PERIPHERAL MUSCLE STRENGTH, FUNCTIONAL EXERCISE CAPACITY AND PHYSICAL ACTIVITY BEFORE AND AFTER LUNG TRANSPLANTATION

by

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A thesis submitted in conformity with the requirements for the degree of Masters of Rehabilitation Science
Graduate Department of Rehabilitation Sciences
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Abstract

Little is known about the early recovery of functional outcomes in the lung transplant population. This thesis investigated skeletal muscle strength, functional exercise capacity, health-related quality of life and daily physical activity pre- and early post-lung transplantation in a cohort of fifty participants.

Significant functional limitations were observed pre-transplant, however levels of physical activity were higher on rehabilitation days as compared to non-rehabilitation days. Post-transplant, improvements in functional exercise capacity and physical activity lagged behind the early improvements in pulmonary function and health-related quality of life. Muscle strength was reduced at hospital discharge compared to pre-transplant levels, but improved to pre-transplant levels by three months post-transplant.

In summary, significant functional limitation exists pre-transplant, and lung transplantation leads to significant improvement of functional outcomes; however functional recovery occurs at different time periods and to varying degrees, and does not reach levels of a healthy reference population by three months post-lung transplant.
Dedication

To my children, Ryan & Reid

and to their future success in academia
Acknowledgments

*Without inspiration the best powers of the mind remain dormant, there is a fuel in us which needs to be ignited with sparks.*

_Johann Gottfried Von Herder (1744-1803)_

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Keywords

**ANOVA** – analysis of variance

**BMD** – bone mineral density

**BMI** – body mass index

**BODE index** – body-mass index, airflow obstruction, dyspnea and exercise capacity

**BORG** – Borg scale of perceived exertion

**BOS** – bronchiolitis obliterans syndrome

**CF** – cystic fibrosis

**COPD** – chronic obstructive lung disease

**D\textsubscript{LCO}** – diffusing capacity for carbon monoxide

**DLTX** – double lung transplant

**FEV\textsubscript{1}** – forced expiratory volume in one second

**FVC** – forced vital capacity

**GOLD** – Global Initiative for Chronic Obstructive Lung Disease

**HGF** – hand grip force

**HLTX** – heart-lung transplant

**HRQOL** – health-related quality of life

**ICU** – intensive care unit

**ILD** – interstitial lung disease

**IPF** – idiopathic pulmonary fibrosis
IQR – interquartile range

LOS – length of stay

MET – metabolic equivalent

MVPA – moderate-vigorous physical activity

PH – pulmonary hypertension

QT – quadriceps torque

RR – respiratory rate

SAS – statistical analysis software

SD – standard deviation

SF-36 – Medical Outcomes Short Form

SGRQ – St. George’s Respiratory Questionnaire

SpO₂ – percent saturation of hemoglobin with oxygen as measured by pulse oximetry

SLTX – single lung transplant

TLC – total lung capacity

VO₂PEAK – peak oxygen consumption

VO₂MAX – maximal oxygen consumption

6MWD – 6-minute walk distance

6MWT – 6-minute walk test
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Chapter 1
Introduction and Literature Review

1.1 INTRODUCTION

The aims of this thesis are to quantify and investigate the relationships between muscle strength, functional exercise capacity, health-related quality of life and daily physical activity in individuals before and after lung transplantation. The research objectives fit within the World Health Organization’s International Classification of Functioning, Disability and Health (ICF) conceptual framework of disability in the classification of the consequences of disease from different perspectives including the body (body function and structure) and the individual and society (activity and participation) (Figure 1-1). Measuring different domains of function allow the examination of the relationships between body impairment (e.g. lung function, peripheral muscle strength), and activity limitations and participation restrictions (e.g. functional exercise capacity, spontaneous daily physical activity, self-reported physical functioning and physical roles) during the pre- and early post lung transplant period.

The goals of rehabilitation in optimizing functioning and health aim to minimize symptoms and disability through the treatment of impairments, overcoming restrictions and preventing further limitations in function. The majority of research examining exercise capacity and physical activity following lung transplantation have compared transplant recipients to a healthy control group or “normal” reference values, and have shown lower than age-predicted levels of functioning. Although the primary lung impairment is largely removed following lung transplantation, transplant recipients can experience other systemic and peripheral changes as a consequence of years of chronic disease as well as new challenges including side-effects of medications and complications from the surgical procedure which may prevent the normalization of functioning.
The functional potential of lung transplant recipients is not known, and factors that contribute to functional recovery are not fully elucidated. The identification of factors that impact functional potential could assist in targeting rehabilitation interventions to maximize functional outcomes following lung transplantation. The translation of changes in lung function, skeletal muscle strength, functional exercise capacity and health-related quality of life into a physically active lifestyle and participation in society is an important outcome in the long-term management of lung transplant recipients.

Leidy describes four different dimensions of functional status (functional capacity, performance, reserve and capacity utilization), where performance is a function of capacity, but capacity alone does not determine performance. The alleviation of the primary lung impairment and improvement in exercise capacity will significantly increase overall capacity and reserve, yet behaviour patterns, environmental, societal and lifestyle issues may dictate performance such as levels of spontaneous physical activity. The ICF model incorporates an individual’s functioning and health behaviour into a context that considers personal and environmental factors. Gender and an age ranging from eighteen years into the late seventies, may influence levels of activity and participation in the adult lung transplant recipient. Other factors such as expected or desired roles, societal norms, cultural values and lifestyle prior to chronic disease may have an impact on physical activity and participation beyond physiological measures of pulmonary function or exercise capacity.

This chapter will summarize the literature of functional limitations of exercise capacity, muscle strength, health-related quality of life and physical activity in lung transplant candidates and recipients, and outline the overall objectives, hypotheses and scope of this research.
1.2 LUNG TRANSPLANTATION

Lung transplantation is an established treatment for a variety of end-stage lung diseases to increase function, health-related quality of life (HRQOL) and survival. The main indications for lung transplant include chronic obstructive pulmonary disease (35%), interstitial lung disease (23%), cystic fibrosis (17%), alpha 1 anti-trypsin deficiency (6%) and pulmonary arterial hypertension (3%). Data from the latest International Society of Heart and Lung Transplantation (ISHLT) registry show that the reported number of lung transplants performed worldwide is steadily increasing, with 3272 reported procedures performed in 2009. Survival rates, primarily short-term survival, are improving and are reported as 79% at one year, 64% at three years, 53% at five years and 30% at ten years, with an overall median survival of 5.5 years. Over the past decade, the mean age of recipients has consistently increased, as well as the
number of transplant recipients over 65 years. In 2000, 1.6% of recipients were over 65 years, and in 2010 this figure increased to 12%. Common morbidities reported among 1- and 5-year survivors include hypertension, renal dysfunction, hyperlipidemia, diabetes and bronchiolitis obliterans syndrome (BOS). BOS is also the leading cause of long-term mortality.

Pulmonary function improves significantly following lung transplantation. In single lung transplant recipients, change in lung function will partially depend on the native lung pathology (i.e. a restrictive defect in restrictive lung disease, and an obstructive defect in obstructive lung disease). Recipients of a double lung transplant generally reach a low normal range with FEV$_1$ of 75-85% predicted.

1.2.1 Limitations to exercise pre-lung transplantation

Lung transplant candidates demonstrate severely limited maximal exercise capacity (VO$_2$peak of 24-34% predicted) and low maximum workload which are attributed to ventilatory limitations, abnormalities in gas exchange, and in some individuals an element of circulatory impairment. Skeletal muscle changes are also present in chronic lung disease including decreased muscle mass, strength and endurance, increased fatigability and a greater reliance on anaerobic metabolism. Factors contributing to decreased muscle function can include poor nutritional status, corticosteroid use, oxidative stress, systemic inflammation, exacerbations of the disease, deconditioning, aging and co-morbidities.

1.2.2 Limitations to exercise post-lung transplantation

In a cross-sectional analysis of functional status from the ISHLT registry, over 80% of lung transplant recipients report no activity limitation at one, three and five years. Although significant improvements of 1.5- to 2.0-fold increase in maximal exercise capacity and work rate are observed following lung transplant, cardiopulmonary exercise testing consistently reveals a low peak work rate, reduced VO$_2$peak of 40-60% of predicted levels and an early lactate threshold. These deficits are observed in the absence of abnormalities in gas exchange, or ventilatory or cardiovascular limitations, indicating a peripheral limitation to exercise.
Exercise is terminated at a similar intensity and symptoms regardless of pre-transplant lung disease or transplant procedure.\textsuperscript{11,12,22} Investigations of peripheral muscle function demonstrate decreased muscle mass and strength, reductions in type I (oxidative) muscle fibres, decreased calcium uptake and release, a low resting intracellular pH and an earlier drop in muscle pH, decreased potassium regulation with exercise, decreased mitochondrial enzyme activity, and impaired oxidative capacity with a greater reliance on anaerobic metabolism for energy.\textsuperscript{15,17,19,23,26-29}

In addition to the systemic effects of pre-transplant lung disease contributing to skeletal muscle dysfunction, additional post-transplant factors including prolonged immobilization and possible critical illness myopathy during the peri-operative period, nutritional status, immunosuppressive medications, episodes of infection and rejection and a sedentary lifestyle may further increase muscle dysfunction and/or impair full recovery of the peripheral muscles and consequently exercise capacity. The role of the potentially myotoxic effects of immunosuppressive medications is thought to be a major contributing factor. Chronic use of glucocorticoids is known to result in a selective atrophy of Type IIb muscle fibers and decreased force-generating capacity.\textsuperscript{30} Calcineurin inhibitors such as Cyclosporine A and Tacrolimus have been shown to inhibit skeletal muscle mitochondrial respiration and endurance exercise time in rats.\textsuperscript{31,32} In addition, kidney, liver and heart transplant recipients who take similar medications following transplant have a similar exercise profile to lung transplant recipients including a decreased VO\textsubscript{2}peak, early anaerobic threshold and absence of significant cardiovascular or ventilatory limitations.\textsuperscript{33-35}

1.2.3 Rehabilitation pre-lung transplantation

A recent national survey on rehabilitation programs for organ transplant populations in Canada report that the majority of lung transplant centres offer pre-transplant rehabilitation, and in four out of five centres that offer rehabilitation this is a mandatory component of the pre-transplant care.\textsuperscript{36} Pre-transplant rehabilitation programs often are based on pulmonary rehabilitation guidelines and use similar outcome measures.\textsuperscript{36} Despite the prevalence of pre-transplant rehabilitation, there has been little research studying its effects. Only one study with nine lung
transplant candidates found that participation in either an education program or an education program plus exercise improved quality of well-being and 6-minute walk distance (6MWD).  

1.2.4 Rehabilitation post- lung transplantation

Rehabilitation is a standard component of post-transplant care in many lung transplant centres. A systematic review of seven studies examining exercise training in lung transplant recipients showed that exercise was effective in improving maximal and functional exercise capacity, skeletal muscle function, bone mineral density and health-related quality of life. These studies used a variety of study designs, outcome measures (lumbar bone mineral density, 6MWD, quadriceps torque (QT), hand-grip force (HGF), health-related quality of life (HRQOL), maximal exercise capacity, endurance time, hemodynamic responses to exercise and mitochondrial bioenergetics), exercise interventions (aerobic exercise, aerobic with resistance exercise, and lumbar resistance exercise) and exercise prescription (frequency, intensity, duration). Significant improvements in outcomes were found in every study and no adverse effects were reported. The length of time after transplantation before exercise interventions were initiated varied from as early as one month post-transplant to more than six months post-transplantation.

It is difficult to separate the effects of exercise training post-lung transplant with the natural recovery process that could occur with the gradual return to normal activities following lung transplantation. Due to the prevalence of post-transplant rehabilitation as a standard part of medical care in the early post-transplant period in Canada, a randomized study design could be ethically challenging at this time. Stiebellehner and colleagues compared exercise capacity after a period of normal daily activities in nine lung transplant recipients and found that normal daily activities had no effect on exercise performance, whereas a subsequent six week aerobic endurance training program significantly increased submaximal and peak exercise performance in the same group of lung transplant recipients. Since the participants were between 6-18 months post-transplant, it is likely that any natural recovery would have already occurred.

Since the publication of this systematic review on exercise training after lung transplantation, three studies have been published that have examined exercise training in lung transplant
recipients. Ihle and colleagues compared inpatient rehabilitation (23 day length of stay) with structured outpatient physiotherapy in 60 stable, long-term survivors of lung transplantation (mean 4.5 years post-transplant). Both groups showed significant increases in maximal and submaximal exercise capacity, with no difference between the two groups. Vivodtzev and colleagues studied 12 stable lung transplant recipients with healthy controls to examine the effects of three months of home-based endurance training with a cycle ergometer (39 sessions), and to examine any differences between responders and non-responders in the lung transplant group. Muscle strength and percentage of quadriceps type I fibres differed significantly between healthy controls, responders (n=6) and non-responders (n=6). In responders, there was a significant increase in VO$_2$-peak, endurance time and percentage of quadriceps type I fibres that showed a similar level of improvement from baseline as the healthy controls, but still remained below predicted levels. Non-responders did not improve on any functional parameters. All transplant recipients had received four weeks of inpatient rehabilitation immediately following transplant, but no further training was reported. The non-responders were enrolled at a later period following lung transplant than the responders (55 months vs. 18 months post transplant) and had lower baseline muscle function. It is unknown how prolonged exposure to immunosuppressive medications, especially in the absence of regular exercise training affects muscle function. Recently, Langer and colleagues randomized 40 lung transplant recipients who had an uncomplicated post-operative course (hospital stay < six weeks) at hospital discharge to either three months of supervised training involving endurance, resistance training and physical activity counseling (intervention group) or to physical activity counseling alone (control group). Following three months of exercise training, the intervention group spent significantly more time walking and had higher daily steps, 6MWD and muscle strength. At one year follow-up these functional differences were maintained, and the intervention group also spent more time in moderate intensity physical activity and had higher peak work rates and higher sub-scores on the SF-36 questionnaire for physical functioning and role physical. Interestingly, at one year follow-up the intervention group had lower values for average 24 hour ambulatory diastolic and systolic blood pressure, and had a lower incidence of treatment for diabetes. The control group was prescribed more anti-hypertensive medication at one year follow-up.
1.3 PERIPHERAL MUSCLE FUNCTION BEFORE AND AFTER LUNG TRANSPLANTATION

Lung transplant candidates have demonstrated decreased quadriceps strength between 50-74% predicted\textsuperscript{15,43-45} as measured by hand-held and computerized dynamometry, reflecting some of the systemic effects of chronic lung disease such as muscle atrophy and weakness. These systemic consequences of the disease may also impact prognosis, and quadriceps strength has been found to predict mortality in moderate to severe COPD.\textsuperscript{46} There are inconsistent reports about the recovery of peripheral muscle strength following lung transplant. Maury and colleagues documented an immediate drop in quadriceps strength at hospital discharge in a cohort of 36 lung transplant recipients from pre-transplant values (from 72% predicted to 51% predicted),\textsuperscript{44} with only a partial recovery returning to 87% of pre-transplant levels (59% predicted) following three months of subsequent rehabilitation. A significant negative relationship was found between the time spent in the intensive care and medium care units and the reduction of skeletal muscle force, and a linear regression analysis suggested a decline of 0.8 Nm of quadriceps torque per day. Reinsma and colleagues compared quadriceps strength before and one year following transplant in 25 individuals and found a small increase post-transplant from 62% predicted to 67% predicted.\textsuperscript{15} Lands and colleagues measured peak power on a cycle ergometer as an indicator for peripheral muscle strength in ten single-lung transplant recipients and nine double-lung transplant recipients greater than 18 months post-transplant and found limited leg power of 69% and 76% predicted respectively; however pre-transplant measures were not taken.\textsuperscript{25} Langer and colleagues measured quadriceps torque (QT) in lung transplant recipients at hospital discharge, three months and one year following hospital discharge using a randomized control design.\textsuperscript{42} In the intervention group who received exercise training, QT was 63% predicted at hospital discharge, 82% predicted after three months of exercise training, and 92% predicted one year after discharge, whereas the QT for the control group was reported as 56% predicted at discharge, 60% predicted at three months post discharge and 71% predicted one year after discharge.\textsuperscript{42}

To assess if the abnormalities seen post-operatively are due to pre-transplant dysfunction or from effects of the transplant surgery, hospital stay and medical management, Mathur et al.\textsuperscript{47} compared muscle volume, composition, strength and endurance of the thigh muscles in six stable lung transplant recipients and six control subjects with COPD. They found similar changes in
both groups with regards to muscle size and strength; however lung transplant recipients exhibited lower isometric muscle endurance of the quadriceps. Further studies quantifying muscle structure and function in a larger sample pre- and post-transplant are needed to fully understand the mechanisms of skeletal muscle dysfunction in lung transplant recipients and to identify which components can be addressed through different rehabilitation strategies in the intensive care, inpatient and outpatient settings.

1.4 FUNCTIONAL EXERCISE CAPACITY IN LUNG TRANSPLANT CANDIDATES AND RECIPIENTS

The 6-minute walk test (6MWT) is widely used in deciding transplant candidacy and monitoring changes in functional exercise capacity in lung transplant candidates and recipients. The 6MWT is also incorporated into the algorithm for BODE (body-mass index, airflow obstruction, dyspnea and exercise capacity) scores as a predictor of survival in COPD and is used in the referral and selection of lung transplant candidates with COPD. Lung transplant candidates have a decreased functional exercise capacity with 6MWD of 45-48% predicted reported, and most individuals listed for lung transplant have 6MWDs less than 400m. Shorter 6MWDs have been reported to represent an increased mortality risk in lung transplant candidates. The degree of desaturation during the 6MWT has also been related to disease severity and prognosis in idiopathic interstitial pneumonia. Pre-transplant 6MWD was associated with post-transplant outcomes such as hospital length of stay and number of days intubated in a retrospective study of 423 lung transplant recipients.

The 6-minute walk distance (6MWD) improves significantly following lung transplant. Two studies report no immediate change in 6MWD at hospital discharge following transplant, but increases of 191% from pre-transplant levels and 6MWDs reaching 79% of predicted healthy values after 3 months of rehabilitation. Natural recovery of the 6MWD also occurs, as a recent randomized controlled trial showed a 132 m improvement from pre-transplant levels in the control group (no rehabilitation) three months after hospital discharge. Typically 6MWDs within the 450-700m range are reported. Since the 6MWT evaluates global and integrated responses of many systems including pulmonary, cardiovascular, neuromuscular and systemic and peripheral circulation, it may reflect different contributing factors in the pre- and
post-transplant periods that could potentially limit functional exercise capacity. The main outcome of the 6MWT is distance walked, but little is reported on the relevance and importance of gait aids used or rest periods required during the test which may affect the 6MWD. Since the 6MWT does not measure maximal exercise capacity and individuals are instructed not to run, a ceiling effect can occur, and may be of limited utility in detecting changes post-transplant in individuals with a high 6MWD.

1.5 HEALTH-RELATED QUALITY OF LIFE BEFORE AND AFTER LUNG TRANSPLANTATION

Health-related quality of life (HRQOL) is an important consideration in lung transplant decision-making, and in measuring the utility of the transplant procedure. Although physical limitations typically lower the overall HRQOL pre-transplant, HRQOL post-transplant may not solely be influenced by physical condition such as lung function or functional exercise capacity. Two common measures of HRQOL that are utilized in this field are the Medical Outcomes Short Form (SF-36) questionnaire and the St. George’s Respiratory Questionnaire (SGRQ). The SF-36 questionnaire is a generic health index with eight scales and two summary scores (the physical and mental component summary). It is scored from 0-100, with higher scores indicating better health. A respiratory disease-specific SGRQ has three main domains; symptoms (distress due to respiratory symptoms), activity (effects on mobility and physical activity) and impacts (psychosocial impact of disease), as well as a total score. This is also scored from 0-100, however higher scores indicate worse health.

Stavem and colleagues measured HRQOL using the SF-36 and SGRQ in 15 lung transplant candidates of mixed diagnosis (mean 10 month waiting time) and 31 lung transplant recipients (mean 38 months post-transplant) and found better HRQOL in transplant recipients in all areas of the SGRQ except symptoms, and all areas of the SF-36 except bodily pain. Eskander and colleagues examined HRQOL in a cohort of 112 lung transplant candidates with COPD and reassessed 55 who were subsequentially transplanted (mean 4 months since transplant) to find dramatic improvements in the SGRQ, and improvements with the physical component score on the SF-36. Health-related quality of life was measured retrospectively with a generic
questionnaire (Quality of Life Profile for Chronic Disease) in 280 lung transplant recipients between 3 months and 14 years following transplant as compared to a healthy population. HRQOL was high in all dimensions and within a similar range as the healthy population, and was dependent on the incidence of infections, rejection and onset of bronchiolitis obliterans syndrome (BOS). The development of BOS is associated with significantly reduced HRQOL and physical restrictions in lung transplant recipients.

1.6 PHYSICAL ACTIVITY

Physical activity is defined as “any bodily movement produced by skeletal muscles that results in energy expenditure”. Physical activity is a broad concept that can be categorized into leisure (hobbies, recreation, sports), occupational, household and transportation-related physical activity. Exercise is a subcategory of physical activity and is defined as planned, structured and repetitive bodily movement done to improve or maintain fitness. Physical activity can also be categorized into light, moderate and vigorous intensity. Moderate intensity physical activity requires a rate of energy expenditure of 3-6 metabolic equivalents (METS), which represents 3-6 times the oxygen consumption that is required at rest and would include activities such as brisk walking, sweeping floors, vacuuming, or mowing the lawn. Current physical activity recommendations to obtain health benefits is to engage in at least 150 minutes per week of moderate-to-vigorous physical activity (MVPA) accumulated in 10-minute bouts. An alternative physical activity target is the accumulation of 10,000 steps per day. Pedometer-determined classifications for physical activity in healthy adults as measured by daily steps have been divided into the following categories: sedentary (< 5000 steps/day), low active (5000 – 7499 steps/day), somewhat active (7500 – 9999 steps/day), active (10 000 – 12 4999 steps/day), highly active (> 12 500 steps/day). Regular moderate physical activity (30 minutes at least five times per week) can reduce the risk of premature mortality in the general population and in individuals with cardiovascular disease, hypertension, colon cancer, and diabetes mellitus in the general population, and is important in skeletal health, physical fitness, weight control and lipid profile. The impact of physical activity on survival and other common side effects and co-morbidities seen in lung transplant recipients such as increased cardiovascular risk factors has not been fully investigated.
1.6.1 Measurement of physical activity

There are a number of methods of measuring daily physical activity including self-report (questionnaires or activity diaries), direct observation, doubly-labeled water, direct and indirect calorimetry, heart rate monitors, pedometers and accelerometers. All these measures have certain advantages and disadvantages, and differ in relation to cost, invasiveness, participant burden, bias and accuracy. There is no definite gold standard of measuring physical activity outside the laboratory setting. Different methods of measuring physical activity use various techniques that incorporate physiological, biochemical and biomechanical principles to estimate physical activity. Since the raw data is expressed in different units depending on the method used (i.e. heart beats, movement counts, time, steps) it is not easy to directly compare the results of different methods of assessment of physical activity.

The use of questionnaires and diaries to estimate physical activity during daily life offers the advantages of simplicity and affordability, however data obtained using self-report instruments is subjective and subject to recall bias and misinterpretation of physical activity categories. Accelerometers are small electric sensors that are lightweight, non-invasive, and have the ability to record an extensive amount of detailed information over an extended time period. Measures of physical activity are derived by sensing movement of body segments using either uniaxial or tri-axial piezoresistive sensors. Accelerometers measure segment or limb acceleration rather than overall acceleration, and wearing the monitors at the hip (the preferred placement site) accurately measures ambulatory movement. The device is calibrated in a laboratory and the relationship between accelerometer output (counts) and a physiological variable of energy expenditure such as METS is determined using regression equations to predict estimates of energy expenditure. Accelerometer output can be segmented from vast amounts of information into discrete time periods with a user-specified time intervals. Three different methods of looking at the data include total movement counts, energy expenditure prediction that converts the raw movements counts into estimates of energy expenditure (Kcal/min) or a time-based approach such as the cut-point method with monitors that have been calibrated to determine the relationship between counts and different intensities of activities (sedentary, light, moderate, vigorous). A common disadvantage of accelerometers worn at the hip is the under-prediction of energy expenditure.
with non-ambulatory activities such as upper body movement or activities such as cycling where little acceleration occurs at the hip.\textsuperscript{70} Accelerometers also do not account for the increased energy cost of walking on inclines or carrying or moving a load. The reliability of accelerometer output relies on the correct and consistent positioning securely on the body, as well as appropriate laboratory calibration.\textsuperscript{70} The validation of accelerometers typically involves the comparison of energy expenditure estimates with indirect calorimetry or doubly labeled water as a criterion measure.\textsuperscript{70} Studies that have used accelerometers in COPD have found two to three days of consecutive wear time were sufficient to obtain a reliable measure of physical activity.\textsuperscript{71,75,77}

### 1.6.2 Physical activity in the general population

A recent population-based study of the levels of physical activity of a general Canadian population between 20 to 79 years using hip-mounted accelerometers revealed that Canadians are less physically active than previous self-report estimates report, and the majority of people did not reach the current physical activity recommendation guidelines.\textsuperscript{72} Only 15\% of individuals accumulated the recommended MVPA per week, and only 35\% of individuals achieved the 10,000 steps per day target. Specifically, men accumulated an average of 27 minutes of MVPA per day and 9544 daily steps, and women accumulated an average of 21 minutes of MVPA per day and 8385 daily steps. The younger age groups (20-59 years) were more physically active than the older age cohort (60-79 years), and healthy weight individuals were significantly more physically active than overweight and obese individuals.\textsuperscript{72}

### 1.6.3 Physical activity in chronic lung disease

In individuals with chronic lung disease, decreased physical activity can be considered both a consequence and a symptom of the disease,\textsuperscript{73} as the spiral of inactivity begins with dyspnea limiting activities, and resultant deconditioning occurs due to this inactivity. The majority of studies examining physical activity in chronic lung disease have been performed in the COPD population where physical activity has been found to decrease early in the disease process.
Troosters and colleagues measured physical activity level in 70 individuals with COPD of varying severity and found a significantly lower physical activity compared to healthy controls, which was evident by Global Initiative for Obstructive Lung Disease (GOLD) Stage II, and lower levels of physical activity were observed with greater severity of lung disease despite the weak correlation between physical activity and lung function. Ten individuals in this study had severe disease (GOLD Stage IV) and took an average of 2718 daily steps and spent 14.3 minutes in moderate intensity physical activity. Similarly, Watz and colleagues measured physical activity in 170 individuals with COPD to determine at what clinical stage physical activity level starts to decline, and found a significant limitation in physical activity in GOLD stage II and BODE score 1. In this study, 36 of the subjects were GOLD stage IV, and took less than 3000 daily steps. Pitta and colleagues quantified physical activity in 50 individuals with COPD using an accelerometer to demonstrate that the majority of these individuals spend significantly less time walking and standing, and more time in sedentary activities such as sitting and lying as healthy controls, as well as exhibiting lower movement intensity during walking. They found that walking time was highly correlated with 6MWD in individuals who walked less than 400m, however in individuals with higher 6MWD (> 400m) physical activity levels were highly variable and the 6MWD was not able to accurately predict daily walking time. Regular physical activity (equivalent to walking or cycling at least two hours/week) has also been associated with a 30-40% reduction in the risk of hospital admission and respiratory mortality in COPD.

A few studies have examined physical activity in other chronic lung conditions. Mainguy and colleagues recently studied physical activity in 15 individuals with stable idiopathic pulmonary arterial hypertension (IPAH) and 10 individuals with pulmonary arterial hypertension associated with limited systemic sclerosis (PAH-SSC). The IPAH group was matched with healthy controls and the PAH-SSC group was matched with individuals with systemic sclerosis without pulmonary arterial hypertension. The mean energy expenditure and duration of physical activity > 3 METS were reduced and daily steps (IPAH 5041 steps, PAH-SSC 3234 steps) were lower than their respective controls (healthy controls 9189 steps, SSC control 5810 steps). Daily steps correlated with 6MWD, and both steps and functional exercise capacity decreased progressively as New York Heart Association (NYHA) functional class worsened. Troosters and colleagues measured physical activity in 20 individuals with mild cystic fibrosis (CF) with a FEV₁ of 65% predicted, and a 6MWD of 702m (91% predicted) to find that while the number of daily steps
was similar to healthy controls (9398 steps vs. 10281 steps), individuals with CF spent significantly less time in moderate intensity physical activity (14.8 minutes vs. 34.5 (minutes).  

Although moderate intensity is defined by an activity requiring a rate of energy expenditure of 3-6 METS, other factors affect energy expenditure such as age and functional status, and intensity cut-points calibrated for healthy individuals may not be applicable in individuals with chronic disease. 

1.6.4 Physical activity in lung transplant candidates and recipients

There has been limited investigation into the objective measurement of physical activity in lung transplant candidates. One study assessed daily physical activity using a pedometer in lung transplant candidates with COPD and reported very low levels (1407 steps/day). The use of accelerometers to measure physical activity in lung transplant candidates of various disease states has revealed a marked reduction in physical activity comparable to individuals with COPD GOLD stage IV, the accumulation of between 2400-3200 daily steps and spending 69% of the day in sedentary activities. A study by Langer et al found that the 6MWD was the strongest determinant of physical activity in lung transplant candidates with COPD and ILD.

Daily physical activity has been quantified in two cross-sectional studies in lung transplant recipients. Bossenbroek and coworkers measured physical activity with a pedometer and reported that lung transplant recipients with pre-existing COPD assessed five years post-transplant took a similar number of steps per day (6642 steps/day) as a healthy reference population. There was a moderate correlation between steps per day and pulmonary function, lower body strength and number of months post transplantation. This sample is not fully representative of the lung transplant population as only long-term survivors were assessed, and all subjects had a pre-transplant diagnosis of COPD. Conversely, Langer and colleagues found that daily steps, standing time and moderate-intensity activity of 22 stable lung transplant recipients one year post-transplant were significantly reduced relative to healthy controls (daily steps 4977 vs. 8645) and daily sedentary time was increased by 30%. Significant correlations were observed between measures of physical activity and physical fitness and HRQOL. Daily steps was correlated with quadriceps force, six-minute walk distance (6MWD), maximum
workload and the physical component summary scale of the SF-36. Moderate inverse relationships were found between the daily time spent sedentary (sitting or lying), physical fitness and the physical component summary scale of the SF-36. Due to the cross-sectional nature of this study the analysis could not adjust for different degrees of pre-transplant physical activity and physical functioning. A recent longitudinal randomized controlled study by Langer et al found that physical activity increased at three months and one year post-transplant from pre-transplant levels. Daily steps increased from 3225 pre-transplant to 5194 three months post-transplant and to 7406 one year post transplant in the intervention group who underwent three months of rehabilitation following hospital discharge. The control group increased daily steps from 2426 pre-transplant to 3451 at three months post-transplant and to 4462 at one year post-transplant. Both groups spent less time in sedentary activities and more time in standing, walking and activities requiring > 3 METS per day at three months and one year post-transplant. The majority of the participants in this study (85%) had a pre-diagnosis of COPD, and only individuals with an uncomplicated hospital stay and between the ages of 40-65 were included. It is not known how physical activity changes in the early post-transplant period in individuals with other chronic lung diseases, who are < 40 years or > 65 years of age, or had a complicated hospital course post-transplant.

1.7 OBJECTIVES, HYPOTHESES AND SCOPE OF THESIS

The four objectives of this research are:

i) Describe muscle strength, functional exercise capacity, health-related quality of life and physical activity in lung transplant candidates.

ii) Examine and compare functional changes (muscle strength, functional exercise capacity, HRQOL and physical activity) over time (pre-transplant, post-transplant at the time of hospital discharge and 3 months post-transplant).

iii) Explore the relationships between measures of muscle strength, functional exercise capacity, health-related quality of life and physical activity pre-transplant.

iv) Determine if differences in functional recovery exist between genders, age groups and different length of hospital stay post-transplant.
The hypotheses of this research are:

i) Muscle strength, functional exercise capacity and physical activity will be severely impaired in all lung transplant candidates compared to the general population.

ii) A significant increase in all functional outcomes post-transplant will occur with the greatest improvement observed between hospital discharge and 3 months post-transplant.

iii) Physical activity will correlate with measures of muscle strength and functional exercise capacity, and the 6-minute walk test will show the strongest correlation with physical activity pre-transplant.

iv) There will be a gender and age effect for muscle strength, functional exercise capacity and physical activity post-transplant with men and younger individuals achieving higher levels of functioning. Functional outcomes will be decreased in individuals requiring a prolonged hospitalization (> 6 weeks).

This thesis includes a study specifically examining physical activity in a subgroup of pre-transplant candidates with interstitial lung disease in Chapter two where it introduces use of the accelerometer in the measurement of physical activity. Chapter three describes the pre-transplant characteristics of all participants, and the early functional changes at hospital discharge and three months post transplant. A general discussion, conclusions and future directions are described in Chapter four.
1.8 REFERENCES


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Chapter 2
Physical Activity Profile of Lung Transplant Candidates with Interstitial Lung Disease

2.1 ABSTRACT

Physical activity has not been objectively assessed in lung transplant candidates with interstitial lung disease (ILD) undergoing rehabilitation. This study measured levels of physical activity using an accelerometer and compared levels of physical activity on days when lung transplant candidates with ILD underwent a supervised exercise-based rehabilitation program with non-rehabilitation days. It also explored the relationships between physical activity and additional functional outcomes.

Twenty four lung transplant candidates (14 men) with ILD on long-term oxygen therapy underwent measures of physical activity (daily steps and time spent in moderate intensity physical activity), functional exercise capacity (6-minute walk distance), strength (quadriceps torque) and health-related quality of life (SF-36 and St. George’s Respiratory Questionnaire).

Levels of physical activity were significantly lower than the general population, however individuals with ILD were more active on rehabilitation days than on non-rehabilitation days (daily steps 3780 ± 2196 vs. 2103 ± 1332, p < 0.001; time in moderate intensity 4.5 (IQR 2-17) minutes vs. 2.1 (IQR 1-4) minutes, p < 0.001). The six-minute walk distance showed moderate correlation to daily steps (r=0.57, p < 0.01) and time spent in moderate intensity physical activity (r=0.57, p < 0.01).

Lung transplant candidates with advanced ILD are inactive, however they are able to participate in a supervised rehabilitation program and have higher physical activity levels on rehabilitation days.
2.2 INTRODUCTION

Interstitial lung disease (ILD) is a heterogeneous group of disorders characterized by lung inflammation and fibrosis. Depending on the specific lung pathology, ILD varies in the natural clinical course, response to therapy and prognosis. Exercise limitation in ILD is thought to arise from a combination of factors including ventilatory, diffusion and circulatory limitations, gas exchange abnormalities, alterations in respiratory drive, abnormal breathing patterns and peripheral muscle dysfunction. There is an emerging body of evidence suggesting that pulmonary rehabilitation is effective, safe and feasible in ILD, with studies demonstrating short-term improvements in dyspnea, health-related quality of life (HRQOL) and functional exercise capacity. Pulmonary rehabilitation is also recommended in lung transplant candidates in order to increase fitness for surgery and improve post-transplant outcomes. ILD is one of the major indications for adult lung transplantation, and consequently pre-transplant rehabilitation programs include a greater proportion of participants with ILD than is seen in traditional pulmonary rehabilitation programs.

One goal of pulmonary rehabilitation is to increase physical activity. Physical activity is related to many health outcomes, and can be characterized into occupational, leisure, household, sport and transportation, with exercise specifically described as a subcategory that is a planned, structured and repetitive activity with the objective of improving or maintaining physical fitness. Physical activity is an outcome that has received increased attention in COPD over the past decade, and the widespread availability of accelerometers allows a more objective measure of physical activity than self-report questionnaires. Physical activity has been shown to be reduced early in the disease progression of COPD and continues to decline with higher GOLD stages or BODE scores. Furthermore, low levels of physical activity are associated with an increased risk of hospital admissions and respiratory and all-cause mortality in COPD. Little is known about physical activity in the ILD population. The primary objectives of this study were 1) to measure levels of daily physical activity in individuals with ILD who were lung transplant candidates and 2) compare levels of physical activity on days when these individuals underwent a supervised exercise-based rehabilitation program with non-rehabilitation days. A secondary objective was to explore the relationships between physical activity and muscle strength, functional exercise capacity, and HRQOL in advanced interstitial lung disease.
2.3 METHODS

2.3.1 Study Design

For this prospective cohort study, all individuals with ILD on the lung transplant waiting list at the Toronto General Hospital, Toronto, Canada were considered for study recruitment. Subjects were excluded if they had a lung diagnosis other than ILD, were admitted to hospital while on the transplant waiting list or were experiencing a rapid clinical deterioration, acute infection or exacerbation. Ethics approval was obtained from the University Health Network (REB# 10-0261-BE). All participants gave written informed consent (Appendix A).

2.3.2 Measures

Pulmonary function was completed at the time of the transplant evaluation, and at the time of the study assessment, demographic and anthropometric measures were taken and the daily dose of oral corticosteroids and time on the transplant waiting list were recorded from the medical chart. All measures of strength, functional exercise capacity, HRQOL and physical activity were taken within a two-week time period.

Daily physical activity was measured with an activity monitor (Actigraph GT3X, Pensacola, FL, USA) worn during the waking hours for seven consecutive days. This light weight (27g), compact (1.5 x 1.44 x 0.7 inch) triaxial accelerometer was worn at the hip attached to a waist belt and recorded the amount, type and pattern of activity (frequency, intensity, duration) including step count. The Actigraph has been validated against portable indirect calorimetry for measuring energy expenditure in physically active adults. Regression equations are used to estimate the intensity of the activity from the accelerometer output (activity counts). Intensity-specific count ranges are used to classify accelerometer output according to different movement intensities or metabolic equivalents (METS). The accelerometer signal is summed over a user-specified time interval, which for this study were 30-second epochs. Valid days for data collection were defined as greater than 8 hours per day of wear time. Participants were asked to remove the accelerometer while sleeping and bathing. All participants kept an activity diary.
during the week the accelerometer was worn and were asked to maintain their normal level of daily activity. The main study measurements were steps per day and minutes spent in moderate intensity activity per day (defined as activity requiring a rate of energy expenditure of 3-6 METS).

Quadriceps torque (QT) was measured on the dominant limb as isometric peak torque (Newton-metres) with the hip positioned at 90 degrees of flexion and knee at 60 degrees of flexion using an isokinetic dynamometer (Biodex System 4, Biodex Medical Systems, Inc.). A maximum voluntary contraction of 5 seconds was performed with a one minute rest between attempts. The highest value of 5 attempts (following one warm-up contraction) was used for analysis. Standardized instructions, encouragement and verbal and visual feedback were provided. Results were compared to predicted values. 27

Functional exercise capacity was measured using the six-minute walk test (6MWT) that was conducted according to published guidelines. 28 Only one test was performed at the study assessment as subjects had previously done multiple tests during the transplant evaluation and rehabilitation program. The test was performed using the flow rate of supplemental oxygen prescribed for activity and the gait aid typically used outside the home. The 6-minute walk distance (6MWD) was compared to reference values for a Canadian population as described by Hill and colleagues. 29 Health-related quality of life was measured both by a generic questionnaire (Medical Outcomes Study Short Form (original SF-36)), and a respiratory-specific questionnaire (St. George’s Respiratory Questionnaire (SGRQ)). The SGRQ has been validated in individuals with interstitial lung disease. 30

2.3.3 Rehabilitation Program

All study participants were required to participate in a supervised, exercise-based pulmonary rehabilitation program three times per week for the duration of the waiting period prior to transplant. All subjects had been enrolled in the lung transplant rehabilitation program for at least four weeks at the time of the study assessment. The exercise program took place in a hospital outpatient setting and was designed and supervised by physiotherapists. Exercise training was individualized and included stretching, resistance training, endurance training and
functional exercises (step-ups, squats). The session lasted 90 minutes in duration. Intensity was prescribed according to oxygen titration guidelines prescribed by the respirologist (typically ≥ 88%), within symptom tolerance (Borg dyspnea score 3-4), and below a heart rate of 85% age-predicted maximum. Oxygen prescription for exercise was increased as needed to maintain adequate oxygenation. Endurance training on both the treadmill and cycle was targeted for 20 consecutive minutes. A weekly support group, educational sessions and psychosocial support were also available to lung transplant candidates and their families provided by the multidisciplinary team.

2.3.4 Statistical analysis

Statistical analysis was performed using the SAS statistical package (v. 9.3, SAS institute Inc. Cary, NC, USA). Assumption of normality was tested using the Shapiro-Wilk test. Descriptive statistics are reported as mean and standard deviation, or median and interquartile range (IQR) for non-normally distributed variables. The average amount of physical activity performed on days when participants underwent rehabilitation versus days that no rehabilitation occurred was compared using either a paired t-test or a Wilcoxon signed rank test. Bivariate correlation analyses were performed using Pearson product moment correlation or Spearman rank correlation coefficient to examine the relationships between physical activity and 6MWD, muscle strength and HRQOL. A p-value of less than 0.05 was considered to be statistically significant.

2.4 RESULTS

All lung transplant candidates with ILD were screened for inclusion in the study between September 2010 and August 2011. During this period, 52 individuals with various forms of ILD were identified. Six candidates underwent a lung transplant before the study procedures could be completed. Eleven candidates were considered unstable at time of recruitment (admitted to hospital and/or experiencing a rapid clinical deterioration, acute infection or exacerbation). Seven candidates refused participation due to the extra time commitment (n=4) or lack of interest
Four candidates were not recruited due to language barriers. Transplant listing status of participants included status 1, status 2 and rapidly deteriorating ambulatory outpatients.

### 2.4.1 Subjects

Twenty-four participants (14 male) were included in the study. Participant characteristics are outlined in Table 1. The median age of the study sample was 62 (IQR 53-65) years and the diagnosis of ILD was confirmed by lung biopsies or high-resolution computed tomography. There were a total of 16 participants with interstitial idiopathic pneumonia (12 idiopathic pulmonary fibrosis (IPF), 2 mixed IPF/COPD, 1 non-specific interstitial pneumonia (NSIP), and 1 unspecified interstitial idiopathic pneumonia). Five had collagen vascular disease (3 scleroderma, 1 polymyositis/rheumatoid arthritis, 1 Sjogren’s syndrome). Two participants had sarcoidosis, and one participant had extrinsic allergic alveolitis. There were no current smokers.

Participants had severe restrictive lung disease characterized by severe reductions in lung volumes and diffusing capacity for carbon monoxide. Fifteen participants (63%) were taking oral corticosteroids at the time of the study assessment, with a mean daily dose of 14 ± 7 mg/day. Participants were retired or on sick leave at the time of study assessment, with the exception of one participant who was attending university. There were no participants that had significant musculoskeletal conditions that limited participation in a rehabilitation program.

All participants were on long-term oxygen therapy and used various methods of oxygen administration and flow rates during exercise. Fourteen participants used nasal prongs (13 continuous flow, one pulsed flow) with oxygen requirements ranging from 4-8 L/min. Five participants used a venturi mask at 50%, one participant used an oximeter at 10L/min and four participants used 15L partial non-rebreather masks. The average duration of exercise on rehabilitation days was 20 consecutive minutes of cycle ergometry and 18 ± 6 minutes on a treadmill (average speed of 2 ± 0.5 mph). This speed represented 94% ± 19 of the speed on their 6MWT.

Results of the 6MWT and HRQOL are summarized in Table 2. The six-minute walk test was 51 ± 10 % predicted and oxygen desaturation was evident (mean SpO2 85± 7%) despite supplemental oxygen during the test. Six participants used rollator walkers during the test, and
one participant required a 50 second rest during the test. Isometric QT was 121 ± 35 Nm (81% ± 23 predicted). There was no difference in QT in participants who were currently taking oral corticosteroids and those who were not (123 ± 10 Nm vs. 117 ± 11 Nm, p = 0.68). HRQOL was significantly lower than normal values, particularly in the physical health domains.

2.4.2 Daily Physical Activity in ILD

Participants wore the accelerometer for an average of 6.6 ± 1 days with a mean daily wear time of 14.6 ± 1.6 hours. Total daily steps were 2707 ± 1581 and total daily time spent in moderate intensity physical activity was 3.7 (IQR 1.6-7.7) minutes per day. Figures 1 through 3 show the pattern of daily physical activity in one participant with steps and activity counts on a rehab and a non-rehab day. Figures 4 and 5 show the average daily steps and time spent in moderate intensity physical activity for all participants as compared to the general Canadian population. No vigorous intensity activity (> 6 METS) was done the week of the study assessment.

2.4.3 Rehabilitation versus non-rehabilitation days

On average, participants wore the activity monitor for an average of 2.3 ± 0.9 rehabilitation days and 4.3 ± 2 non-rehabilitation days during the week of their study assessment. Participants wore the accelerometer for similar amounts of time on rehabilitation and non-rehabilitation days (14.6 ± 2 vs. 14.3 ± 2 hours, p=0.45). On rehabilitation days, they took a significantly greater number of steps (3784 ± 2145 vs. 2103 ± 1332 steps, p<0.001) and spent significantly longer in moderate intensity physical activity compared to a non-rehabilitation day (4.5 (IQR 2-17) minutes vs. 2.1 (IQR 1-4) minutes, p<0.001).

2.4.4 Correlations with Physical Activity

Total daily steps were correlated with 6MWD (r=0.57, p< 0.01); Figure 6 and QT (r=0.50, p=0.02). Time spent in moderate intensity physical activity was correlated with 6MWD (r=0.57, p< 0.01).
2.5 DISCUSSION

This is the first study to objectively quantify daily physical activity in lung transplant candidates with ILD who were undergoing pulmonary rehabilitation. Recent data using a hip-mounted accelerometer collected in a general Canadian population allow for comparison of physical activity levels. Participants in this study showed a considerable decrease in physical activity both in terms of steps and time spent in moderate intensity physical activity, as individuals with ILD took a third the number of daily steps as the general population. In the general population the older cohort (> 60 years) were less active than the 20-59 year old cohort. Our study sample had 63% of individuals who were over 60 years of age, and these individuals also took one third the number of daily steps of the general population of similar age. In the general population, women’s daily activity is only 88% of men’s values, and a similar result was found in our study participants. Individuals with advanced ILD were more physically active on rehabilitation days, and were able to tolerate a regular exercise-based rehabilitation program.

Physical activity has been previously reported to be reduced in the COPD population, including those on supplemental oxygen and with severe disease. Individuals with COPD have been found to have reduced walking and standing time and lower movement intensity during walking, with higher sitting and lying time compared to healthy controls. Troosters and colleagues assessed ten individuals with very severe COPD who took 2718 steps per day and spent 14.3 minutes in moderate intensity activity. Watz and colleagues examined 36 individuals with GOLD stage IV reported less than 3000 steps per day, which is similar to this study sample, however time spent in moderate intensity physical activity was higher (approaching 50 minutes per day). Both these studies used an accelerometer worn on the arm, which differed from the hip-mounted accelerometer used in this study. Due to frequent use of rollator walkers in our population we chose not to use an armband accelerometer, as these gait aids may interfere with the accurate assessment of physical activity when using these types of monitors.

Physical activity has been measured in one study in 15 lung transplant candidates with a diagnosis of COPD using a pedometer and found the daily steps were 1407. Langer and colleagues report that physical activity is severely reduced in lung transplant candidates and comparable to COPD Gold Stage IV. In a study with 96 lung transplant candidates including 27 with ILD, daily steps were reported as 2958 (ILD cohort 3158) with reduced walking and
standing time, which was comparable to the number of daily steps taken in our study cohort. In univariate analyses, colder seasons and the use of long-term oxygen therapy (LTOT) were related to decreased physical activity. Sandland and colleagues also found that individuals with severe COPD on LTOT had a further 50% reduction in activity counts than individuals with similar lung function who were not on LTOT. High oxygen requirements for exertion are not uncommon in ILD and individuals may require several portable oxygen tanks when leaving the home setting due to a limited time before the tanks need to be refilled. This extra oxygen equipment, possible need for a rollator walker, fear of running out of oxygen, and stigma of wearing oxygen in public may affect the level of physical activity outside the home. The environment can also impact on the level of physical activity, as extreme heat, humidity, cold and wind can increase dyspnea, and snow or icy conditions can hinder travel if using a walker.

We found a reduced QT in the ILD population compared to predicted values in a healthy population. Quadriceps strength has been reported to be decreased in IPF and sarcoidosis. Decreased quadriceps strength has also been described in lung transplant candidates with ILD of 74% predicted. The cause of quadriceps weakness in ILD is unknown, but factors that may contribute include corticosteroid use, deconditioning, hypoxemia, systemic inflammation, nutrition, and aging. Daily steps were correlated with QT in this study. A modest correlation of quadriceps strength to walking time has been reported in COPD.

Physical activity levels (steps per day and time spent in moderate intensity physical activity) were both correlated with the 6MWD in this study sample. This has also been observed in the COPD population with moderate correlations between the 6MWD and steps and time spent in moderate intensity activity. The 6MWD has also been correlated with walking time and standing time. In lung transplant candidates, multiple regression identified the 6MWD as the strongest determinant of physical activity. Possible strategies to increase daily physical activity in stable individuals with ILD could include a referral to pulmonary rehabilitation, and appropriate oxygen prescription to support exercise training. Greater levels of physical activity may be achieved if rehabilitation is offered earlier in the disease, particularly in IPF when dyspnea and oxygen desaturation with exertion is less severe. As the 6MWT is significantly correlated with daily physical activity, this could be used as an outcome measure in the clinical setting.
Limitations

The study sample was limited to lung transplant candidates with ILD, who are a highly select group of individuals with sufficient motivation and social support, who participated in a mandatory rehabilitation program. Individuals with ILD who were experiencing rapid deterioration, acute exacerbation, acute infection or hospitalization were not included, therefore the results may not be generalizable to all individuals with advanced ILD and even lower levels of physical activity may be observed in less stable individuals. The total daily physical activity of the study participants may have been underestimated in this study. Accelerometers worn on the hip cannot accurately measure activities involving upper extremity effort, ascending stairs, or distinguish walking on a grade from level ground, and therefore may underestimate overall activity. Stationary exercise such as cycling and resistance training done during the rehabilitation program may not have been captured in this study, as well as many common household chores that contribute to time spent in moderate intensity activity. The actigraph has not been validated in the ILD population, and relative intensity for activities typically requiring 3-6 METS may be higher due to the low cardiopulmonary fitness of individuals with end-stage lung disease.

Some lung transplant candidates have to relocate closer to the transplant centre during the waiting period and are therefore not in their usual home environment or living with all their regular family members, which may have influenced their daily physical activity. The study data were collected over the course of the year and in both extremes of Canadian climate (snow/cold in the winter and heat/humidity in the summer) which may have impacted on physical activity, particularly on activities such as walking outdoors.

2.6 CONCLUSION

This study is the first to describe daily physical activity in lung transplant candidates with ILD undergoing pulmonary rehabilitation. Individuals with advanced ILD awaiting lung transplantation have decreased physical activity compared with the general population, however, they were more active on days in which they participated in an exercise-based rehabilitation program. Future research should examine to what extent physical activity levels improve
following lung transplantation, and if pre-transplant physical activity levels are related to prognosis in ILD and post-transplant outcomes.
2.7 TABLES AND FIGURES

Table 2-1: Demographics, anthropometrics and pulmonary function (n=24)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6 ± 3.5</td>
</tr>
<tr>
<td>Time on wait list (months)</td>
<td>4.2 ± 3.5</td>
</tr>
</tbody>
</table>

Pulmonary function

| FEV₁ (L)                               | 1.4 ± 0.5 |
| FEV₁ (% pred)                          | 45 ± 15   |
| FVC (L)                                | 1.9 ± 0.6 |
| FVC (% pred)                           | 47 ± 14   |
| TLC (L)                                | 3.4 ± 1.2 |
| TLC (% pred)                           | 56 ± 18   |
| DₐLCO (ml/min/mmHg)                    | 8 ± 3     |
| DₐLCO (% pred)                         | 43.5 ± 12 |

Values are expressed as mean ± SD

BMI, body mass index; FVC, forced vital capacity; TLC, total lung capacity; DₐLCO, diffusing capacity for carbon monoxide
Table 2-2: Functional exercise capacity and health-related quality of life (n=24)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-minute walk test</td>
<td></td>
</tr>
<tr>
<td>Distance (m)</td>
<td>347 ± 66</td>
</tr>
<tr>
<td>%predicted</td>
<td>51 ± 10</td>
</tr>
<tr>
<td>Resting SpO2 (%)</td>
<td>98 ± 2</td>
</tr>
<tr>
<td>End SpO2 (%)</td>
<td>85 ± 7</td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>96 ± 9</td>
</tr>
<tr>
<td>End HR (bpm)</td>
<td>118 ± 15</td>
</tr>
<tr>
<td>End HR (% pred)</td>
<td>73 ± 0.1</td>
</tr>
<tr>
<td>Resting Borg dyspnea</td>
<td>1.5 ± 1</td>
</tr>
<tr>
<td>End Borg dyspnea</td>
<td>4.1 ± 1</td>
</tr>
<tr>
<td>Resting Borg leg fatigue</td>
<td>1.4 ± 1</td>
</tr>
<tr>
<td>End Borg leg fatigue</td>
<td>2.9 ± 2</td>
</tr>
<tr>
<td>End respiratory rate</td>
<td>41 ± 16</td>
</tr>
</tbody>
</table>

Health-related Quality of Life

SF-36
- Physical function   20 ± 16
- Role physical       18 ± 20
- Bodily pain          69 ± 24
- General health       30 ± 16
- Vitality             39 ± 14
- Social function      57 ± 22
- Role emotional       61 ± 43
- Mental health        70 ± 16
<table>
<thead>
<tr>
<th>Category</th>
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<tbody>
<tr>
<td>Symptoms</td>
<td>62 ± 18</td>
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<td>Activity</td>
<td>83 ± 8</td>
</tr>
<tr>
<td>Impact</td>
<td>47 ± 17</td>
</tr>
<tr>
<td>Total</td>
<td>62 ± 11</td>
</tr>
</tbody>
</table>
Non-rehab day – (1790 daily steps)

**Figure 2-1:** Daily steps on a non-rehabilitation day for a 69 year old woman with IPF. The area between the dashed lines is when the monitor was worn.
Figure 2-2: Daily steps on a rehabilitation day for a 69 year old woman with IPF. The area between the dashed lines is when the monitor was worn. The area between the dotted line is when the 90 minute exercise session was completed on the rehabilitation day.
Figure 2-3: Activity counts on a rehabilitation (dotted line) and non-rehabilitation (dashed line) day in a 69 year old woman with IPF. The area between the solid lines indicate when the exercise program was completed.
**Figure 2-4:** Daily steps for 23 participants (men- white diamonds, women- black diamonds) and the dashed line indicating the group average. The average daily steps for general Canadian population is indicated by the dotted line (men) and solid line (women).
Figure 2-5: Time spent in moderate intensity physical activity for all participants (men- white diamonds, women- black diamonds) and the dashed line indicating the group average. The average time spent in moderate physical activity for general Canadian population is indicated by the dotted line (men) and solid line (women).
**Figure 2-6:** Relationship between daily steps and 6MWD
2.8 REFERENCES


Chapter 3

Functional Outcomes pre- and early post-lung transplantation: a cohort study

3.1 ABSTRACT

There has been limited research examining functional changes and outcomes in a cohort of individuals pre- and early post-lung transplantation. In this study, peripheral muscle strength (quadriceps torque), functional exercise capacity (6-minute walk distance), health-related quality of life (Medical Outcomes Short Form (SF-36) and St. George’s Respiratory Questionnaire (SGRQ)) and physical activity (daily steps and time spent in moderate intensity per day) were assessed in 50 lung transplant candidates with a variety of end-stage lung diseases (23 men, aged 55 (IQR 41-63) years), and reassessed in transplant recipients at hospital discharge (n=34) and three months post-lung transplantation (n=29).

Significant improvements in lung function (FEV₁ 1.1 ± 0.5 L vs. 1.9 ± 0.5 L, p <0.001) and health-related quality of life (SF-36 physical functioning 26 ± 16 vs. 47 ± 25, p <0.001, SGRQ activity domain 79 ± 15 vs. 49 ± 31, p<0.001) were observed at hospital discharge (median length of stay 17 days (IQR 14-32)). There was no change in functional exercise capacity (6MWD 385 ± 99m vs. 404 ± 106m, p=0.23) or physical activity (daily steps 2675 ± 1119 vs. 2630 ± 1449, p=0.97, time spent in moderate intensity per day 4.1 (IQR 1.4-9.8) minutes vs. 5.4 (IQR 1.5-9.8) minutes, p=0.64) at hospital discharge post-transplant, whereas and peripheral muscle strength showed a decline (114 ± 46 Nm vs. 95 ± 41 Nm, p <0.001). Rehabilitation resumed following hospital discharge (22 (IQR 18-36) days post-transplant) and continued until three months post-transplant (22 ± 6 rehabilitation sessions). Pulmonary function and HRQOL continued to improve from hospital discharge to three months post-transplant (FEV₁ 1.9 ± 0.3 vs. 2.2 ± 0.4, p=0.03, SF-36 physical functioning 47.4 ± 25 vs. 77 ± 13, p<0.001, SGRQ activity domain 49.8 ± 30 vs. 25 ± 20, p<0.001). By three months post-transplant peripheral muscle strength returned to pre-transplant levels (126 ± 36 Nm vs. 125.4 ± 40 Nm, p=0.9), and functional exercise capacity and physical activity exceeded pre-transplant levels (6MWD 385 ±
95 m vs. 517 ± 90m, p<0.001, daily steps 2793 ± 1098 vs. 4639 ± 1864, p<0.001, time spent in moderate intensity per day 4.3 (IQR 1.4-9.8) minutes vs. 14.7 (IQR 8.6-23.3) minutes, p<0.001). Despite significant improvements, functional exercise capacity was not normalized (6MWD 71% predicted) and physical activity did not reach levels obtained by the general population at three months post-transplant, with 52% of lung transplant recipients classified as sedentary.

These findings demonstrate different patterns and degrees of improvement of functional outcomes in the early post-lung transplant period, with the slowest recovery observed in peripheral muscle strength. Rehabilitation strategies should target muscle function in the early post-transplant period and aim to further increase physical activity levels. Optimal recovery of muscle strength, functional exercise capacity and physical activity may require a longer post-transplant period of rehabilitation.
3.2 INTRODUCTION

Lung transplantation is an established treatment option for a variety of end-stage lung diseases with the aim of increasing function, health-related quality of life (HRQOL) and survival. Lung transplant candidates demonstrate severely limited exercise capacity and health-related quality of life due to ventilatory limitations and symptoms. Despite significant improvements in lung function that occur after lung transplant, exercise capacity does not return to normal predicted levels, and this limitation is thought to result from a peripheral limitation to exercise.

Only a few studies have described functional changes in the early post-operative period. Maury and colleagues assessed lung function (forced expiratory volume, FEV1), quadriceps strength and functional exercise capacity (six-minute walk distance, 6MWD) in 36 patients pre-transplant, at hospital discharge and following three months of rehabilitation post-transplant. They found significant improvements in lung function immediately following transplant. The 6MWD did not show immediate improvement, but after three months of rehabilitation was significantly higher than pre-transplant values. Quadriceps strength was reduced immediately following transplant and after three months of rehabilitation recovered to 87% of the pre-transplant values. The authors also found a significant gender effect for the 6MWD following transplant with men achieving higher distances, as well as a trend towards a slower recovery of muscle strength in women. Langer and colleagues assessed FEV1, quadriceps strength, 6MWD and physical activity in 40 patients pre-transplant, following hospital discharge post-transplant, and after three months of either rehabilitation and physical activity counseling (intervention group) or physical activity counseling alone (control group). Both groups showed significant improvements in lung function at hospital discharge with no change in 6MWD or physical activity parameters, and a decline in quadriceps strength compared to pre-transplant values. Three months following hospital discharge, there were improvements in the 6MWD and physical activity in both groups, however quadriceps strength only recovered to pre-transplant levels in the intervention group. One year after hospital discharge, quadriceps strength exceeded pre-transplant values in the intervention group, whereas quadriceps strength was still slightly below pre-transplant levels in the control group. Monro and colleagues assessed FEV1, 6MWD and HRQOL at one, two and three months following lung transplantation in 36 stable lung
transplant recipients who underwent post-transplant rehabilitation and found improvements in functional outcomes between all time points, however pre-transplant values were not available.\textsuperscript{18}

Daily physical activity is an additional outcome that may contribute to deconditioning pre-transplant and functional recovery post-transplantation, and may reflect activity limitation and participation restriction. Physical activity is a complex health-related behaviour, and thus may be influenced by contextual factors (personal and environmental factors) as well as measures of lung function or skeletal muscle strength. Only one recent longitudinal study has objectively examined physical activity before and immediately following lung transplantation.\textsuperscript{17} Lung transplant recipients in this study by Langer et al primarily had a diagnosis of COPD, were between the ages of 40-65 years and experienced an uncomplicated post-transplant hospital course (<6 weeks).\textsuperscript{17} The objectives of our study were to quantify lung function, muscle strength, functional exercise capacity, HRQOL and physical activity in lung transplant recipients with a variety of pre-transplant lung diseases and across all age ranges, describe the changes that occur at hospital discharge and three months post-transplant explore the relationships between functional measures in the early post-transplant period while examining the effects of age, gender and length of hospital stay.

3.3 METHODS

All lung transplant candidates on the lung transplant waiting list at the Toronto General Hospital, Toronto, Canada and who had been participating in the pre-transplant rehabilitation program for a minimum of four weeks were considered for study recruitment. Individuals were excluded if they were awaiting a re-transplant or multi-organ transplant, were admitted to hospital and/or were experiencing a rapid clinical deterioration. Individuals with language barriers and significant cognitive impairments were not recruited. Ethics approval was obtained from the University Health Network (REB # 10-0261-BE). All participants gave written informed consent. Recruitment took place between September 2010 and September 2011.
3.3.1 Measures

Measures of strength, functional exercise capacity, HRQOL and physical activity were completed at three time points; pre-transplant, hospital discharge and three months post-transplant. At each time point, all measures were collected within a two week timeframe.

*Peripheral muscle strength*

Quadriceps torque (QT) was measured on the dominant limb as isometric peak torque (Newton-metres) with the hip positioned at 90 degrees of flexion and knee at 60 degrees of flexion using an isokinetic dynamometer (Biodex Medical Systems, Inc.). A maximum voluntary contraction of 5 seconds was performed with a one minute rest. The highest value of 5 attempts following one warm-up contraction was recorded. Standardized instructions, encouragement and feedback were provided. Results were compared to predicted values.\(^{19}\) This is a measure that has been described previously in the lung transplant literature.\(^{16,17}\)

*Functional exercise capacity*

Functional exercise capacity was measured using the six-minute walk test (6MWT) that was performed according to published guidelines.\(^{20}\) Only one test was performed at the study assessment as subjects had previously done multiple tests during the transplant evaluation and rehabilitation program. The test was performed using the flow rate of supplemental oxygen prescribed for activity and the gait aid typically used outside the home. The 6-minute walk distance (6MWD) was compared to reference values for a Canadian population.\(^{21}\)
**Health-related quality of life**

Health-related quality of life was measured using two instruments (generic and disease-specific) to capture the various health issues that occur both pre- and post-transplant. The generic instrument (SF-36) includes eight scales and two summary scores and is scored from 0-100, with higher scores indicating better health. 22 Results from the SF-36 were compared to Canadian norms. 23 The minimal clinically important difference for the SF-36 has not been defined. 5 The respiratory-specific St.George’s Respiratory Questionnaire (SGRQ) has three domains; symptoms (distress due to respiratory symptoms), activity (effects to mobility and physical activity) and impacts (psychosocial impact of disease) and is also scored from 0-100, with higher scores indicating worse health. 24 The minimal clinically important difference for the SGRQ is 4 units. 25 Both questionnaires have been used in lung transplant candidates and recipients. 5

**Physical activity**

Physical activity was measured with an activity monitor (Actigraph GT3X, Pensacola, FL, USA) worn during the waking hours for seven consecutive days. This light weight (27g), compact (1.5 x 1.44 x 0.7 inch) triaxial accelerometer was worn at the hip attached to a waist belt and recorded the amount, type and pattern of activity (frequency, intensity, duration) including step count. The Actigraph has been validated against portable indirect calorimetry for measuring energy expenditure in physically active adults. 26 Regression equations are used to estimate the intensity of the activity from the accelerometer output (counts). Intensity-specific count ranges are used to classify accelerometer output according to different movement intensities or metabolic equivalents (METS). The accelerometer signal is summed over a user-specific time interval, which for this study were 30-second epochs. Valid days for data collection were defined as greater than 8 hours per day of wear time. Participants were asked to remove the accelerometer while sleeping and bathing. All participants kept an activity diary during the week the accelerometer was worn and were asked to maintain their normal level of daily activity. Participants had to have at least 2 valid days during the week of the assessment to be included in the analysis. The main study measurements were steps per day and minutes spent in moderate intensity activity per day (defined as activity requiring a rate of energy expenditure of 3-6 metabolic equivalents (METS)).
3.3.2 Rehabilitation program pre- and post-lung transplant

All lung transplant candidates were required to participate in a supervised, exercise-based pulmonary rehabilitation program three times per week for the duration of the waiting period prior to transplant. Exercise training was individualized and included stretching, resistance training, endurance training and functional exercises (stairs, squats) and lasted 90 minutes in duration. Intensity was prescribed according to oxygen titration guidelines prescribed by the respirologist (typically ≥ 88%), within symptom tolerance (Borg dyspnea score 3-4), and below a heart rate of 85% age-predicted maximum. Oxygen prescription for exercise was increased as needed to maintain adequate oxygenation. Endurance training on both the treadmill and cycle was targeted for 20 consecutive minutes. The exercise program took place in a hospital outpatient setting and was designed and supervised by physiotherapists.

Immediately post-transplant early mobility was initiated. In the intensive care unit (ICU), lung transplant recipients were screened post-operative day one to determine medical stability to participate in rehabilitation. If medically stable, they were transferred to a chair for 1-2 hours, and ambulated up to 100m with bagging off the ventilator if they were still intubated. A daily progression of sitting time and ambulation frequency, distance and duration was performed. If individuals had a prolonged ICU stay (greater than one week), a portable treadmill, cycle ergometer, Wii, light weights and/or stair climbing were prescribed to increase physical activity, endurance and strength. Upon transfer to the acute step-down unit and ward, mobility was continually progressed with oxygen titration to room air and with increasing independence from gait aids. If individuals were not medically stable in the ICU, range of motion exercises, bed exercise and possible electrical muscle stimulation were performed. Medical stability was reassessed daily and mobility was initiated as soon as it was feasible and safe. In cases of a prolonged hospital stay leading to significant functional limitations that did not allow a safe discharge home, individuals were referred to an inpatient rehabilitation facility for high tolerance, high intensity, short duration rehabilitation.

Upon discharge home, lung transplant recipients resumed an outpatient rehabilitation program three times per week until three months post-transplant that consisted of aerobic and resistance training that was progressed weekly to optimize endurance and strength. Exercise training was
90 minutes in duration and included treadmill, cycling, stairs, and resistance exercises with free weights or pulleys of one set of ten repetitions, with upper extremity exercises limited to ten pounds until three months post-transplant. If required, supplemental oxygen was used to maintain oxygen saturation > 90%. Aerobic exercise was targeted for 20 consecutive minutes with a Borg leg fatigue score of 3-4, and a heart rate of < 85% predicted. Treadmill speed and incline were progressed weekly, and selected patients were allowed to do intermittent periods of running for 30-60 seconds during the treadmill session.

3.3.3 Statistical analysis

Statistical analyses were performed using SAS statistical package (version 9.3, SAS Institute Inc. Cary, NC). Descriptive statistics were used to express measures of pulmonary function, physical activity, functional exercise capacity, HRQOL and muscle strength. The assumption of normality was assessed by the Shapiro-Wilk statistic. Data was expressed as mean and standard deviation unless it deviated significantly from the normal distribution in which case it was expressed as medians and interquartile range (IQR). Pearson or Spearman rank correlation analysis was performed to examine the associations between length of stay (ICU and total acute care hospital) and functional measures (6MWD and QT). Repeated measures analysis of variance (ANOVA) or the equivalent non-parametric test (Friedman’s) was performed to examine the functional change over time by checking for a time effect (pre-transplant, hospital discharge, three months post-transplant). A Tukey-Kramer post-hoc analysis for pairwise comparisons was performed. A gender x time interaction and age x time interaction for functional recovery were also examined. For all analyses, a p value of < 0.05 was considered statistically significant. Power analyses and sample size calculation is described in Appendix B.

3.4 RESULTS

Figure 3.1 shows the subject flow throughout the study. Fifty lung transplant candidates (23 men, aged 55 (IQR 41-63) years, BMI 24.2 ± 4 kg/m²) underwent pre-transplant measures. Table 3.1 describes the underlying lung pathologies. All participants showed significant lung impairment
compared to healthy predicted values. Due to the mix of restrictive and obstructive lung diseases, pulmonary function results were summarized by diagnostic group (Table 3.2). At the time of the study assessment, participants had been on the waiting list for transplant for a median of 2 (IQR 1.5-4) months.

3.4.1 Pre-transplant wait time and functional change

Total time on the waiting list prior to transplant was 5 (IQR 3-9) months. Time between the study assessment and transplant was 2 (IQR 1-6) months. Lung transplant candidates underwent repeated 6MWTs every three months while on the waiting list to monitor any significant functional changes pre-transplant. Fifteen participants had a 6MWT repeated between the study assessment and transplant and showed a decrease of 4 ± 32 m, which is not a clinically significant change in 6MWD.²⁷ All study participants who underwent transplant had maintained a rehabilitation program three times per week pre-transplant. All recipients were outpatients at the time of transplant with the exception of one participant who was admitted to hospital with an exacerbation of IPF for the two weeks prior to transplant. This participant participated in a modified exercise program of resistance exercise and walking on the inpatient unit between hospital admission and transplant.

3.4.2 Length of hospital stay and post-transplant rehabilitation

Thirty-nine participants have undergone a transplant (37 double lung transplants, 2 single lung transplants), (Figure 3.1). The median intensive care unit (ICU) length of stay was 3 (IQR 2-6) days, and total acute hospital length of stay was 17 (IQR 14-32) days. Length of stay was not normally distributed, and transplant recipients’ ICU length of stay ranged from 1 to 32 days. All patients were discharged home with the exception of two patients who were transferred to an inpatient rehabilitation facility for 24 ± 8 days. The time between transplant and starting outpatient rehabilitation was 22 (IQR 18-36) days. Participants underwent 22 ± 6 supervised outpatient exercise sessions between hospital discharge and 3 months post-transplant.
3.4.3 Change in functional outcomes over time

Twenty-nine participants have completed the three month post-transplant assessment (Figure 3.1). Figure 3.2 shows the mean and 95% confidence intervals for study participants who completed measures at all three time points for FEV\textsubscript{1}, QF, 6MWD, HRQOL (physical functioning scale of the SF-36 and the activity domain of the SGRQ), steps and time spent in moderate intensity physical activity. The subscale of physical functioning on the SF-36 and the activity domain on the SGRQ were used as they specifically pertain to limitations in physical functioning. There was a significant time effect for all functional outcomes variables. Pulmonary function improved between pre-transplant and hospital discharge (FEV\textsubscript{1} 1.1 ± 0.5L vs. 1.9 ± 0.5L, p < 0.001) and between hospital discharge and three months post-transplant (FEV\textsubscript{1} 1.9 ± 0.5L vs. 2.2 ± 0.4 L, p=0.03).

Nine of the 29 participants were ≤ 40 years of age. There was an age effect (higher values for younger participants) for 6MWD (p < 0.001), time spent in moderate intensity physical activity (p=0.05), SF-36 physical functioning (p < 0.001) and SGRQ activity domain (p=0.005), but there was no age x time interactions with regards to recovery over time with these variables (6MWD p=0.86, time in moderate intensity physical activity p=0.59, SF-36 p=0.09, SGRQ p=0.69). There was an age x time interaction for QT (p=0.04) indicating a faster recovery of QT in younger transplant recipients. There were gender effects for QT (p<0.01) and normalized QT (p < 0.01) at all three time points, but no gender x time interaction for QT (0.59) or any other functional outcome including the 6MWD (p=0.1).

Muscle strength

Peripheral muscle weakness was evident pre-transplant (QT 113 ± 38 Nm, 75 ± 23 % predicted, n=50). In lung transplant recipients at hospital discharge, QT decreased 17% from pre-transplant levels (114 ± 46 Nm vs. 95 ± 41 Nm, p < 0.001, or 72 ± 29 % predicted to 57 ± 18 % predicted, p < 0.001, n=24). Despite a decrease in body mass index (BMI) at hospital discharge (22.8 ± 4 kg/m\textsuperscript{2} vs. 22.2 ± 4 kg/m\textsuperscript{2}, p=0.05), when QT was normalized for BMI the decrease persisted (5.6 ± 1.7 Nm/kg/m\textsuperscript{2} vs. 4.7 ± 1.5 Nm/kg/m\textsuperscript{2}, p<0.001). There was a recovery of QT to pre-transplant levels by three months post-transplant (126 ± 36 Nm vs. 125 ± 40 Nm, p=0.51) and normalized...
QT (5.6 ± 1.7 Nm/kg/m² vs. 5.4 ± 1.8 Nm/kg/m², p=0.4). A moderate correlation was observed between ICU stay and QT (r = - 0.54, p=0.006), but no statistically significant correlation between total acute care hospital length of stay (LOS) and QT (r = - 0.38, p=0.07).

Functional exercise capacity

Pre-transplant, 14 of the 50 participants (28%) used a rollator walker during the 6MWT, two participants took a rest due to dyspnea, and forty-seven of the 50 participants (94%) wore supplemental oxygen. Thirty-four participants used nasal prongs with flow rates ranging between 1-8 L/min (mean 4.4 ± 1.8 L/min). Additional methods of oxygen supplementation included eight participants using a venturi mask (one at 40%, seven at 50%), one participant using 10L oxymask and four participants using 15L partial non-rebreather masks. Despite supplemental oxygen, moderate desaturation was evident with an end-SpO₂ of 86 ± 7 %. The mean 6MWD of all 50 participants was 374 ± 91 m (52 ± 10 % predicted).

Although there was no significant change in the 6MWD at hospital discharge post-transplant compared to pre-transplant values, other test outcomes including end-test SPO₂, Borg dyspnea and respiratory rate (RR) were significantly improved (Table 3.3). All 6MWTs were performed on room air at hospital discharge except in one single lung transplant recipient who used supplemental oxygen (4 L/min). Eight participants used a rollator walker and one participant required a rest during the test due to fatigue. Of the eight participants who used the rollators, five used them pre-transplant, and the three remaining participants had a prolonged hospital stay (median 31 IQR (30.5-39) days) and exhibited a greater decline in strength (40% decrease in QT at hospital discharge) thereby requiring a rollator for a few weeks. There was an increase in 6MWD from hospital discharge and three months post-transplant (404 ± 106m vs. 517 ± 90m, p <0.001), which exceeded the suggested minimal clinically importance difference of 54 to 80 m. No participant required a rest, supplemental oxygen or a rollator walker during the 6MWT at three months post-transplant, and oxygen desaturation did not occur (mean SpO₂ 95 ± 4%). A modest correlation was observed between length of ICU stay and 6MWD (r = - 0.37, p=0.04) and hospital LOS and 6MWD (r = - 0.37, p=0.04).
Health-related quality of life

Table 3.4 describes HRQOL at all three time periods and includes Canadian normative data for the SF-36. Pre-transplant, all subscales of the SF-36 were decreased, with a greater impairment in the physical domains, specifically physical functioning, role physical, general health and vitality. All domains of the SGRQ were impaired, with the greatest impairment in the activity domain. At hospital discharge, only the domains of physical functioning, general health and vitality of the SF-36 were significantly improved, and bodily pain was worse compared to pre-transplant scores. All domains of the disease-specific SGRQ showed improvement at hospital discharge exceeding the minimal clinically important difference five to eight-fold (21-32 units). Further improvements were observed by three months post-transplant in all subscales/domains of both questionnaires.

Physical Activity

Table 3.5 shows daily steps, time spent in moderate intensity physical activity, number of valid days and accelerometer daily wear time at all three time points. There was no change in physical activity at hospital discharge, and at the pre-transplant and hospital discharge time periods, no participants spent any time in vigorous intensity physical activity (defined as an activity requiring a rate of energy expenditure over 6 METS). At three months post-transplant physical activity increased above pre-transplant levels (daily steps \(2793 \pm 1098\) vs. \(4639 \pm 1864\), \(p <0.001\), time spent in moderate intensity \(4.3\) (IQR 1.4-9.8) minutes vs. \(14.7\) (IQR 8.6-23.3) minutes, \(p <0.001\)). At three months post-transplant six participants engaged in a limited number of short bouts of vigorous intensity physical activity (two bouts per participant lasting \(2\) (IQR 0.5-3.5) minutes and nine participants had \(4 \pm 4\) bouts of moderate intensity physical activity that lasted over 10 minutes. These results are a summary of physical activity over the week the accelerometer was worn, and included rehabilitation and non-rehabilitation days.
3.5 DISCUSSION

This study describes the early functional changes including physical activity in a cohort of individuals pre- and early-post lung transplant. By three months post-transplant lung function, HRQOL, functional exercise capacity and levels of physical activity improved from pre-transplant levels, whereas peripheral muscle strength decreased immediately after transplant at hospital discharge, and recovered to pre-transplant levels by three months post-transplant.

Functional exercise capacity showed significant improvements between hospital discharge and three months post-transplant exceeding pre-transplant levels, but did not reach normal predicted levels (71% predicted). In this study, eight participants used rollator walkers during the 6MWT at hospital discharge, whereas at three months post transplant there was no rollator use. Improvement in functional exercise capacity from hospital discharge to three months post-transplant may not be fully captured if only the 6MWD is examined, as the rollator may have facilitated an increased 6MWD at hospital discharge then could have been achieved without a gait aid. Maury and colleagues also found no immediate change in the 6MWD at hospital discharge. They also reported a significant gender x time interaction effect for the 6MWD showing a slower recovery in women, which is in contrast to this study where there was no interaction for gender and 6MWD.

There was no immediate change in physical activity at hospital discharge, and although physical activity increased by three months post-transplant, it did not reach levels of the general population. In this study the average daily steps at three months of 4660 is similar to the 4977 daily steps reported in stable lung transplant recipients one year post-transplant by Langer and colleagues, and the 5194 steps achieved by the exercise intervention group three months post hospital discharge. In classifying activity level with step count, 96% of participants pre-transplant would be considered sedentary (< 5000 steps per day) and 4 % as low active (5000-7499 steps per day), whereas at three months post-transplant 52% are considered as sedentary, 40% as low active and 8% as somewhat active (7500-9999 steps per day). At three months post-transplant, although they are undergoing post-transplant rehabilitation, participants are still traveling regularly to the hospital for tests, and this period may not represent their regular activity level once they return to their regular medical care in their community after three months post-transplant. It is worthwhile to note that only 35% of the general Canadian
population achieves the 10000 steps per day target and on average would be considered somewhat active (7500 – 9999 steps per day).

There was a significant decrease in QT of 17% at hospital discharge. Although body mass decreased at hospital discharge, when quadriceps torque was normalized to BMI, the decrease persisted. Many transplant recipients are on diuretics due to fluid retention at hospital discharge, which may limit the usefulness of using body mass index to represent lean body mass, and may not be able to distinguish changes in muscle quantity. Maury and colleagues report a drop in QF of 32%, which was a larger decrease than was observed in this study. The length of stay in Maury’s cohort was longer than in this study (median ICU LOS 6 days (IQR 4-11) vs. 3 days (IQR 2-6) and total acute care LOS (30 days (IQR 23-44) vs. 17 days (IQR 14-32)). In this study, QT recovered to pre-transplant levels by three months post-transplant, and reached 76 ± 15% of predicted levels. This is in contrast to the study by Maury et al who found that QF did not recover and only reached 87% of pre-transplant levels after three months of post-transplant rehabilitation (59 ± 26% predicted). In our study, there was a general gender effect for QT, but no gender x time interactions for any variable, whereas Maury et al reports a trend towards a gender x time interaction in QT, with women showing a slower recovery. The study by Maury had a greater number of rehabilitation sessions (27 ± 10 vs. 22 ± 6 sessions) which was begun later post-transplant (median 37 days (IQR 29-61) vs. 22 days (IQR 18-36). They did not report any pre-transplant rehabilitation in their cohort. It is possible that participants in our study underwent earlier mobilization post-transplant which may have facilitated an increased recovery in quadriceps strength by three months post-transplant. The study by Langer et al that included only recipients with an uncomplicated hospital length of stay (ICU LOS 5 ± 2 days, hospital LOS 27 ± 7 days) report a similar decline in quadriceps strength as our study (15-20%) in both the exercise intervention and control groups at hospital discharge. Similar to our study quadriceps strength returned to pre-transplant levels (82% predicted levels) in the exercise intervention group.

In this study, while ICU LOS was significantly associated with QT, total acute hospital LOS was not. Maury and colleagues also reported that the number of days in the ICU was significantly related to deterioration in muscle strength post-transplant. This could be due to the patients’ increased dependence on invasive lines, gait aids and assistance from healthcare professionals.
for mobility in the ICU environment as compared to the increased independent mobility achieved while on the inpatient ward.

Limited physical activity and functional exercise capacity at hospital discharge may reflect the effects of a prolonged hospital stay, and decreased muscle strength. Immediate improvements were observed in pulmonary function and HRQOL at hospital discharge, and are likely related to the relief of the ventilatory limitation, decreased symptoms and liberation from supplemental oxygen. The disease-specific SGRQ which measures disease symptoms and impact showed significant improvements in all domains at hospital discharge, and may be more responsive to the improvement in lung function post-transplant. The generic SF-36 questionnaire only showed improvements in some subscales at hospital discharge (physical functioning, general health, vitality and role emotional), whereas role physical, social functioning and mental health did not change, and bodily pain worsened. Social functioning and physical roles are unlikely to be normal during hospitalization since individuals are not in their home environment and are dependent on healthcare professionals for many basic and instrumental activities of daily living. The increase in bodily pain at hospital discharge is likely related to post-operative incisional pain that was not experienced pre-transplant and subsequently underwent natural healing by three months post-transplant.

In this study there was an age effect for 6MWD, time spent in moderate physical activity, SF-36 and SGRQ, and an age x time interaction for QT recovery post-transplant which may be influenced by contextual factors such as employment, family responsibilities, and socially accepted and expected levels of physical activity. Individuals under 40 years of age were not included in the studies by Maury et al or Langer et al,\textsuperscript{16,17} therefore this study is the first to quantify early functional changes and physical activity in lung transplant recipients ≤ 40 years of age.

Limitations of this study include incomplete data as not all candidates have undergone transplant or finished the three month post-transplant assessment. There is missing data due to pre- and post-transplant mortality, a prolonged post-transplant hospitalization > three months, and the inability to obtain all functional measures within a two week time period due to missed appointments, readmissions to hospital and invalid accelerometry data due to non-compliance or technical difficulties (Figure 3.1). Individuals who experienced these medical complications
and/or non-compliance with the testing procedures may have had a different pattern of functional recovery. The accelerometer used in this study was hip-mounted, and likely underestimated the time spent in moderate intensity physical activity that would have occurred with upper extremity and other non-ambulatory activities.

3.6 CONCLUSION

This study has described the early changes in functional outcomes following lung transplant at hospital discharge and three months post-transplant. Functional improvement appears to occur at different time periods and to varying degrees of change. Further studies should focus on measuring aspects of skeletal muscle (muscle mass, endurance, metabolism, composition), assessing different training strategies to improve strength and physical activity, and to determine if functional improvement continues to occur after three months post-transplant.
Figure 3.1: Study Flow Sheet
**Table 3.1: Pre-transplant lung diagnoses (n=50)**

<table>
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<td>12</td>
</tr>
<tr>
<td>- IPF/COPD</td>
<td>2</td>
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<tr>
<td>- NSIP</td>
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</tr>
<tr>
<td>- Scleroderma</td>
<td>3</td>
</tr>
<tr>
<td>- Polymyositis/ Rheumatoid arthritis</td>
<td>1</td>
</tr>
<tr>
<td>- Sjogren’s syndrome</td>
<td>1</td>
</tr>
<tr>
<td>- Sarcoidosis</td>
<td>2</td>
</tr>
<tr>
<td>- Extrinsic allergic alveolitis</td>
<td>1</td>
</tr>
<tr>
<td>COPD (n=10)</td>
<td></td>
</tr>
<tr>
<td>- Emphysema</td>
<td>9</td>
</tr>
<tr>
<td>- Alpha 1 antitrypsin deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Cystic Fibrosis (n=9)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Hypertension (n=4)</td>
<td></td>
</tr>
<tr>
<td>- IPAH</td>
<td>1</td>
</tr>
<tr>
<td>- APAH due to CHD</td>
<td>1</td>
</tr>
<tr>
<td>- PVOD</td>
<td>1</td>
</tr>
<tr>
<td>- CTEPH</td>
<td>1</td>
</tr>
<tr>
<td>Bronchiectasis (n=3)</td>
<td></td>
</tr>
</tbody>
</table>

IPF: idiopathic pulmonary fibrosis; COPD: chronic obstructive pulmonary disease; NSIP: non-specific interstitial pneumonia; IIP: interstitial idiopathic pneumonia; RA: rheumatoid arthritis; IPAH: idiopathic pulmonary arterial hypertension; APAH: associated pulmonary arterial hypertension; CHD: congenital heart disease; PVOD: pulmonary veno-occlusive disease; CTEPH: chronic thromboembolic pulmonary hypertension.
Table 3.2: Pre-transplant pulmonary function by diagnostic group (n=50)

<table>
<thead>
<tr>
<th></th>
<th>COPD (n=10)</th>
<th>ILD (n=24)</th>
<th>CF (n=9)</th>
<th>PH (n=4)</th>
<th>Bronchiectasis (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (L)</td>
<td>0.6 ± 0.2</td>
<td>1.4 ± 0.5</td>
<td>0.8 ± 0.2</td>
<td>2.1 ± 0.7</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (% pred)</td>
<td>20 ± 5.5</td>
<td>45 ± 15</td>
<td>22 ± 5</td>
<td>63 ± 18</td>
<td>34 ± 8</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.4 ± 0.8</td>
<td>1.9 ± 0.6</td>
<td>1.8 ± 0.5</td>
<td>3.1 ± 0.5</td>
<td>2.1 ± 0.5</td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td>64 ± 18</td>
<td>47 ± 14</td>
<td>44 ± 9</td>
<td>77 ± 11</td>
<td>56 ± 21</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>7.7 ± 1.5</td>
<td>3.4 ± 1.2</td>
<td>5.7 ± 1.5</td>
<td>5.7 ± 0.3</td>
<td>4.9 ± 0.4</td>
</tr>
<tr>
<td>TLC (% pred)</td>
<td>134 ± 24</td>
<td>56 ± 18</td>
<td>104 ± 21</td>
<td>97 ± 11</td>
<td>87 ± 13</td>
</tr>
<tr>
<td>D&lt;sub&gt;LCO&lt;/sub&gt;</td>
<td>7 ± 3</td>
<td>8 ± 3</td>
<td>12 ± 5</td>
<td>15 ± 7</td>
<td>10 ± 0</td>
</tr>
<tr>
<td>(ml/min/mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D&lt;sub&gt;LCO&lt;/sub&gt; (% pred)</td>
<td>31 ± 10</td>
<td>43 ± 12</td>
<td>67 ± 12</td>
<td>64 ± 25</td>
<td>54 ± 0</td>
</tr>
</tbody>
</table>

data expressed as mean ± SD

COPD: chronic obstructive lung disease; ILD: interstitial lung disease; CF: cystic fibrosis; PH: pulmonary hypertension; FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; D<sub>LCO</sub>: diffusing capacity for carbon monoxide
Figure 3.2: Functional Outcomes over Time

- FEV₁ (L)
- SF-36
- SGRQ
- QT (Nm)
- 6MWD (m)
- Steps
- moderate PA (minutes)

Pre-transplant | Hospital discharge | 3 months post-transplant
Data expressed as mean + 95% confidence interval
**Table 3.3:** 6-minute walk test: Pre-transplant, hospital discharge and 3 months post-transplant

<table>
<thead>
<tr>
<th></th>
<th>Pre-transplant (n=50)</th>
<th>Hospital discharge (n=31)</th>
<th>3 months post (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD (m)</td>
<td>374 ± 91</td>
<td>407 ± 105</td>
<td>518 ± 89 †,‡</td>
</tr>
<tr>
<td>6MWD (% pred)</td>
<td>52 ± 10</td>
<td>55 ± 13</td>
<td>71 ± 10 †,‡</td>
</tr>
<tr>
<td>End-test SpO₂ (%)</td>
<td>86 ± 7</td>
<td>95 ± 3 †</td>
<td>95 ± 4 †</td>
</tr>
<tr>
<td>End-test Borg</td>
<td>4.3 ± 2</td>
<td>2.3 ± 1 †</td>
<td>2.4 ± 2 †</td>
</tr>
<tr>
<td>End-test Borg dyspnea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-test Borg leg fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-test RR</td>
<td>35 ± 13</td>
<td>29 ± 6 †</td>
<td>27 ± 6 †</td>
</tr>
</tbody>
</table>

data expressed as mean ± SD

In bold are the variables with a significant time effect in repeated measures ANOVA. P values refer to the post-hoc tests as follows:

† p<0.05 vs. pre-transplant

‡ p<0.05 vs. hospital discharge

* Pre-transplant 47/50 participants used supplemental oxygen, at hospital discharge 1/31 participants used supplemental oxygen, at 3 months post-transplant no participants used supplemental oxygen
**Table 3.4:** Health-related quality of life: Pre-transplant, hospital discharge and 3 months post-transplant

<table>
<thead>
<tr>
<th></th>
<th>Pre-transplant (n=50)</th>
<th>Hospital discharge (n=32)</th>
<th>3 months post-transplant (n=29)</th>
<th>Canadian population norm *</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role physical</td>
<td>23 ± 16</td>
<td>47 ± 25 T</td>
<td>77 ± 13 T, l</td>
<td>86 ± 20</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>74 ± 25</td>
<td>43 ± 20 T</td>
<td>72 ± 22 l</td>
<td>76 ± 23</td>
</tr>
<tr>
<td>General Health</td>
<td>25 ± 18</td>
<td>55 ± 17 T</td>
<td>61 ± 15 T</td>
<td>77 ± 18</td>
</tr>
<tr>
<td>Vitality</td>
<td>38 ± 16</td>
<td>47 ± 21 T</td>
<td>72 ± 17 T, l</td>
<td>66 ± 18</td>
</tr>
<tr>
<td>Social function</td>
<td>52 ± 24</td>
<td>52 ± 27</td>
<td>78 ± 21 T, l</td>
<td>86 ± 20</td>
</tr>
<tr>
<td>Role emotional</td>
<td>68 ± 41</td>
<td>73 ± 39</td>
<td>85 ± 30 T, l</td>
<td>84 ± 32</td>
</tr>
<tr>
<td>Mental Health</td>
<td>73 ± 15</td>
<td>74 ± 15</td>
<td>83 ± 12 T, l</td>
<td>78 ± 15</td>
</tr>
<tr>
<td>SGRQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>60 ± 22</td>
<td>35 ± 26 T</td>
<td>17 ± 16 T, l</td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td>81 ± 12</td>
<td>49 ± 31 T</td>
<td>25 ± 20 T, l</td>
<td></td>
</tr>
<tr>
<td>Impact</td>
<td>48 ± 16</td>
<td>27 ± 17 T</td>
<td>12 ± 9 T, l</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>61 ± 13</td>
<td>36 ± 20 T</td>
<td>17 ± 12 T, l</td>
<td></td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD

In bold are the variables with a significant time effect in repeated measures ANOVA. P values refer to the post-hoc tests as follows:

T p<0.05 vs. pre-transplant

l p<0.05 vs. hospital discharge

* for all ages (Hopman et al. 22)
Table 3.5: Physical activity: pre-transplant, hospital discharge and 3 months post-transplant

<table>
<thead>
<tr>
<th></th>
<th>Pre-transplant (n=50)</th>
<th>Hospital discharge (n=28)</th>
<th>3 months post (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily steps</td>
<td>2666 ± 1364</td>
<td>2692 ± 1458</td>
<td>4639 ± 1864</td>
</tr>
<tr>
<td>Time in moderate intensity (minutes)</td>
<td>4.3 (1.4-9.8)</td>
<td>4.1 (1.4-9.6)</td>
<td>14.7 (8.6-23.3)</td>
</tr>
<tr>
<td>Valid days</td>
<td>6.6 ± 1</td>
<td>5.4 ± 2</td>
<td>5.6 ± 2</td>
</tr>
<tr>
<td>Wear time (hours/day)</td>
<td>14.2 ± 2</td>
<td>13.7 ± 2</td>
<td>13.8 ± 2</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD

In bold are the physical activity variables with a significant time effect in repeated measures ANOVA. P values refer to the post-hoc tests as follows:

Ț p<0.05 vs. pre-transplant

ƚ p<0.05 vs. hospital discharge
3.9 REFERENCES


Chapter Four
Discussion, Conclusion and Future Directions

4.1 GENERAL DISCUSSION

This thesis provides a detailed description of muscle strength, functional exercise capacity, health-related quality of life (HRQOL) and daily physical activity in lung transplant candidates of varying diagnoses and ages, and examines the early recovery of these functional outcomes following lung transplant at hospital discharge and three months post-transplant.

Hypotheses Revisited

Hypothesis #1: Muscle strength, functional exercise capacity, HRQOL and physical activity will be severely impaired pre-transplant compared to the general population. Results from studies 1 and 2 show that all functional outcomes were impaired in the 50 lung transplant candidates who were recruited, although the severity of impairment varied depending on the outcome measured. Peripheral muscle weakness was evident pre-transplant; however quadriceps torque showed only a modest decrease to 75 ± 23% of predicted levels. Other functional outcomes showed more pronounced limitations; functional exercise capacity (6-minute walk distance) was 52 ± 10% predicted, HRQOL was low with all sub-scales of the SF-36 other than mental health and bodily pain well-below Canadian norms, and all domains of the respiratory-specific SGRQ indicated poor health. Physical activity levels were very low, with lung transplant candidates accumulating a third the number of daily steps and time spent in moderate intensity activity compared to the general population.

Hypothesis #2: A significant increase in all functional outcomes post-transplant will occur with the greatest improvement observed between hospital discharge and three months post-transplant. There was a significant increase in all functional outcomes except muscle strength, which decreased at hospital discharge and returned to pre-transplant levels by three
months post-transplant. The greatest improvement in functional exercise capacity and physical activity occurred between hospital discharge and three months post-transplant, as there was no improvement in these outcomes at hospital discharge from pre-transplant levels. Health-related quality of life improved significantly at both time-points (pre-transplant to hospital discharge, and hospital discharge to three months post-transplant), for all of the SGRQ domains and some of the SF-36 sub-scales (physical functioning, general health and vitality).

**Hypothesis #3:** Physical activity will correlate with measures of muscle strength and functional exercise capacity with the 6MWT having the strongest correlation with physical activity pre-transplant. Pre-transplant, the number of daily steps showed a moderate correlation with quadriceps torque and the 6MWD, and time spent in moderate intensity activity showed a moderate correlation with the 6MWD in the subset of participants with interstitial lung disease.

**Hypothesis #4:** Men and younger individuals (≤ 40 years) will have higher levels of muscle strength, functional exercise capacity and physical activity pre- and post-transplant. Functional outcomes will be decreased in participants requiring a prolonged hospitalization. There was an age effect for the 6MWD and time spent in moderate intensity physical activity with younger recipients ≤ 40 years exhibiting higher 6MWDs and more time spent in moderate intensity; however there was no age x time interaction that would indicate a different recovery profile post-transplant for younger transplant recipients. There was a gender effect for muscle strength, with men exhibiting a higher quadriceps torque (QT), but no gender x time interaction. There was a modest correlation between length of stay in the intensive care unit (ICU) and acute care hospital with the 6MWD, as well as a moderate correlation between ICU stay and muscle strength.
Novel findings

This was the first study to measure daily physical activity in a cohort of adult lung transplant recipients of all ages pre- and post-transplant. Pre-transplant, individuals were inactive, despite undergoing pre-transplant rehabilitation, and levels of physical activity did not improve at hospital discharge post-transplant which may have been due to pre-transplant deconditioning and limited mobility during hospitalization. By three months post-transplant and after participation in a post-transplant rehabilitation program for 6-9 weeks, physical activity levels increased significantly but did not reach levels of a general population.

This was also the first study to measure daily physical activity in lung transplant candidates undergoing rehabilitation. In a subset of participants with interstitial lung disease (ILD), physical activity levels were increased on rehabilitation vs. non-rehabilitation days. Physical activity was also moderately correlated with the 6MWD in this population.

This study included participants less than 40 years of age, which is a group that has not been studied in previous studies of early functional change in muscle strength, HRQOL, functional exercise capacity or physical activity pre- to post-transplant. In this small sample, while younger candidates and recipients ≤ 40 years spent more time in moderate intensity physical activity, there was no interaction indicating a different pattern of recovery in physical activity post-transplant.

This research confirmed an early decrease of peripheral muscle strength post-transplant, and an unchanged 6MWD at hospital discharge. The drop in QT from pre-transplant to hospital discharge post-transplant was less than the study by Maury et al (17% vs. 32%), but similar to Langer et al. In contrast to the study by Maury et al we did not observe a gender x time interaction for 6MWD recovery.

Limitations

Only lung transplant candidates who were outpatients and ambulatory were recruited for this study, and therefore individuals experiencing a rapid deterioration, acute exacerbation, infection or hospitalization are not represented. Post-transplant, only individuals who were discharged
home within three months post-transplant were included, therefore this study does not include lung transplant recipients who experience a very complicated post-transplant course necessitating a prolonged hospital length of stay. Functional recovery is likely to be slower in these individuals than what was observed in this research.

The use of the hip-mounted accelerometer to measure physical activity may have underestimated energy expenditure in this study, particularly for upper extremity movement and other non-ambulatory activities. We cannot compare the time spent in moderate intensity physical activity in this study to other studies in lung transplant candidates or recipients where other types of motion sensors with a different body placement were used.

Not all the participants who were recruited have received a transplant or have undergone the three month post-transplant assessment. There is missing data due to pre- and post-transplant mortality, prolonged hospitalization greater than three months, and the inability to obtain all functional measures within a two week time period due to readmission to hospital and missed appointments, and noncompliance and technical difficulties with the accelerometer. These issues may have created a selection bias of participants who experienced a less complicated post-transplant course and potentially achieved better functional outcomes.

**Clinical Implications**

This research provides a description of the expected functional outcomes pre- and early post-lung transplantation. Improving physical activity pre-transplant may improve functioning post-transplant, and therefore rehabilitation should be recommended to lung transplant candidates and individuals with severe lung disease to increase physical activity. Although physical activity levels were higher on rehabilitation days in transplant candidates, they were lower than the general population, likely due to severe ventilatory limitations of abnormalities of gas exchange and symptoms of dyspnea. Ensuring that individuals are supported with appropriate oxygen during exercise is essential, and providing gait aids, other supportive equipment and educating about energy conservation may further facilitate increased physical activity in the home environment. Adjuncts to traditional exercise training should be considered in an attempt to increase intensity and duration of exercise and therefore physical activity, and could include strategies such as interval training, one-legged cycling and the use of non-invasive
ventilation\textsuperscript{9} or helium-hyperoxia\textsuperscript{10} during exercise. The 6MWD is moderately correlated with physical activity pre-transplant, and since this is a common outcome used in pulmonary rehabilitation and in lung transplant population the 6MWD may provide an indication of an individual’s physical activity level.

A longer ICU and acute care hospital stay were related to a decrease in functional exercise capacity and muscle strength at hospital discharge, supporting the use of early mobility and intensive inpatient rehabilitation as part of the early post-transplant management. Individuals with a prolonged hospital stay may require a longer and more intensive period of rehabilitation post-transplant and may not achieve the same level of functional improvement post-transplant. At hospital discharge, a drop in muscle strength was observed, and rehabilitation efforts should focus on the recovery of muscle strength post-transplant through aerobic, resistance and functional exercise. Early post-transplant rehabilitation was able to be initiated within three weeks of transplant in our study cohort, and therefore lung transplant recipients can be referred to post-transplant rehabilitation program upon discharge from hospital.

Health-related quality of life improves early after lung transplant. The disease-specific SGRQ showed greater changes in the early post-transplant period with all domains showing improvement at hospital discharge and three months post-transplant, and is likely due to the relief of the lung impairment and respiratory symptoms. In the longer-term post-transplant, particularly in stable lung transplant recipients in the absence of bronchiolitis obliterans syndrome, the SGRQ may not be a sensitive measure of HRQOL, and a generic measure such as the SF-36 may be more appropriate.

Levels of physical activity were not normalized by three months post-transplant. Physical activity counseling in addition to exercise prescription or participation in a rehabilitation program may further increase physical activity levels in lung transplant recipients. Improving physical activity post-transplant may help to reduce the development of co-morbidities including hypertension, diabetes, obesity and hyperlipidemia post-transplant.\textsuperscript{4} Targeting higher intensity training and encouraging transplant recipients to continue with a regular exercise program after the intensive medical follow-up at the transplant centre is completed at three months post-transplant may further increase physical activity levels. Younger transplant recipients (≤40 years) may show greater improvements in physical activity after three months post-transplant if
they return to paid employment or participate in higher intensity extracurricular activities such as sports.

4.2 CONCLUSIONS

This thesis examined muscle strength, functional exercise capacity, health-related quality of life and physical activity in individuals pre- and early post-lung transplantation at hospital discharge and three months post-transplant. The findings confirm an early drop in quadriceps torque at hospital discharge which provides further evidence of peripheral muscle limitation in lung transplant recipients and highlights the potential role of pre- and post-transplant rehabilitation to target and improve muscle strength. Other functional outcomes of HRQOL, functional exercise capacity and physical activity recover at different time periods and at varying rates of improvement, and are not normalized by three months post-transplant.

4.3 DIRECTIONS FOR FUTURE RESEARCH

Future research should determine if functional outcomes in lung transplant recipients can reach levels of the general population with a prolonged period of rehabilitation or specific rehabilitation strategies. Alternatives to hospital-based supervised outpatient programs including home and community-based exercise should be explored. Studies should specifically target peripheral muscle dysfunction following lung transplantation, and all aspects of muscle structure and function should be assessed to determine specific limitations and to focus rehabilitation efforts. This should include different measurements of muscle strength (isometric and isokinetic torque including concentric and eccentric contractions), contractility, muscle volume and atrophy, muscle endurance and fatigue, intramuscular fat infiltration, cellular features and muscle metabolism to measure overall muscle quality. Interventional studies should study rehabilitation strategies that incorporate different intensities, volume and duration of exercise, as well as various methods of training muscle strength, endurance and power to determine the optimal exercise prescription for lung transplant candidates and recipients.
Further study could determine if a different functional recovery profile and response to rehabilitation exists between younger and older transplant recipients. Pre-transplant, investigations using adjuncts to traditional exercise training should be done to determine if it is possible to further increase physical activity, strength and functional exercise capacity in lung transplant candidates. It should also be determined if pre-transplant levels of physical activity are related to health status or post-transplant outcomes.

Investigation of how exercise training and levels of physical functioning relates to survival and other co-morbidities such as obesity, cardiovascular and metabolic disease would be valuable for the long-term management of lung transplant recipients. Investigations should also assess if intensive and targeted rehabilitation strategies in the ICU and hospital such as neuromuscular electrical stimulation and early mobilization can prevent the early drop in muscle torque at hospital discharge. Functional recovery, response to exercise training and inpatient rehabilitation needs of individuals with a prolonged hospitalization should also be assessed. Pre-transplant assessment of frailty and other potential predictors of a prolonged hospitalization could be important in identifying transplant candidates who will show better post-transplant outcomes.
4.4 REFERENCES


APPENDIX A: Informed Consent Form

A-1  Informed Consent Form

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

INFORMED CONSENT

Introduction:

You are being asked to take part in a research study. Please read this explanation about the study and its risks and benefits before you decide if you would like to take part. You should take as much time as you need to make your decision. You should ask the study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish. Participation in this study is voluntary.

Background and Purpose:

You have been asked to take part in this research study because you have been placed on the lung transplant waiting list at the University Health Network (UHN). While we know that functional ability improves significantly after lung transplant, there are persistent limitations in muscle strength and exercise capacity when compared to a healthy population. It is not clear what factors affect recovery after lung transplant, or what the optimal training guidelines are to maximize improvements in muscle function and exercise capacity following transplant. This study will look at skeletal muscle strength, functional exercise capacity and levels of daily physical activity pre-transplant and in the early post-transplant period. This study will also examine the relationship between these measures and explore the contributing factors that impact on functional recovery such as age, gender and length of hospital stay. About 50 people from the lung transplant program at UHN will be in this study.
**Study Design:**

This is a longitudinal cohort study. This means that assessments will be take place over a period of time. There will be four visits during the study. Most visits will last for one hour and will be scheduled around times you are at UHN for rehabilitation or other medical appointments. If you decide to participate, you will be enrolled in this study before your transplant and remain until six months following your lung transplant.

**Study Visits and Procedures:**

There will be four study visits: before transplant, at hospital discharge after transplant, 3 months after transplant and 6 months after transplant. Three procedures will be performed at UHN and one procedure will be performed at the University of Toronto. On all four visits the following will take place:

1. Six-minute walk test – this is a standard-of-care procedure to measure your functional ability and will be performed at UHN. This test requires you to walk as far as possible in 6 minutes.
2. Health-related quality of life questionnaires – this is a research-related procedure and will ask questions about your functional health and well-being, and will be performed at UHN.
3. Instruction on the use of physical activity monitor, activity diary and log page – this is a research-related procedure that will demonstrate how to use the physical activity monitors. These will be worn at home during the waking hours for seven consecutive days. Filling out the activity diary and log page will take between 5 to 10 minutes each day.
4. Strength measures – this is a research-related procedure done at the University of Toronto. This test uses a machine that will test your leg strength in a sitting position for five repetitions.

If there is a significant decrease in the distance you can walk in 6 minutes while you are waiting for transplant, the questionnaires, physical activity monitoring and strength measures will be repeated.
Reminders:

It is important to remember the following things during this study:

- Ask your study team about anything that worries you
- Tell the study staff anything about your health that has changed
- Return the physical activity monitor, activity diary and log page (or arrange pick-up times)
- Tell the study staff if you change your mind about being in the study

Risks related to being in the study

This study has risks including possible delayed muscle soreness following the strength testing.

Some questions are very personal having to do with your ability to perform tasks of everyday living. It is important that you know that you do not have to answer any question you do not wish to answer, and that you can stop at any time. It also may be embarrassing for you, if the results of your questionnaire became known publicly. For this reason the research team will do everything possible to maintain the confidentiality of all surveys. No names will be collected with surveys. No participant will be given access to the surveys of other participants. Individual results will not be published. Only group findings will be made public.

Benefits to being in the study

You will not receive any direct benefit from being in this study. Information learned from this study may help other people undergoing lung transplant in the future.

Voluntary Participation

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now and then change your mind later. You may leave the study at any time without affecting your care. You may refuse to answer any question you do not want to answer.
We will give you new information that is learned during the study that might affect your decision to stay in the study.

Confidentiality

If you agree to join this study, the study investigator and his/her study team will look at your personal health information and collect only the information they need for the study. Personal health information is any information that could be used to identify you and includes your:

- name,
- address,
- date of birth,
- new or existing medical records, that includes types, dates and results of medical tests or procedures.

The information that is collected for the study will be kept in a locked and secure area by the study investigator for 10 years. Only the study team or the people or groups listed below will be allowed to look at your records. Your participation in this study also may be recorded in your medical record at this hospital.

Representatives of the University Health Network Research Ethics Board may look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study followed proper laws and guidelines.

All information collected during this study, including your personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law. You will not be named in any reports, publications, or presentations that may come from this study.

If you decide to leave the study, the information about you that was collected before you left the study will still be used. No new information will be collected without your permission.
In case you are harmed in the study

If you become ill, injured or harmed as a result of taking part in this study, you will receive care. The reasonable costs of such care will be covered for any injury, illness or harm that is directly a result of being in this study. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and professional responsibilities. You do not give up any of your legal rights by signing this consent form.

Expenses associated with participation in the study

You will not have to pay for any of the procedures involved in this study. You will be reimbursed for any extra parking or transportation costs up to $20 per study visit.

Conflict of interest

Lisa Wickerson is pursuing this research as part of her graduate studies and therefore has an interest in completing this study. Her interest should not influence your decision to participate in this study. You should not feel pressured to join this study.

Questions about the study

If you have any questions, concerns or would like to speak to the study team for any reason, please call: Lisa Wickerson at 416 340 3800 ext. 3982.

If you have any questions about your rights as a research participant or have concerns about this study, call the University Health Network Research Ethics Board (REB) or the Research Ethics office number at 416-946-4438. The REB is a group of people who oversee the ethical conduct of research studies. These people are not part of the study team. Everything that you discuss will be kept confidential.

Consent

This study has been explained to me and any questions I had have been answered.
I know that I may leave the study at any time. I agree to take part in this study.

Print Study Participant’s Name  Signature  Date

(You will be given a signed copy of this consent form)

My signature means that I have explained the study to the participant named above. I have answered all questions.

Print Name of Person Obtaining Consent  Signature  Date

Was the participant assisted during the consent process?  ☐ YES  ☐ NO

If YES, please check the relevant box and complete the signature space below:

☐ The person signing below acted as a translator for the participant during the consent process and attests that the study as set out in this form was accurately translated and has had any questions answered..

__________________________________________  ________________________________
The consent form was read to the participant. The person signing below attests that the study as set out in this form was accurately explained to, and has had any questions answered.

Print Name of Witness

Signature

Date

Relationship to Participant

Language

☐ The consent form was read to the participant. The person signing below attests that the study as set out in this form was accurately explained to, and has had any questions answered.

Print Name of Witness

Signature

Date

Relationship to Participant
APPENDIX B: Sample Size Calculation

B-1 Sample size calculation

Power analyses were based on data available in the literature on the correlation between daily physical activity and functional outcomes in lung transplant recipients.\textsuperscript{1,2} It was anticipated that a sample size of 35 subjects would yield 80\% power ($\alpha = 0.05$) to detect moderate associations ($r = 0.60$) between measures of physical activity during daily life and measures of exercise capacity, strength and HRQOL. The sample size was inflated in the pre-operative period to compensate for incomplete data collection due to pre-operative and early post-operative mortality, and in cases where subjects are not discharged from hospital by 3 months post-transplant or are unable to ambulate at 3 months post-transplant and could thereby not undergo measurements of strength, functional exercise capacity and physical activity. In order to have a sample size of 35 subjects at the 3 month time period, it was anticipated that 50 subjects would need to be recruited pre-operatively. This estimation was based on statistics from 2007-2009 transplant databases at the Toronto General Hospital, which showed that 13\% of patients died on the waiting list per year and 10\% of patients died within 6 months post-transplant per year. In addition, 15\% of patients were referred to inpatient rehabilitation post-operatively per year, and it is estimated that a small portion of these patients may not be discharged or ambulating within 3 months post-transplant to be included in the study. This expected attrition created a potential bias in the study population. All data collected was analysed, even if subjects did not complete all three assessments.
