternative methods of measuring strength may need to be explored. Hand-held dynamometry may be appropriate to measure the strength of some muscle groups. However whilst the method has been used to measure QF strength in LT recipients (16), it has been shown to underestimate the strength of QF (121) and lack sensitivity to detect changes in strength in some individuals (193). A seated apparatus that is portable and measures QF strength via a strain gauge may prove a suitable alternative (25).

Whilst there are a number of ways to measure lean muscle mass, not all of these are readily applied in the clinical setting. Bio-electrical impedance may be readily used in the clinical setting however provides only an overall lean body mass, and is not specific to individual muscles. Ultrasound has been used in inpatient and outpatient clinical settings (194, 195). However as DEXA is used to measure LT recipients bone mineral density as part of routine monitoring in some facilities, rehabilitation programs could request the addition of measurement of muscle mass to these testing sessions in order to obtain accurate measures of lean muscle mass of the lower and upper limbs without placing significant additional burden on the LT recipient.

To date, there is a paucity of studies to guide prescription of exercise training in people following LT. Earlier work has shown that high intensity cycling training produces improvements in QF strength in this population (14). Such training is also likely to optimise QF endurance. Although high intensity cycle-based training may place adequate load on the QF to condition this muscle, this mode of training requires access to equipment and has little relevance to activities of daily living. In contrast, many pulmonary rehabilitation programs in Australia focus on walking-based training as this requires no equipment and is highly relevant to daily life (196). Although walking-based exercise is an excellent form of aerobic exercise, and as seen in the general population, is likely to produce health benefits such as reduction in cardiovascular disease (197), earlier work has shown that this type of training

places less specific load on the QF than cycle-based training (30). Therefore, in people following LT, it is unlikely that this form of exercise will condition the QF and additional strategies will be required. High-intensity resistance exercises that challenge both the strength and endurance of the muscles may be advantageous. Given that high intensity gym-based resistance exercises such as leg presses and knee extensions i.e. performed at 40 to 75% of one repetition maximum, even when performed with low repetitions, have been shown to be effective early after LT (93), such training may be useful in the longer term. In addition activities such as stair climbing, step ups and squats to condition QF may be advantageous and are easily replicated in the home environment.

In addition to the effect on peripheral muscle, weight bearing and resistance exercise may also optimise bone mineral content. Osteoporosis and osteopenia are common in LT candidates (66-71, 73) and worsens in LT recipients (67, 72). This loss of bone mineral content was seen in the TG in this current study with the TG having 37% lower bone mineral content when compared to the CG. In LT recipients, improvements in bone mineral density (BMD) of the vertebrae have been demonstrated on completion of an exercise program that required 15 to 20 repetitions of concentric/eccentric back extensor resistance exercises, performed until voluntary muscle fatigue, conducted weekly (75). In people following LT, a study that conditioned the QF using a program of concentric and eccentric exercise, stair climbing and squats, and measured outcomes such as exercise capacity, ST, PA and lower limb BMD would be of great value.

There may be value in considering adjunct therapy to enhance strength and build muscle mass. For example the use of testosterone therapy in combination with strength training has been shown to increase muscle mass with associated muscle fibre hypertrophy in healthy young men (198) and in men with COPD with low testosterone levels (199).

Targeting the strength of muscles during rehabilitation may be even more important in the presence of corticosteroid medications which are well recognised to be deleterious to peripheral muscle mass and strength (15, 120, 142, 143, 200) and are commonly used in LT recipients. Whilst the participants in the TG in this current study were well, 20% of the available cohort of BLT and HLT recipients were excluded as they were unwell with conditions associated with their LT e.g. BOS. It is during these periods of acute rejection that pulses of corticosteroids are often used and at these times reductions in QF strength have been demonstrated (200). Whilst

this current study did not measure this unwell cohort there is evidence that resistance training is beneficial in preventing reductions in QF strength in other acute conditions where higher doses of corticosteroids are also used e.g. acute exacerbations of COPD (201) and there may be benefit in additional QF strength training being undertaken by LT recipients during these times. Further, during periods of acute deterioration, neuromuscular electrical stimulation, which can be applied with minimal ventilatory load, could be considered in order to condition QF (202).

An unexpected finding of this study was the number of BLT and HLT cohort (24%) who were unable to participate in the study because of a physical condition which prevented the assessment of QF strength and endurance and/or 6MWD (e.g. paraplegia, necrosis of the femoral head) and/or BB strength (e.g. sternal instability or BB tendon rupture). This highlights the complexity associated with exercise prescription in this population.

Data from this study suggests that lifestyle targets around reducing ST and optimising the time spent participating in MVPA may be appropriate for this population. Whilst neither the ST nor time spent undertaking different intensities of PA were different between the TG and the CG, earlier work has demonstrated significant differences in the number of steps taken and time spent in MVPA between LT recipients and either matched or population controls (6, 34). Use of devices such as those used in this study to measure ST and time spent participating in MVPA should be considered in LT recipients. Where recommended levels are not met, programs that encourage recipients to have less ST and spend more time participating in MVPA may also assist to condition the QF. Strategies to decrease ST and increase time spent undertaking MVPA are continuing to evolve. Phone coaching has been demonstrated to increase self-reported levels of PA in healthy individuals (203) and step count in people with severe COPD (204). Commercially available pedometers, have been shown to improve daily steps taken (205) and combinations of coaching and the use of a pedometer has been shown to increase daily step count in people with COPD (206). Newer technology such as phone applications that remind people to be active and/or with an inbuilt exercise program may be an alternative and have been used successful to encourage exercise in frail LT candidates (207).

CHAPTER 6 CONCLUSION

The research questions addressed in this study were, in people following bilateral lung transplant (BLT) or heart-lung transplant (HLT);

1. Is the strength of the quadriceps femoris (QF), when expressed as Nm, reduced when compared with healthy controls of similar age and gender?
2. Is the strength of the QF, when expressed as Nm per kilogram of muscle mass, reduced when compared with healthy controls of similar age and gender?
3. Is the strength of the QF (which is affected by local and systemic factors) reduced relative to the strength of the biceps brachii (BB) muscle (which is affected predominantly by systemic factors)?
4. Is the endurance of the QF reduced, when compared with healthy controls of similar age and gender?
5. What component of QF function (i.e. strength vs. endurance) explains a greater proportion of the variance in measurements of functional exercise capacity, sedentary time (ST) and daily physical activity? Are similar relationships seen in a group of healthy controls?

6.1 Research question 1 and 2

The transplant group (TG) in this study had impaired muscle strength of the QF with muscle strength that was 67% of that measured in the control group (CG). However the lean muscle mass of the QF was also reduced in the TG compared to the CG, being 79% of that measured in the CG. When QF strength was expressed per kilogram of muscle mass no difference was seen between the TG and the CG. Given that strength was found to be impaired in the TG and that this appears to be related to the size of the muscle, it is recommended that exercise training programs following lung transplant (LT) focus on building muscle strength and muscle mass.

6.2 Research question 3

Data in this study demonstrated that both QF and BB were similarly impaired in terms of muscle strength, suggesting systemic factors, such as immunosuppressant medication used in LT, may be impacting more than local factors, such as disuse of muscles. Given that immunosuppressant medications are essential for organ survival and are often increased in periods of organ rejection, exercise training

focussed on building strength and muscle mass should target both lower and upper limbs rather than just focussing on QF.

6.3 Research question 4

Studies measuring endurance of the QF in LT recipients are limited and this is only the second study to compare endurance in a group of LT recipients with a healthy control group.

Data in this study showed the endurance of QF was impaired in the TG compared with the CG, with time to task failure (T_{lim}) during assessment of endurance being 70% of that measured in the CG. Additionally the rate of decline of QF torque measured during maximal voluntary isometric contractions performed each minute during the endurance protocol was faster in the TG when compared to the CG. Whilst these differences may reflect reduced participant effort, in the TG measures of perceived effort during the assessment of endurance were similar being groups and physiological measures of muscle function using electromyography provided data showing that reductions in endurance were associated with physiological indicators of muscle fatigue.

6.4 Research question 5

In this study, data demonstrated that in the TG, QF strength, but not endurance, was associated with functional measures including six-minute walk distance (6MWD), sedentary time (ST) and time spent undertaking moderate or vigorous intensity physical activity (MVPA). These associations were not seen in the CG. One interpretation of these data is that strength, rather than endurance, contributes to the impairments in functional outcomes such as 6MWD, ST or time undertaking MVPA. However, it is also possible that the lack of relationship between QF endurance and these outcomes reflected the high variability in the measure of QF endurance and the small participant numbers available for these analyses, which served to compromise the power needed to detect these relationships.

6.5 Other insights

People who undergo BLT or HLT are a complex group and may have significant comorbid conditions. Although it looked as though there was a decent ‘pool’, recruitment to this study was challenging, with a number of LT recipients having had

a complicated post-operative course and/or ongoing significant factors limiting their participation in exercise testing. However, those LT recipients who were recruited were able to tolerate a rigorous assessment protocol involving a range of testing for approximately two hours on two separate occasions nine to 14 days apart, this suggesting that these LT recipients would tolerate strength testing in clinical practice without problems.

Additionally, although impairment in 6MWD was evident in the LT recipients, this impairment was small and therefore, rather than focussing on these measures following LT, more focus could be given to assessing muscle function, as this is an area of considerable deficit for these people.

6.6 Future directions

The study is the first of its kind to be undertaken in a Western Australian cohort. It represents an important first step towards the development of a training strategy that will address the specific deficits in peripheral muscle function and thereby optimise functional outcomes for individuals following BLT and HLT. Whilst this study only included a small number of participants in the TG this is reflective of the complex nature of the LT population. Recruitment to this study was highly selective in including only healthy, well-motivated BLT and HLT recipients who had no comorbidities preventing them from participating fully in all components of the study. Further research is required to determine the effect of different exercise training modalities and prescription on muscle function in this population, in addition to investigating effective optimal exercise training approaches to use in the early post-operative period, and for recipients who develop comorbidities. In addition, given that most studies of muscle function in LT recipients have only small numbers of participants, larger multicentre studies are needed.

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APPENDICES

Appendix 1 Screening tools

Transplant Group Screening Tool

Subject Number: _____

	YES	NO
Inclusion criteria:		
Aged between 18 and 70 years	☐	☐
Exclusion criteria:		
Musculoskeletal (severe arthritis, recent joint replacement, amputee)	☐	☐
Neurological (Stroke, Parkinson's disease, multiple sclerosis, other neurological disorder that would affect ability to be tested)	☐	☐
Cardiovascular (angina on exertion, myocardial infarction)	☐	☐
Resting blood pressure > 150/100mmHg	☐	☐
Resting heart rate > 100 beats per minute	☐	☐
An upper respiratory tract infection within the previous 30 days period	☐	☐
Use of gait aid	☐	☐
Inability to understand English or follow instructions	☐	☐
Leg length discrepancy > 3 cm with abnormal gait pattern	☐	☐
Metal implants (joint replacement, other)	☐	☐
Pregnancy	☐	☐
Obesity (>120kg)	☐	☐

Healthy Group Screening Tool

Subject Number: _____

	YES	NO
Inclusion criteria:	☐	☐
Aged between 18 and 70 years	☐	☐
Forced expiratory volume in one second (FEV_1) ≥ 80% of the predicted normal value and FEV_1 to forced vital capacity ratio ≥ 65%		
Exclusion criteria:		
Smoking history greater than 10 pack-years	☐	☐
History of significant condition that may adversely affect performance:	☐	☐
Musculoskeletal (arthritis, recent joint replacement, amputee, do they walk with a limp, etc)	☐	☐
Neurological (Stroke, Parkinson's disease, multiple sclerosis, ever seen a Neurologist...if so, why?)	☐	☐
Cardiovascular (angina on exertion, previous myocardial infarction, history of arrhythmias, pacemaker, ever seen a Cardiologist...if so, why?)	☐	☐
Respiratory (asthma, COPD, steroid medications, ever seen a Respiratory Physician ...if so, why?)	☐	☐
Resting blood pressure > 150/100mmHg	☐	☐
Resting heart rate > 100 beats per minute	☐	☐
Use of beta-blockers	☐	☐
An upper respiratory tract infection within the previous 30 days period	☐	☐
Use of gait aid	☐	☐
Inability to understand English or follow instructions	☐	☐
Leg length discrepancy > 3 cm with abnormal gait pattern	☐	☐
Metal implants (joint replacement, other)	☐	☐
Corticosteroids Medications	☐	☐
Pregnancy	☐	☐
Obesity (>120kg)	☐	☐

Appendix 2 Participant information and consent form

ROYAL PERTH HOSPITAL

PARTICIPANT INFORMATION SHEET

A study of problems with the thigh muscles in people following lung or heart-lung transplant.

Investigators:

Dr Eli Gabbay, WA Heart-Lung Transplant and Pulmonary Vascular Service

Dr Kylie Hill, Research Fellow, Curtin University of Technology

Dr Sue Jenkins, Associate Professor, Curtin University of Technology

Dr Peter Eastwood, Associate Professor, University of Western Australia

Dr Garry Allison, Physiotherapist, Royal Perth Hospital and Associate Professor, Curtin University of Technology

Ms Carol Watson, Physiotherapist, Royal Perth Hospital, Masters Student, Curtin University of Technology

You are being invited to participate in a research study because either you have previously had a lung transplant or a heart-lung transplant at Royal Perth Hospital or we are asking you to participate as a healthy 'control'. This information sheet explains the study and describes what will be involved should you decide to participate. Please read the information carefully and ask any questions you might have. You may also wish to discuss the study with a relative or friend or your GP.

Study background and purpose

Lung transplant (LTx) or heart-lung transplant (HLTx) is performed for some people with lung problems. After transplant, people describe dramatic improvements in quality of life and symptoms, but continue to have difficulty exercising. They report being inactive during their day-to-day life and this might be due to weak thigh muscles and poor endurance.

This study will compare the strength and endurance of an important thigh muscle, the quadriceps, in people following LTx or HLTx with healthy people, and look at the possible reasons why these muscles might be weakened in people who have had LTx or HLTx. It will also look at whether problems with quadriceps lead to difficulty exercising and low levels of activity during day-to-day life following transplant. It is expected that the study will include 19 people who have had LTx or HLTx and 34 people who have not have LTx or HLTx.

Your role in the study

If you decide to participate in the study, you will be asked to complete **two test sessions**, which will last about 2.5 hours each. One session will be at the Physiotherapy Department at Royal Perth Hospital, Wellington St Perth, and the other at the School of Physiotherapy, at Curtin University of Technology in Bentley.

During these sessions we will record you age, gender, height, weight, ask you about which medications you have taken over the last 12 months, which medications you are currently taking and the date and time of your LTx or HLTx. We will then ask you to complete a simple breathing test and will measure; (i) exercise capacity, (ii) body fat and bone density, (iii) strength and endurance of your thigh muscles and, (iv) strength of an arm muscle (biceps).

We will also measure your physical activity using a small motion sensor over seven days at home.

These tests and measures are described in more detail below in the section "Measurements". None of these additional tests involve needles and are not painful.

Study tests and measurements

Exercise capacity

You will be asked to walk as far as possible in 6-minutes. This is a common test in people with lung problems.

Body fat and bone mineral density

This will be measured using a machine called a DEXA scanner. The DEXA is similar to an X-ray and measures body fat as well as the density of your bones. Radiation from the DEXA is less than 10% of the standard dose of a chest x-ray.

Thigh muscle strength

This will involve straightening your knee with as much force as you can against a machine. This test requires practice to get the most accurate result, so we will ask you to straighten your knee several times (up to 20 times). You will be able to rest in between each practice.

Thigh muscle endurance

This will involve you straightening you knee and resting for specific periods of time until your muscle if too tired to continue. We will put electrodes on your thigh that measure the nerve input to your muscles during this test. These electrodes are painless.

Arm muscle strength

This will involve bending your elbow with as much force as you can against a machine. This test requires practice to get the most accurate result, so we ask you to bend you elbow several times (up to 20 times). You will be able to rest in between each practice.

Physical activity

This will involve wearing a motion sensor device around your right ankle and your right upper arm during waking hours, for 7 days. The devices are small (ankle device is about the size of a match box and armband is similar to an iPod in size) and comfortable to wear.

Health Related quality of life questionnaire

This will involve answering a short questionnaire about your health and well-being. The questionnaire will take 10-20 minutes to complete.

Information from your medical records

We will look through your medical records and record information about your medication dosage and the results of your most recent blood tests.

Possible risks, side effects and discomforts

The following side-effects might occur:

Muscle soreness after the strength and endurance testing (in about 50% of people, lasts less than 72 hours);

Skin irritation under the physical activity monitor (in about 5% of people, lasts less than 24 hours);

Problems such as dizziness or chest pain during the walking test (extremely rare).

What if something goes wrong?

In the event that you suffer an expected or unexpected side effect or medical accident during this study that arises from your participation, you will be offered all full and necessary treatment by Royal Perth Hospital. The Ethics Committee has approved this study on the basis (amongst others) that the reported risk of such an event is either small or acceptable in terms of the risk you face as a result of your current illness.

How your personal information will be handled

Several parties have an interest in the results of the trial and will be permitted to handle your data. These include the researchers at Royal Perth Hospital and Curtin University of Technology. Because of this wider circle, special arrangements are in place to ensure that your data is handled in strict confidence and in compliance with all privacy laws (in Australia, this is the Privacy Act 1988). Your name will not appear on trial documents and only duly authorised persons will have access to your data. Your name will not appear on any document or publication.

Cost of participation in the trial

Participation in the study will be at no cost to you and we will re-imburse you reasonable expenses for travel and parking associated with study visits.

Voluntary participation and withdrawal

Participation in this study is entirely voluntary. You do not have to participate and your decision to participate or not will in no way affect your current or future care at RPH. You are also free to withdraw from the study at any time without reason or justification.

Study contacts and further information

If you have questions about this study, please contact Dr Eli Gabbay on phone (08) XXXX XXX, Dr Kylie Hill on (08) XXXX XXXX or Carol Watson (08) XXXX XXXX.

This study has been approved by the Royal Perth Hospital Ethics Committee. If you have any concerns about the conduct of the study or your rights as a research participant, please contact Prof Frank van Bockxmeer, Chairman of the RPH Ethics Committee, on phone (08) XXXX XXXX and quote the ethics approval number (EC 2009/120).

ROYAL PERTH HOSPITAL

CONSENT FORM

A study of problems with the thigh muscles in people following lung or heart-lung transplant.

Investigators:

Dr Eli Gabbay, WA Heart-Lung Transplant and Pulmonary Vascular Service

Dr Kylie Hill, Research Fellow, Curtin University of Technology

Dr Sue Jenkins, Associate Professor, Curtin University of Technology

Dr Peter Eastwood, Associate Professor, University of Western Australia

Dr Garry Allison, Physiotherapist, Royal Perth Hospital and Associate Professor,

Curtin University of Technology

Ms Carol Watson, Physiotherapist, Royal Perth Hospital, Masters Student, Curtin University of Technology

I,..... agree to participate in the above study. I have read and understood the attached Information Sheet and I have retained a copy of the signed document. I have been given the opportunity to ask questions about the study by the investigator. I understand that I may withdraw from the study at any time without affecting any future medical treatment (if necessary), or the treatment of the condition which is the subject of the trial (where appropriate).

I understand that the investigator and sponsor of the trial will adhere to usual standards of confidentiality in the collection and handling of my personal information and that the standards of the Privacy Act 1988 will apply to the way my information is handled.

Signed.....
Date.....

Signature of Investigator.....
Date.....

Appendix 3 Instructions to participants for each assessment session

Study of problems with thigh muscles in people following lung or heart lung transplant.

Instructions to Participants

Session 1

Venue: Royal Perth Hospital Physiotherapy Department Nicolay Block Level 3.

Parking: Parking is available in Moore Street Carpark which has a direct access pathway through to the North Block of the Hospital which then links via an overpass to South Block; Alternative parking is available at Pier Street Carpark or Murray Street adjacent to the Old Fire Station however this parking is further away.

Public Transport: Buses to the city are available, and McIver Train Station is located adjacent to the hospital and connected via a covered walkway and lifts.

Appointment Date/Time: _____

Tests to be completed

- General interview about your health, medications etc
- Spirometry – breathing test to assess your lung volumes
- Height/Weight
- Health-Related Quality of Life Survey
- 6 Minute Walk Test – this is completed twice with a rest in between. You will be required to wear a monitor during this test which is worn around your chest under your clothes. A thick gel is applied to the monitor to ensure contact with your skin. You will also have a monitor placed on your finger which measures oxygen levels in your blood. For this to work properly your fingernails must be free of nail polish.
- Activity Monitoring – education about devices to be worn

What to wear: Comfortable loose fitting clothes, good walking shoes or joggers.

Other instructions: Do not have a heavy meal and avoid caffeine for at least 2 hours prior to the test.

How long will the tests take: Approx 2 hours

Session 2

Venue: Curtin University School of Physiotherapy Building Number 408 (see map provided)

Parking: Bays are reserved for research participants close to the building (see map provided). You will be provided with a 'ticket' at Session 1 which is to be placed on your dashboard in full sight. Parking bay numbers are painted on the ground. If for some reason the bay allocated to you is occupied please park in any empty bay, if you have a pen handy note that the bay allocated was occupied on the permit, leave the permit on your dashboard in full sight and advise me on your arrival.

Report to Reception Level 3. You will be met by a Research Assistant, Ms Nikki Newton who will take you to the testing room. Part of the testing is also to be conducted in another building – Building 404. We will take you to this testing venue.

Appointment Date/Time: _____

Tests to be completed

- Activity monitoring – Return the devices for capturing of data collected.
- DEXA scan
- Humac Muscle strength and endurance of quadriceps (thigh) muscle
- Humac Muscle strength of biceps brachii (upper arm) muscle

What to wear for the test: In order to align some of the knee machine with your knee joint accurately and to be able to fix the sticky electrodes on your thigh muscle it is recommended that you wear shorts for the muscle tests. For the DEXA scan it is important that you do not have any metal on during the scan e.g. jewellery, belts, bras. We will provide you with a gown to wear during this test if necessary.

Other instructions: One of the muscle tests requires some time to set up and position you correctly. The actual test requires you to be supported firmly in the seat and to do this we will use a seatbelt. The seatbelt is adjusted firmly across your lower pelvis/hips. Given the testing may take some time you will feel more comfortable if you go to the toilet before commencement of the test. Toilets are located opposite the lifts on Level 3 of the building (the knee machine is on Level 4). You will be able to take a break between each major component of the muscle tests. Avoid stair climbing on the day of these tests.

How long will these tests take: Approx 2 - 3 hours

If you have any concerns or need to contact me I can be contacted via the Physiotherapy Department at Royal Perth Hospital phone (08) XXXX XXXX or via my personal mobile _____.

Carol Watson

Appendix 4 Calibration procedure for HUMAC Norm: Expected and measured torques by date of assessment

Date	Expected Value ft lbs	Measured ft lbs	% Error	% Full Scale error
08/02/2011	155	155.4	0.1	0
02/05/2011	151	151	0	0
20/07/2011	151	151	0	0
29/07/2011	151	151.1	0.1	0
30/09/2011	151	150.9	0.1	0.2
11/11/2011	151	150.9	0	0
25/11/2011	151	150.9	0.1	0
12/01/2012	151	150.9	0.1	0
20/01/2012	151	150.9	0	0
08/02/2012	151	151	0	0
16/03/2012	151	150.9	0.1	0
23/03/2012	151	151	0	0
29/06/2012	151	151	0	0
17/07/2012	151	150.8	0.1	0.1
30/07/2012	151	151	0	0
24/08/2012	151	150.9	0.1	0
31/08/2012	151	151	0	0
10/09/2012	151	151.1	0.1	0
17/05/2013	151	150.9	0	0
24/05/2013	151	150.9	0	0
02/08/2013	151	150.9	0.1	0
23/08/2013	151	150.6	0.1	0.2
12/09/2013	151	150.8	0.1	0
20/09/2013	151	151	0	0
26/09/2013	151	151	0	0
11/10/2013	151	150.8	0.1	0

Appendix 5 Predicted six-minute walk distance in the transplant and control groups

Group	Age	Sex	Predicted 6MWD (m)[a]	6MWD (m)	6MWD% pred
Transplant	34	M	767.14	752	98.03
	52	M	713.32	702	98.41
	25	M	794.05	795	100.12
	49	M	722.29	661	91.51
	40	M	749.2	765	102.11
	58	F	692.39	649	93.73
	25	F	791.06	650	82.17
	49	F	719.3	682	94.81
	31	F	773.12	647	83.69
	47	F	725.28	527	72.66
Control	58	M	695.38	758	109.01
	32	M	773.12	798	103.22
	57	M	698.37	810	115.98
	30	M	779.1	816	104.74
	43	M	740.23	781	105.51
	22	M	803.02	845	105.23
	21	M	806.01	838	103.97
	50	M	719.3	779	108.30
	29	M	782.09	765	97.81
	49	M	722.29	773	107.02
	37	M	758.17	741	97.74
	50	F	716.31	831	116.01
	26	F	788.07	836	106.08
	24	F	794.05	809	101.88
	52	F	710.33	707	99.53
	29	F	779.1	840	107.82
	52	F	710.33	651	91.65
	55	F	701.36	813	115.92
	61	F	683.42	661	96.72
	21	F	803.02	796	99.13

*Definition of abbreviations: Six-minute walk distance (6MWD). [a]Predicted 6MWD = 868.8 - [Age*2.99] - [Sex*74.7] where best 6MWD is expressed in metres, age is in years and sex is "female (F) = 1" and "male (M) = 0"; r = 0.64, r^2 = 0.41, p < 0.001 (157).*

Appendix 6 Comparison of measures of muscle strength and mass between participants in the transplant group with cystic fibrosis and those without cystic fibrosis

	Cystic fibrosis group (n = 6)		Non-cystic fibrosis group (n = 4)		p-value*
	median [IQR]	min to max	median [IQR]	min to max	
MT_{QF} (Nm)	210.3 [86]	118.9 to 239.2	138.6 [31.5]	107.0 to 148.6	0.11
MT_{BB} (Nm)	43.7 [24.0]	28.1 to 58.8	26.6 [26.9]	21.3 to 48.1	0.17
Lean lower limb mass (kg)	7.1 [2.1]	5.7 to 8.1	6.3 [2.3]	5.4 to 8.1	0.48
Lean upper limb mass (kg)	2.1 [0.6]	1.7 to 2.7	1.9 [1.1]	1.7 to 2.8	0.35

*Definition of abbreviations: Interquartile range (IQR). *Differences between groups assessed using Mann-Whitney U tests.*

Appendix 7 Predicted maximal torque of quadriceps femoris in the transplant and group groups

Group	Age	Sex	Weight (kg)	Predicted MT_{QF} (Nm)[a]	MT_{QF} (Nm)	MT_{QF} % pred
Transplant	34	M	57	206.22	221.72	107
	52	M	83	212.72	139.29	65
	25	M	61	233.23	220.33	94
	49	M	79	212.23	239.22	113
	40	M	54	187.62	200.23	107
	58	F	78	134.66	148.59	110
	25	F	48	154.19	118.93	77
	49	F	56	115.75	137.97	119
	31	F	70	180.09	147.07	82
	47	F	64	135.05	107.01	80
Control	58	M	72	179.88	168.32	94
	32	M	78	248.02	295.00	136
	57	M	73	183.87	189.8	103
	30	M	70	237.31	263.45	111
	43	M	89	243.29	310.57	128
	22	M	94	299.13	338.4	113
	21	M	50	167.48	193.29	115
	50	M	80	212.69	321.93	151
	29	M	60	221.90	218.55	98
	49	M	100	248.90	351.70	141
	37	M	110	293.93	302.39	103
	50	F	67	132.76	133.68	101
	26	F	63	178.68	175.55	98
	24	F	73	201.26	273.85	136
	52	F	70	133.68	119.65	89
	29	F	56	159.59	223.64	140
	52	F	66	126.56	168.44	133
	55	F	70	127.05	157.94	124
	61	F	67	108.45	167.00	154
	21	F	50	167.48	193.29	115

Definition of abbreviations: Maximal torque of the quadriceps femoris (MT_{QF}).
*[a]Predicted MT_{QF} = (-2.21*age) + (55.9*sex) + (1.78*weight) + 124 where MTQF is expressed in Nm, age is in years and sex is "female (F) = 0" and "male (M) = 1" (119).*