Understanding the Progression of Skeletal Muscle Dysfunction in Lung Transplant Candidates

By

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A thesis submitted in conformity with the requirements for the degree of Masters of Rehabilitation Science

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Abstract

Skeletal muscle dysfunction has been linked to physical function limitations in lung transplant (LTx) recipients\(^1\). The purpose of this thesis research was to characterize muscle size, muscle strength, and functional outcomes in LTx candidates.

Thirty-four LTx candidates (60 ± 8 years; 59% males) and 12 healthy controls (56 ± 9.5 years; 50% males) were included. All subjects underwent measures of muscle cross sectional area (CSA) and layer thickness (LT) of quadriceps, calf and biceps using B-mode ultrasound (US). Muscle strength of the corresponding muscles and functional tests were also assessed.

LTx candidates had muscle weakness of lower limbs. Distal leg and upper limb strength and size were not impaired but exercise capacity of upper and lower limbs was significantly impaired when compared with controls. Thus, specific exercise training strategies such as resistance training are required pre- and post-transplant to target improvements in lower limb muscle function.

**Keywords:** Lung transplant, skeletal muscle, exercise capacity, muscle atrophy
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List of Abbreviations, Symbols and nomenclature

**BMI** – body mass index

**BORG** – Borg scale of perceived exertion

**CF** – cystic fibrosis

**CT** – computerized tomography

**COPD** – chronic obstructive lung disease

**CSA** – cross-sectional area

**FVC** – forced vital capacity

**HHD** – hand held dynamometer

**IPF** – idiopathic pulmonary fibrosis

**IQR** – interquartile range

**LT** – Layer Thickness

**LTx** – lung transplant

**MRI** – Magnetic Resonance Imaging

**PASE** – Physical Activity Scale for the Elderly

**RF** – rectus femoris

**RPE** - Rated Perceived Exertion

**RR** – respiratory rate

**SD** – standard deviation
**SPPB** – Short Physical Performance Battery Test

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

**TUG** – Timed up and Go

**US** - ultrasound

**UULEX** – Unsupported Upper Limb Exercise Test

**VI** – vastus intermedius

**VL** – vastus lateralis

**6-MWT** – 6-minute walk distance

**6-MWT %Pred** – 6-minute walk test predicted
Format of the Thesis

This thesis is presented in *traditional format* and includes the following main chapters: Introduction, Literature Review, Methods, Results, Overall Discussion, Conclusion and Directions for Future Research.
Chapter 1
Introduction

Lung transplantation is the treatment of choice for selected patients with end-stage lung disease. Despite the satisfactory recovery in lung function post-transplant, decreased exercise capacity still limits the ability of lung transplant (LTx) recipients to engage in regular physical activities. Skeletal muscle dysfunction is hypothesized to be a key factor limiting the return to age-predicted exercise capacity and function in recipients of LTxs. A further characterization of skeletal muscle dysfunction will assist in the understanding of exercise limitations and rehabilitation strategies to improve physical function in LTx candidates and recipients.

Quadriceps muscle weakness has been reported in multiple studies of LTx candidates and recipients. LTx candidates have demonstrated decreased quadriceps strength between 62 to 86% of age-predicted values and the recovery of quadriceps muscle strength post-transplant occurs to some extent, but does not appear to reach control values. The mechanism of strength loss is not understood and muscle atrophy may be one factor that could account for strength loss in LTx candidates.

Muscle atrophy, or the loss of muscle mass, post-transplant, has only been examined in a limited number of studies. Mathur 2008 compared thigh muscle volume and composition using Magnetic Resonance Imaging (MRI) in six stable LTx recipients and compared with chronic obstructive pulmonary disease (COPD) and demonstrated that LTx recipients had similar changes regarding muscle size to people with COPD. Pinet 2004 studied muscle size of lower limb using computed tomography (CT) in 12 Cystic Fibrosis (CF) LTx recipients (48 months post) and showed that LTx recipients had atrophy of quadriceps muscles when compared with normal controls. Since the studies looking at muscle size are limited to post-transplant, it is unclear whether atrophy is present pre-transplant or develops in the post-transplant phase.

There are numerous factors that can contribute to muscle atrophy and weakness. One key factor in LTx candidates and recipients is muscle disuse due to deconditioning and hospitalization. Experimentally, muscle disuse atrophy in humans has been studied over a relatively prolonged
period (greater than ten days) of bed rest in young, healthy individuals to ensure measurable muscle loss. LeBlanc 1992 examined muscle changes after 17 weeks of induced bed rest and found that bed rest primarily affected the anti-gravity muscles of the lower limbs (quadriceps and plantarflexors). The upper limb muscles had less atrophy following bed rest. This finding has been confirmed by other research. These mechanisms may also play a role in LTx candidates since deconditioning and hospitalization place them in bouts of bed rest. Indeed, exploring muscle size of multiple muscle groups including quadriceps, distal leg muscles (plantarflexors and dorsiflexors) as well as upper limb muscles in LTx candidates may allow us to gain a better understanding of muscle dysfunction in LTx candidates. This information may also help to target specific rehabilitation strategies in this population to prevent or attenuate muscle loss during periods of disuse. Such information would be valuable since the loss of skeletal muscle due to inactivity can be reversed with return of reloading of the limbs.

Indeed, to date no study has objectively assessed muscle size and strength of various muscle groups in the LTx population and little is known about the relative susceptibility to muscle atrophy of upper limb and lower limb muscles following LTx. A report of changes in muscle atrophy across muscle groups will assist in the understanding of the underlying mechanisms of muscle dysfunction. Furthermore, the relationship between structure and function of muscle to actual functional measures of mobility and exercise capacity may be important to developing rehabilitation programs to target muscle dysfunction.

The overall purpose of this thesis research is to characterize muscle size, muscle strength, and functional outcomes in LTx candidates.

The specific objectives of the proposed study are:

1) To characterize upper and lower limb muscle size, muscle strength and functional outcomes (walking capacity, arm exercise capacity and functional mobility) in a cohort of LTx candidates compared to age and sex-matched control subjects.

**Hypothesis 1)** Upper and lower limb muscle size, muscle strength and functional outcomes will be impaired in LTx candidates compared with controls.
2) To examine the relationships between muscle size and muscle strength; and muscle strength to functional outcomes in LTx candidates. Specifically:

2a) To examine the correlation between knee extensor strength and quadriceps muscle cross sectional area (CSA) and layer thickness (LT); and plantarflexor strength and gastrocnemius + soleus LT.

**Hypothesis 2a)** Muscle strength will correlate with the muscle size of the correspondent muscle group.

2b) To examine the correlation between knee extensor and plantarflexion strength to 6-minute walk test (6-MWT), Timed Up and Go (TUG), Short Physical Performance Battery test (SPPB).

**Hypothesis 2b)** Knee extensors and plantar flexors strength will correlate with 6-MWT, TUG and SPPB.

2c) To examine the correlation between elbow flexors strength and biceps LT.

**Hypothesis 2c)** Elbow flexors strength will correlate with biceps LT.

2d) To examine the predictors of arm exercise capacity measured using the Unsupported Upper Limb Exercise Test (UULEX) in LTx candidates.

**Hypothesis 2d)** Age, Biceps strength, and biceps muscle thickness will be significant predictors of performance (time completed) on the UULEX.
Chapter 2
Literature Review

Since the first successful human LTx in 1983\textsuperscript{17} there have been significant efforts to improve morbidity and mortality associated with the procedure, particularly as the number of annual LTx continues to rise\textsuperscript{18}. Patients with underlying Idiopathic Pulmonary Fibrosis (IPF), COPD, CF, alpha-1-antitrypsin deficiency, and pulmonary hypertension comprise the majority of those waiting for LTx which is a lifesaving surgery for their end stage lung disease\textsuperscript{18}.

Data from the latest International Society of Heart and Lung Transplantation\textsuperscript{18} registry show that the reported number of LTx performed worldwide is steadily increasing, with 1700 in 2000 and 3510 reported procedures performed in 2010\textsuperscript{18}. One-year survival rates of LTx recipients have modestly improved from 73.4\% to 80.4\% over the last 10 years in North America\textsuperscript{19}. Over the past decade, the mean age of LTx recipients has also consistently increased, as well as the number of LTx recipients over 65 years old. In 2000, 1.6\% of LTx recipients were over 65 years, and in 2010 this increased to 12\%\textsuperscript{18}. With the remarkable advances within the scope of LTx and the subsequent increase in the number of patients on the waiting list, including older and medically complex individuals, the chances of complications that can lead to poor functional outcomes post-transplant also increases. Therefore, there is a need for pre- and post-transplant rehabilitation programs to improve fitness for surgery and to optimize function and quality of life post-transplant.

2.1 Pulmonary rehabilitation for lung transplant candidates and recipients

The American Thoracic Society and the European Respiratory Society currently defines pulmonary rehabilitation as “a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies which include, but are not limited to, exercise training, education and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to
health-enhancing behaviors\textsuperscript{20}. Exercise-based pulmonary rehabilitation programs have been shown to be effective in improving exercise capacity, physical activity, and quality of life in LTx recipients\textsuperscript{14,21,22}. A recent Canadian national survey on rehabilitation programs for solid organ transplant reported that four out of five LTx centers recommended rehabilitation pre-transplant, and all had rehabilitation as a mandatory component of post-transplant care\textsuperscript{23}. Although rehabilitation is provided before and after lung transplantation for most LTx candidates, the lack of guidelines and training protocols to target skeletal muscle dysfunction is still observed. Trojetto\textsuperscript{23} reported that the exercise programs in the studied centers ranged from two to five days a week for 90 to 120 minutes per training session and were comprised of aerobic training, upper and lower limb strengthening, balance, flexibility and functional training as well as education but specific details such as intensity and parameters used for progression were not stated. There are also no specific training guidelines developed for LTx candidates and recipients, and principles from other chronic lung diseases are typically applied. Further development of exercise training guidelines for LTx candidates and recipients is needed to address the specific needs of this population, such as greater functional limitations and oxygen requirements pre-LTx; potential for greater functional gains post-LTx and potential limitations such as risk of infection and rejection that could interfere with training, and the expected side effects of immunosuppressant’s on muscle function.

2.2 Exercise Limitation in Lung transplant candidates and recipients

The inability to engage in physical activity has been documented in the literature for individuals who undergo lung transplantation despite satisfactory recovery in lung function\textsuperscript{14}. Skeletal muscle dysfunction is considered to be an important factor that contributes to exercise intolerance in chronic lung diseases, such as COPD and IPF\textsuperscript{24–26}. The mechanisms by which reduced exercise capacity occurs are complex; however, skeletal muscle dysfunction has been linked as a limiting factor to the return to normal exercise capacity and physical function in recipients of LTx\textsuperscript{4,10,11,27–30}. Regardless of pulmonary function returning to age-predicted levels post-transplant, peak exercise capacity typically remains at 40\% to 60\% of the recipient’s age-predicted levels even at one to two years after lung transplantation\textsuperscript{3,6,31,32}. 
Lung transplant candidates have a decreased functional exercise capacity measured with 6-MWT of 45-48% predicted reported, and most individuals listed for lung transplant have 6MWDs less than 400m\textsuperscript{1,7,33}. The 6-MWT improves significantly following lung transplant with reports of 6-MWT distance results reaching 79% of predicted healthy values after 3 months of rehabilitation\textsuperscript{33}. Shorter 6MWTs have been reported to represent an increased mortality risk in lung transplant candidates\textsuperscript{34,35}.

### 2.3 Skeletal muscle dysfunction in lung transplant candidates and recipients

A number of factors have been proposed as possible causes of skeletal muscle dysfunction pre- and post-transplant (see Table 2.1). The main pre-transplant factor influencing muscle function is likely to be inactivity, which occurs due to severe lung disease and shortness of breath on exertion. Other factors affecting muscle include the use of corticosteroids, hospitalization or bedrest in the pre-transplant phase, hypoxemia, inflammation and malnutrition.

In the post-transplant phase, factors which have been suggested to contribute to muscle dysfunction or to prevent recovery of muscle function include prolonged intensive care admission and medications, especially calcineurin antagonist drugs (cyclosporine A, tacrolimus) which are key immunosuppressing agents\textsuperscript{31} and corticosteroid drugs such as Prednisone. Nava 2002\textsuperscript{36} showed that treatment with steroids in patients with acute lung rejection after LTx induced muscle weakness in approximately 45% of patients. This observation may also apply to LTx recipients who are treated with daily corticosteroids throughout the postoperative period. Corticosteroids are required for muscle proteolysis associated with starvation and may contribute to inflammation-associated muscle atrophy\textsuperscript{37,38}. Reports implicate glucocorticoid myopathy as a cause of respiratory muscle weakness\textsuperscript{37}. Cyclosporine A, a common immunosuppressive agent used in post-transplant patients, has been shown to affect muscle metabolism (mitochondria dysfunction)\textsuperscript{39}. Episodes of rejection that can occur in the acute or chronic stages post-transplant may further impact muscle dysfunction since higher dosages of immunosuppressant and pulsed steroids are needed to resolve this complication\textsuperscript{40}. 
At the level of the skeletal muscle, LTx recipients have reduced muscle strength\textsuperscript{7,13,30,41}, reduced muscle size\textsuperscript{1,10}, lower proportion of type I muscle fibers\textsuperscript{42}, impaired mitochondrial oxidative capacity\textsuperscript{12,43}, and impaired skeletal muscle calcium and potassium regulation\textsuperscript{44}. A summary of the key changes observed in muscle structure and function is provided in Table 2-2.

A number of studies have been done in lung-transplant candidates and recipients looking at skeletal muscle function. The following section summarizes the literature on changes in muscle size and strength in LTx.

### 2.3.1 Muscle size before and after lung transplantation

Two studies have examined muscle size in LTx recipients. Mathur 2008\textsuperscript{1} compared thigh muscle volume and muscle composition using MRI in 6 LTx recipients (6 - 84 months post-transplant) to people with COPD. Their findings demonstrated that LTx recipients had similar degree of muscle atrophy and intramuscular fat infiltration to the COPD group. Pinet 2004\textsuperscript{10} studied LTx recipients with CF (48 months post-transplant) and showed a preferential reduction in CSA of quadriceps muscle using CT, when compared with abdominal muscles and diaphragm. Pinet 2004\textsuperscript{10} also reported that quadriceps CSA of LTx recipients were 31% lower on average than healthy controls. Both of these studies examined LTx recipients only; therefore, it was not clear whether muscle atrophy was present before the transplant or developed post-transplant. Furthermore, the susceptibility of the upper limb muscles to atrophy compared to the lower limb muscles has not previously been explored in LTx candidates or recipients.

### 2.3.2 Muscle strength before and after lung transplantation

Individuals with advanced lung disease suffer from skeletal muscle weakness even before they undergo lung transplantation\textsuperscript{3,5,7,8,14}. There is also some recovery in muscle strength post-transplant; although, there is a wide range of data presented in the literature. Quadriceps strength of LTx candidates has been found to range from 66-75\% of predicted\textsuperscript{4,7,33} when measured by
isokinetic dynamometer and 66-86% of predicted when measured by hand held dynamometer (HHD)³,⁶,⁸,³³. Quadriceps strength of LTx recipients has been found to be slightly higher, and range from 51-90% of predicted values across studies measured using isokinetic dynamometers⁷,¹¹,³³. The wide range in the results might be explained by different protocols used to assess muscle strength such as differences in type of device used (isokinetic versus HHD), type of contraction (isometric, isokinetic), joint angle or the equation used to calculate the percent-predicted values. For example, Langer 2009/2012³³,⁴⁵ and Maury 2008⁷ measured isometric peak torque with the knee joint at the angle of 60° of flexion and used the Decramer 1996³⁷ equation to calculate the percent predicted; whereas Wickerson 2013⁵ used a similar testing protocol but a different prediction equation⁴⁶. Ambrosino 1996¹³ and Nava 2002³⁶ measured isokinetic concentric strength at 120°/sec while Pinet 2004¹⁰ also measured isokinetic strength at a lower velocity of 60°/sec and Mathur 2008¹ measured eccentric and concentric strength at 30°/s. The velocity of movement is known to affect muscle torque production⁴⁷; therefore, measurements among these studies are not comparable.

As described above, studies in LTx candidates and recipients have mostly reported strength of quadriceps, with very few studies reporting muscle strength of other muscle groups such as the hamstrings¹,³⁶, tibialis anterior³⁰, upper limb muscles including the triceps and biceps³,⁶ and respiratory muscles¹¹,³⁰,⁴⁵. No studies to date have looked at plantarflexors which are a very important muscle group involved in gait and balance⁴⁸.

Only two studies used twitch tension, an involuntary assessment of muscle contractility, to look at muscle strength of quadriceps and tibialis anterior⁹,³⁰ in LTx recipients. Pantoja 1999³⁰ demonstrated that dorsiflexors of LTx recipients is 39% weaker than controls and Vivodtzev 2011⁹ also demonstrated that quadriceps strength measured by twitch tension was significantly lower than controls. These studies indicate that in addition to voluntary force production, the contractility of the muscles is also impaired in LTx recipients.
2.4 Functional exercise capacity in lung transplant candidates and recipients

Functional capacity is a fundamental requirement for many of the activities of daily living (ADLs) and is a particular concern for LTx recipients who exhibit impaired exercise capacity post-transplant. The 6-MWT has been the primary test of functional exercise capacity used in LTx candidates and recipients. The 6-MWT correlates with VO2\text{max} and is widely used in deciding transplant candidacy and monitoring changes in functional exercise capacity\textsuperscript{35}. A retrospective study of 454 patients demonstrated that 6-MWT results—both distance and presence of desaturation—could be independently associated with mortality for IPF patients awaiting LTx. In fact, the test performance was a better predictor of six month mortality than spirometry\textsuperscript{49,50}. Also, longer distances in 6-MWT have been correlated with length of hospital stay following transplant\textsuperscript{51}. This demonstrates the relevance of the 6-MWT, beyond the data provided by standard pulmonary function tests.

The evaluation of functional capacity can be done by different means; however, relying on one specific test such as the 6-MWT alone may not provide a composite profile that reflects the functional status of these individuals. Performance on the 6-MWT is affected by multiple factors such as cardiovascular or respiratory limitations, symptoms such as dyspnea and lower limb muscular weakness or fatigue\textsuperscript{52}. However, with the increased inclusion of older and frail patients for lung transplantation, adequate functional assessment tools that can provide information on lower body muscle strength, power and balance, may also be informative regarding post-transplant prognosis, or determining the outcomes of rehabilitation interventions. Functional tests such as the Short Physical Performance Battery (SPBB), Timed Up and Go (TUG) which have been used in the elderly\textsuperscript{53} and COPD\textsuperscript{54,55} may provide information which is more specific to lower extremity strength and function in LTx candidates than the 6-MWT.

Additionally, the upper extremities play an important role in many basic and instrumental activities of daily living such as bathing, dressing, toileting, cooking and shopping\textsuperscript{56}. Patients with COPD frequently experience dyspnea and fatigue when performing simple tasks using their arms and this might be explained because upper limb muscles which are required to perform activities with unsupported arm, also act as accessory muscles of respiration\textsuperscript{57}. The Unsupported Upper Limb Exercise Test (UULEX) is a test that measures peak arm exercise capacity and
most importantly it reflects ADLs\textsuperscript{58}. It has been validated in people with COPD\textsuperscript{58,59} but has not been used in LTx candidates or recipients. The UULEX may provide unique information about upper limb function that is not reflected in the 6-MWT or other tests of lower extremity function. The relationship between upper limb function and post-transplant outcomes is currently unknown.

2.5 Summary

Impaired skeletal muscle dysfunction leading to decreased exercise capacity is an important concern among LTx candidates and recipients. From 16 studies looking at skeletal muscle dysfunction in LTx patients, most studies assessed the strength of quadriceps, and some of them included other muscle groups (e.g. respiratory muscles, biceps and triceps, hamstrings, tibialis anterior). There was a lack of standardized protocols to assess muscle strength among studies, making comparisons of the results difficult. Together with muscle strength two studies also examined muscle size of the quadriceps muscle in LTx recipients but no studies have examined muscle size in LTx candidates. Also, no studies have examined upper and lower limb muscle strength and size in the same cohort of LTx candidates. Therefore, little is known about the relative susceptibility to atrophy of upper limb and lower limb skeletal muscles in this population. Functional measures have been limited to the 6-MWT and measures of upper body function have not been studied in LTx candidates. A better characterization of skeletal muscle dysfunction in LTx candidates will provide insights into the mechanisms of muscle weakness and functional limitations, which may be addressed through rehabilitation.
3.1 Study Design
This was a cross-sectional study of individuals listed for LTx and age-matched healthy, control subjects. All LTx candidates on the waiting list at the Toronto General Hospital who were 40 years or older and who had been participating in the pre-transplant rehabilitation program for a minimum period of four weeks were considered eligible for study recruitment. The pre-transplant rehabilitation program at Toronto General Hospital has been described elsewhere\textsuperscript{5,51}. In brief, patients exercise three times per week, 90 minutes per session, focusing on stretching, lower limb endurance training (treadmill and cycle ergometer), strengthening training of key muscle groups (quadriceps, hamstrings, biceps) and functional exercises (stair climbing, squats). Potential subjects were excluded if they were: 1) awaiting a re-transplant or multi-organ transplant, 2) experiencing a rapid clinical deterioration, 3) reported any history of joint injury or surgery of the hip, knee or ankle that affected their mobility, and/or 4) had a history of muscle disease (e.g. myositis).

Healthy control subjects were volunteers recruited after the LTx group, through poster advertisements in the local community. These subjects were considered eligible if they had no pre-existing cardiovascular, respiratory or metabolic conditions. Healthy controls were age and sex-matched to the LTx group by dividing the LTx group into blocks of five years based on age (e.g. 40-44 years, 45-49 years etc) and matching one or two control subjects by age and sex within each block. The rationale for including a smaller control group was that they were expected to have less variability on primary variables (muscle size and strength) than the LTx group.

Ethics approval was obtained from the University Health Network (REB # 10-0261-BE), St John's Rehab/Sunnybrook (REB # 10-0261-BE) and University of Toronto (REB # 28103) and written informed consent was obtained from all participants prior to undergoing study procedures. A copy of the informed consent form is provided in Appendix A.
3.2 Study Protocol

At the time of the study assessment, subject demographics (age, sex), and anthropometric measures (height, weight) were recorded. In addition, for LTx candidates, diagnosis, daily dose of oral corticosteroids, time on the transplant waiting list, results of standard pulmonary function testing and 6-MWT were recorded from the medical chart. Physical activity level was assessed using the Physical Activity Scale for the Elderly (PASE) score. The PASE score is derived from a series of questions on frequency and levels of exertion in recreational sport and leisure, home, and work activities over a one-week recall period. This questionnaire is validated to measure physical activity levels in older adults\textsuperscript{60} and a higher score indicates a greater level of physical activity (range 0–486). A cut-off score of less than 89.6 has been used to categorize frailty by Cawton 2007\textsuperscript{61}. All subjects underwent measures of muscle size using B-mode ultrasound (US), isometric muscle peak torque (Biodex dynamometer), muscle force (HHD) and functional performance using the SPPB, TUG and UULEX. Testing occurred either in a single session of 2 hours, or in LTx candidates, the option of breaking the assessment in two shorter appointments, within a two-week time period was given, to minimize the effects of fatigue.

3.2.1 Muscle size

B-mode US imaging (GE Logic E system) using a 5-13 MHz linear transducer probe was used to assess muscle CSA of the rectus femoris (RF) and LT of the quadriceps, including the RF, vastus lateralis (VL), vastus Intermedius (VI), calf (gastrocnemius lateralis and soleus) and biceps (long and short head) muscles. The US measurements were performed after the subject had been lying down for about 20 min to allow fluid shifts to occur\textsuperscript{62,63} and were performed prior to any other study procedures to prevent muscle edema from activity. During the measurements, subjects were positioned comfortably with their limb (arm or leg) supported by a pillow. A standard transducer location corresponding to the largest CSA of the muscle was used for each muscle of interest and transmission gel was used to aid acoustic coupling. Three US images were obtained at each site by a single rater. Inter-rater and intra-rater reliability and criterion-related validity of muscle US were established prior to commencing the study (see Appendix B for details).

Each muscle was imaged using the following standard positions:
1) The biceps muscle was imaged at 40% of the distance from the lateral epicondyle to the acromion process (tip of the shoulder). The subject was seated with their elbow in an extended position\textsuperscript{64}.

2) The quadriceps muscle was imaged at 50% femur length (anterior superior iliac spine to superior pole of patella) with the subject in supine and the knee flexed to \textasciitilde30\degree, according to procedures previously described\textsuperscript{65,66}.

3) For the calf muscles, the subject was positioned in prone with the legs extended and feet over the edge of the bed. Images were taken at 30\% of the distance between the tibial plateau (knee joint) and lateral malleolus\textsuperscript{67}.

The US images were captured directly on the GE system, and subsequently transferred to a computer for further analysis. Image analysis was done using publicly available computer software (Osirix for Mac, http://www.osirix-viewer.com/) and measurements of muscle CSA and LT of each muscle were manually outlined. A representative image of CSA and LT measurements of the RF muscle are shown in Figure 3.1A and Figure 3.1B.

3.2.2 Peripheral muscle strength

Biodex

Isometric maximal voluntary contractions of the knee extensors, plantar- and dorsi-flexors and elbow flexors on the dominant limb, were measured using the Biodex dynamometer (Biodex System 4, Biodex Systems, New Jersey). Each muscle group was tested at joint angles that corresponded to their optimal fiber length, i.e., the length at which the muscles generate the greatest force.

The participant position for each muscle tested was measured as follows:

1) Quadriceps strength was measured in a seated position with the hip positioned at 90\degree and knee positioned at 60\degree of knee extension\textsuperscript{5}.

2) Dorsiflexors was measured in seated positions with hips flexed at 90\degree, knee flexed at 30-40\degree, and ankle at 10\degree of plantar flexion as measured with standard goniometer from neutral position (90\degree angle between the fibula and calcaneus)\textsuperscript{68}.
3) Elbow flexor strength was measured with the elbow angle flexed by 90°. The upper arm rested and fixed with a strap belt on a horizontal table with the wrist attached to the lever arm of the dynamometer.

For each muscle group, two warm-up contractions were performed at ~50-75% of perceived maximum effort, followed by 5 maximal efforts to obtain peak torque. A one-minute rest was given between trials to minimize fatigue. The highest value of 5 attempts after the warm up was recorded. Standardized instructions, verbal encouragement and feedback were provided.

**Hand Held Dynamometer (HHD)**

In addition to Biodex testing, manual muscle testing was performed on all participants using HHD (Lafayette Instrument) by a single rater. HHD is an inexpensive and easy-to-handle device, which provides a clinically relevant alternative to the Biodex. HHD has been shown to have consistent intra- and inter-rater reliability.

HHD was performed using the “make technique”, which has been shown to be more reliable than the “break technique”. The “make technique” requires the patient to exert a maximal isometric contraction while the examiner holds the dynamometer in a fixed position, matching the subject’s force. For each group of muscle tested (knee extensors, elbow flexors and dorsiflexors), three maximum voluntary contractions were completed and the best trial was recorded. This test was done on the dominant limb, immediately following the Biodex test and while the participants were seated on the Biodex chair, using same angle and stabilization as per the Biodex protocol described above. Standardized instructions, encouragement and verbal feedback were provided. Plantarflexor muscle strength was not tested using HHD.

**3.2.3 Functional exercise capacity**

**UULEX**

The UULEX is a test of upper limb endurance capacity that has been previously used in people with COPD. This test has not previously been used in LTx candidates. Prior to the study, the
UULEX was pilot tested in one LTx candidate and two LTx recipients (6 weeks and 3 months post-transplant) to ensure safety and feasibility. Both subjects were able to complete the test with oxygen saturation levels greater than 88% and RPE score for shortness of breath and arm fatigue of less than 4. The pre-transplant candidate was provided with supplemental oxygen at the level used for exercise training during rehabilitation. Neither subject reported any pain or discomfort with the testing including no incisional pain in the transplant recipient. For the UULEX, the patient was seated in a straight-backed chair with feet on the floor facing the UULEX board (see Figure 3.2). Before starting the test, LTx candidates were asked about their oxygen prescription to perform strenuous exercise such as the treadmill (during rehabilitation) and they were provided with the same oxygen prescription during the UULEX. A symptom-limited UULEX then was performed using a continuous incremental exercise protocol as previously described\textsuperscript{58}. The test begun with a two-minute warm-up, during which the patients extended their arms simultaneously, lifting the plastic bar of 0.2 kg from a neutral position to the first level. After the warm-up, the vertical amplitude of the lift increased by 0.15 m every minute as the patient progressed through the stages of the test. Once the patient reached his/her maximum vertical height each minute thereafter, the weight of the bar was progressively increased by 0.5 kg to a maximum weight of 2 kg\textsuperscript{58}. Participants were instructed to move their arms up to a maximum time of 13 minutes or until they could no longer keep the pace of 30 beats per minute, either due to shortness of breath or arm fatigue. Rests were not permitted during the test. Measures of SpO\textsubscript{2}, heart rate, dyspnea and arm fatigue scores using the RPE Scale were recorded before and after the test. The final level, final weight and total time were also recorded at the end of the test.

6-MWT

The 6-MWT is performed regularly pre- and post-LTx by the physiotherapists at Toronto General Hospital; therefore the 6-MWT results (distance covered and SpO\textsubscript{2}) were obtained for LTx candidates from their clinical records. In case where the test was more than a month prior to the study assessment date, a new test was performed. The 6-MWT was performed according to the protocol described by the American Thoracic Society\textsuperscript{74}. The 6-MWT was not conducted in control subjects; rather the 6-MWD in LTx subjects was compared to reference values for the Canadian population\textsuperscript{75}. 
**Short Physical Performance Battery (SPPB)**

The SPPB is a test used to assess physical function in older adults and it can predict the preclinical stage of disability\(^{53,76}\). To date there are no published data for this test in LTx candidates or recipients. The SPPB requires three tasks: a timed short distance walk, repeated chair stands, standing balance (described further below). Low scores in the SPPB have predictive value for a wide range of health outcomes: mobility loss, disability, hospitalization, length of hospital stay, nursing home admission, and death in a variety of disease conditions; and higher scores indicating better lower-body function\(^{53,77,78}\). A SPPB total score of less than or equal to 8 indicates low physical performance and a score greater than 8 indicates a normal/high physical performance\(^{53}\). The following is a description of each component of the SPPB:

A) Standing Balance: Standing balance was tested using tandem, semi-tandem and side-by-side stands. The researcher demonstrated the stand and then supported the participant while they positioned their feet. The timer started when the participant was ready in position, and stopped when the participant moved their feet, grasped the researcher for support or 10 seconds had elapsed. We started by asking the participant to stand in semi-tandem (the heel of one foot placed to side of the first toe of the other foot; participants were allowed to choose which foot was forward). Participants unable to maintain this stance for 10 seconds were evaluated with feet in a side-by-side position whereas those able to maintain semi-tandem stance for 10 seconds was evaluated in full tandem with the heel of one foot directly in front of the toes of the other foot.

B) Walking Speed: Participants were instructed to walk 8 feet (2.43m) at their usual speed, just as if they were walking down the street to go to the store. Timing started when the participant began walking and ended when they crossed the 8 feet mark.

C) Chair Stands: A straight-backed chair, without arm rests was used. Participants were asked to fold their arms across their chest and stand up from the chair once. If successful, they were asked to stand up and sit down five times as quickly and as safely as possible. The participant was timed from the initial sitting position to final standing position at the end of the fifth repetition. The total time was recorded. Each component was given a score of 0 to 4, which were assigned based on quartile of length of time to complete the task. The total score is the sum
of all three individual components. The maximum score that a participant can receive is 12 points. A copy of the SPPB scale is provided in Appendix C.

Timed Up and Go

The Timed Up and Go test (TUG) is a widely used clinical test to evaluate balance and mobility that was developed by Podsiadlo & Richardson 1991. The TUG has high intra- and inter-tester reliability and predictive validity for falls in community-living adults. The TUG tests mobility and reflects one’s ability to transfer from sitting to standing and to walk short distances, which are considered basic mobility functions. The TUG has been shown to predict risk of falls in the elderly as it reflects balance deficits. The cutoff score of 11.0 seconds or greater has been suggested by Podsiadlo & Richardson 1991 and Trueblood 2001 to distinguish fallers and non-fallers.

To perform the TUG participants were asked to stand up from a chair, walk 3 meters at a comfortable pace, turn 180 degrees (briskly), walk back to the chair and sit down. The test was timed using a stopwatch. A 3 m walkway was measured out and marked with an “x” on the ground at one end and a horizontal line at the other end. A standardized chair (46 cm high seat, 65 cm arm rests) was placed behind the horizontal line. Verbal instructions on how to perform the TUG were as follows: “When I say the word “go”, you will get up from the chair, walk to the landmark on the floor, turn briskly, walk back to the chair and sit back down. You will do this at your normal pace”. The participants were instructed to perform the test twice since a practice trial is recommended. Subjects did the test using their customary footwear and gait aid.

3.3 Statistical Analysis

Statistical analysis was performed using the SPSS statistical package (IBM Statistics, version 21.0). Assumption of normality was tested using the Shapiro-Wilk test. Descriptive statistics are reported as mean and standard deviation for the normally distributed variables, or median and interquartile range (IQR) otherwise.
For objective 1, mean values of variables were compared using independent samples t-test (parametric) or Mann Whitney test otherwise. The Bonferroni correction is used to reduce the chances of obtaining false-positive results on the multiple comparisons.

For objective 2, bivariate correlation analyses were performed using Pearson product moment correlation (parametric) or Spearman rank correlation (non-parametric) coefficient to examine the relationships between muscle strength and muscle size and muscle strength and functional outcomes. Linear Regression was performed using the UULEX as the dependent variable and age, muscle size, strength as predictors.

3.4 Sample size estimation

This thesis study is part of a larger longitudinal study examining muscle dysfunction pre- and post- LTx and the sample size was initially estimated to detect differences in muscle size between pre- and post-transplant using a longitudinal study design. Based on an estimated difference in muscle size of -1.4cm² we calculated a required sample size of 40 subjects (alpha = 0.05, power = 80%). For the present cross-sectional study design, we expected that the differences between the LTx group and age-matched controls would be even larger, so we recruited 85% of the target sample (34 LTx subjects) to address the objectives of this study.
Chapter 4
Results

Potential study participants were screened for inclusion in the study between November 2012 and April 2013. Figure 4.1 shows the subject flow throughout the study recruitment. Seventy-three participants from the LTx waiting list at Toronto General Hospital were identified during this period and 20 were excluded due to systemic diseases (lupus, scleroderma, rheumatoid arthritis, fibromyalgia). Fifty-three participants were approached. Sixteen refused to participate because of extra time commitment (n=13) or no interest (n=3). Thirty-seven participants gave informed consent; however, one potential subject had the LTx and two subjects died prior to the study assessment. Thirty-four LTx candidates were tested and included in the study.

4.1 Subjects

Thirty-four LTx candidates enrolled in a pulmonary rehabilitation program at Toronto General Hospital (60 ± 8 years; 59% males) and 12 healthy control subjects from the local community (56 ± 9.5 years; 50% males) were included in the study. The LTx candidates had the following pre-transplant diagnoses: IPF=24, COPD=4, Bronchiectasis=2, Bronchiolitis Obliterans=1, Bronchoalveolar Carcinoma=1, combination IPF/COPD=2. There were no current smokers in either group. Participant’s demographics are summarized in Table 4.1. There was no significant difference between the LTx candidates and healthy control groups for age or BMI (see Table 4.1). As expected, LTx candidates had significant lung function impairment (see Table 4.1). At the date of the assessment, LTx candidates were on the waiting list for an average of 4 ± 5 months (range: 1 to 28 months). PASE scores were significantly lower in LTx candidates when compared with controls (p = 0.001; see Table 4.1). Most of the LTx candidates were on long-term oxygen therapy and used various methods of oxygen administration and flow rates at rest and during exercise training. Eighteen participants used nasal prongs with oxygen requirements ranging from 2 to 6 L/min. Four participants used a Venturi mask at 50%, and seven participants used 15L partial non-rebreather masks. Seven participants (21%) were taking oral corticosteroids at the time of the study assessment, with an average dose of 12 ± 7 mg/day.
4.2 Muscle size, muscle strength and functional outcomes

Objective 1, comparison of muscle size, strength and function between LTx candidates and healthy controls, is addressed in this section.

Muscle size data of LTx candidates and healthy controls are summarized in Table 4.2. When compared with controls, the mean percentage difference for CSA of the RF was lower in LTx candidates by 24%, quadriceps LT (sum of RF, VL and VI muscle thickness) by 13%, calf LT (sum of gastrocnemius lateralis and soleus) by 21% and biceps thickness was lower by 10% compared to controls but none of them reach statistical significance.

Muscle strength data of LTx candidates and healthy controls are summarized in Table 4.3. When measured using the Biodex, LTx candidates presented muscle weakness of knee extensors by 26% compared to controls (p=0.005). LTx candidates also showed decreased mean percentage difference ankle plantarflexors by 30%, ankle dorsiflexors by 11% and 15% in elbow flexors strength but these differences did not reach statistical significance. When measured by HHD, LTx candidates had weakness of the ankle dorsiflexors by 56% (p=0.002) and elbow flexors by 40% (p=0.001) but not of the knee extensors (21%, p=0.110).

LTx candidates performed poorly on the TUG when compared with controls (Table 4.4). Podsiadlo & Richardson have suggested that scores of less than 11 seconds indicate low risk for falls, whereas scores of more than 19 seconds indicate moderate to high risk for falls. The majority of LTx candidates finished the task in less than 10 seconds (n=26), seven LTx candidates finished in 10 to 19 seconds and only one participant took more than 20 seconds to finish the test. All the participants of the control group finished this task in less than 8 seconds.

There was no difference between LTx candidates and healthy controls on the SPPB (see Table 4.4). The score of the SPPB ranges from 0 to 12 where 0 is the worst performance and 12 the maximum score. Eight is considered the cut point for the increased risk of developing mobility-related disability in elderly patients and in this study only 8 (23%) LTx candidates scored 8 or less. LTx candidates seemed to be worse in chair stand and walk components rather than in the balance component.
The UULEX total time was 554 ± 164 seconds in LTx candidates, which was significantly lower than the control group (p = 0.009; see Table 4-5). All the participants were able to perform the test; however, only 18% of the LTx candidates and 64% of the controls were able complete the final stage of the test. The mean score post-test for arm fatigue was higher than for dyspnea in both the LTx and control groups (see Table 4.5). Except for one LTx candidate, all the participants who finished before the final stage reported arm fatigue as the main limiting factor. None of the LTx candidates tested experienced oxygen desaturation during the test; however, they all used the same level of oxygen, which was prescribed for strenuous activities such as treadmill walking.

LTx candidates walked an average of 380 ± 102 meters (58 ± 17% predicted). Pre-test oxygen saturation levels were on average 97 ± 2% and oxygen desaturation was evident post-test (mean, 88 ± 5%) despite the usage of supplemental oxygen during the test. During the test, eight participants required mobility devices (rollator walkers, n= 6; cane, n= 2) and three participants required a rest during the test because of severe dyspnea.

4.3 Correlations

Objective 2, relationships between muscle strength to muscle size and function in LTx candidates, is addressed in this section.

4.3.1 Correlations between muscle strength and muscle size

Correlations between variables in LTx candidates are summarized in Table 4-6. Relationships between muscle size and muscle strength were done using the Biodex measures of strength, since it is the gold standard measurement tool.

A strong correlation was found between elbow flexion muscle strength and biceps LT (r=0.71, p< 0.001). A moderate correlation was found between knee extensor strength and quadriceps muscle CSA and LT. Plantarflexors strength did not correlate with gastrocnemius lateralis and soleus LT.
4.3.2 Correlation between muscle strength and functional outcome measures

No significant correlations were found between the measures of muscle strength and the functional outcomes. (see Table 4-6).

4.3.2.1 Predictors of arm exercise capacity measured using the UULEX in LTx candidates

When arm exercise capacity (UULEX total time) was predicted in a model where age, muscle size, and muscle strength (Biodex) were used as predictors, it was found that muscle size was the only significant predictor in this model ($\beta = 0.41, p = 0.016$). Age and elbow flexion muscle strength were not significant predictors. The overall model fit was $R^2 = 0.170$. 
5.1 Discussion

The main finding of this study is, that compared with healthy subjects, LTx candidates have muscle weakness of thigh measured using US and Biodex dynamometry, but upper limb muscle size and strength do not appear to be impaired to the same extent. In addition, LTx candidates have lower functional performance in the measures of mobility TUG compared to an age-matched control group. However, less than a quarter were considered at risk for mobility impairments and only one subject was considered at risk for falls based on criteria derived in an elderly population for these tests. Furthermore, upper limb and lower limb exercise capacity were reduced in LTx candidates, measured by UULEX and 6-MWT, respectively. Strong to moderate associations were found between muscle strength and muscle size in LTx candidates, which is similar to findings reported in people with COPD.

5.2 Muscle Size

Muscle size has only been measured in LTx recipients and the reports are limited to lower limbs using MRI or CT\textsuperscript{1,10}. Therefore, this is a unique study since it is the first cohort study to measure upper and lower limb muscle size of LTx candidates using US imaging. There are several imaging tools available to measure muscle size. MRI is widely regarded as the “gold standard” for the assessment of muscle size. However, MRI is costly and time consuming, and access to MRI for research or clinical purposes is often limited\textsuperscript{62}. CT is also considered a gold standard tool to assess muscle size\textsuperscript{81}; however, it exposes patients to radiation. Brightness mode (B-mode) US can be used to produce high quality images of muscle morphology and similar to MRI, as it shows contrast between muscle and fat tissue. A limitation of US is that it has a relatively limited depth and field of view compared with MRI; however, US provides adequate information about muscle size and shape and is suitable for laboratory and clinical use\textsuperscript{62}. US is also quick to perform, safe, relatively inexpensive and more widely available compared with MRI and CT. Another limitation of US is that it has not been validated to evaluate muscle...
quality such as intramuscular lipid, which can be done with MRI and CT.

In our study LTx candidates had muscle atrophy measured by US of the quadriceps (RF CSA and RF+VL+VI LT) but no difference was found in plantarflexors (gastrocnemius lateralis and soleus LT) and in the biceps size when compared with controls. Seymour 2009 and 2012\textsuperscript{84,85} reported quadriceps size mean percentage difference between COPD patients and controls of 25% which was similar to our results (24% difference). To date there are no reports of upper limb muscle size in people with respiratory lung disease or LTx patients.

Two studies have looked at muscle size in LTx recipients. Pinet C 2004\textsuperscript{10} measured quadriceps CSA by CT in LTx recipients with CF and reported that quadriceps CSA of LTx recipients were 31% smaller when compared with healthy controls. Mathur S 2008\textsuperscript{1} measured thigh muscle volume using MRI of LTx recipients and compared with individuals with COPD and found that quadriceps muscle volume was lower by 6.5% in LTx recipients compared to people with COPD. We can conclude from these two studies that muscle atrophy persists into the post-transplant phase; however, due to the differences in methods, pre-transplant diagnoses and the wide range of time post-transplant in these studies, it is difficult to determine the time course of changes in muscle atrophy post-transplant. Further studies, looking at muscle size of upper and lower limb muscles in the same cohort are warranted to understand the progression of muscle atrophy in LTx patients and if muscle atrophy can be improved through exercise training.

The reports in the literature indicate that muscle atrophy induced by disuse affects lower limb more than upper limb muscles\textsuperscript{15,16,86}. We observed a similar pattern in LTx candidates. Indeed, even though several factors have been linked as possible causes of muscle atrophy such as disuse, hypoxemia, malnutrition, oxidative stress and systemic inflammation\textsuperscript{30,37,45,87} in this study LTx candidates showed accentuated levels of atrophy in lower limbs (quadriceps). Therefore, we can infer that in LTx candidates, one of the underlying mechanisms that contribute to muscle atrophy is likely to be muscle disuse, due to low physical activity levels.
that was observed in this study cohort using the PASE questionnaire. Low physical activity has also been reported in the pre-transplant phase in other studies using accelerometers\textsuperscript{5,45}.

5.3 Muscle strength

Quadriceps weakness was evident in this study. Quadriceps strength of LTx candidates in this cohort was 77\% of predicted which is very similar to the results obtained by Wickerson 2013\textsuperscript{5} (81\% predicted) using a similar testing protocol. Quadriceps weakness has already been well described in LTx candidates and recipients by other groups as well\textsuperscript{3,6-8,33}; however, this is the first study to report lower limb muscle strength of distal muscle groups (plantarflexors and dorsiflexors) in LTx candidates.

Although the quadriceps has been the main focus in characterizing peripheral muscle dysfunction occurring in LTx candidates and recipients\textsuperscript{33}, the distal lower limb muscles are key muscles for walking and balance\textsuperscript{48,88}. Plantarflexor and dorsiflexor muscle weakness has recently been reported in COPD patients\textsuperscript{88,89}. However, we did not find statistical significance for dorsiflexors and plantarflexors between LTx candidates and healthy controls in this cohort. Plantarflexor strength of LTx candidates in our study was found to be 30\% weaker than controls and a recent report from Gagnon 2013\textsuperscript{89} found that plantarflexor strength of COPD patients was ≈ 23\% weaker when compared with controls. Pantoja 1999\textsuperscript{30} observed a mean difference of 39\% of dorsiflexors strength when compared with controls in nine LTx recipients. This may indicate that dorsiflexor strength worsens post-transplant; however, a non-voluntary method to assess MVC (twitch tension) was used by Pantoja 1999\textsuperscript{30} so a direct comparison cannot be made with a voluntary strength assessment, which was used in our study. A decline in twitch tension observed on Pantoja 1999\textsuperscript{30} suggest impaired muscle contractility post-transplant, and would be interesting to measure in LTx candidates. Our findings are in agreement with other authors who have suggested that the antigravity muscles (knee extensors and plantarflexors) are predisposed to greater weakness and atrophy after a period of immobilization\textsuperscript{86,90}. This finding reinforces our hypothesis that disuse plays a role in muscle dysfunction in LTx candidates.
Our finding that biceps muscle strength was less impaired than lower limb muscle strength is consistent with previous findings in LTx candidates\textsuperscript{3,6} and very similar to findings in COPD patients\textsuperscript{73}. Van der Woude 2002\textsuperscript{6} studied muscle strength of upper (biceps and triceps) and lower limb (quadriceps) using HHD of 184 LTx candidates with different lung diseases. Biceps and triceps strength was 83\% and 79\% predicted and they concluded that muscle weakness was more accentuated in lower limb (66\%) when compared with upper limb. Reinsma 2006\textsuperscript{3} studied biceps and triceps strength also using HHD in 25 subjects’ pre-transplant and one-year post LTx (94\% and 90\% of predicted). Pre-transplant, biceps strength was similar to our predicted values (84\%) from both studies. Upper limb strength showed further improvement at one year post-LTx reaching 101\% and 95\% of predicted values for biceps and triceps, respectively. Therefore, upper limb muscle strength does not seem to be impaired as much as lower limb strength in LTx candidates and recipients. In our study, LTx candidates weakness of quadriceps muscles and we did not observe either significant atrophy or weakness in upper limb when compared with controls.

The isokinetic dynamometer, Biodex, is considered as the gold standard to measure muscular performance \textsuperscript{91–93}. Alternatively, HHDs are often used clinically since they are small and portable, and also provide an objective measure of strength. The assessor holds the HHD between his/her hand and the subject’s limb segment and applies force against the subject. Such devices have been proven to have good to excellent reliability in different populations and have previously been used in LTx candidates and recipients\textsuperscript{3,6,94,95}. The advantage of the isokinetic dynamometer over the HHD is that the subject is adequately stabilized to isolate the joint movement, and the assessor’s strength is not an issue\textsuperscript{96–98}. In this study, to minimize the stabilization disadvantage of the HHD, the participants’ were measured on the Biodex chair using the same joint angle and straps to stabilize the joints as used for the Biodex protocol; however, the assessor’s strength may have been a limitation in some of the tests. Even though some extra care was taken to minimize the disadvantages with the HHD, the results still were divergent when compared with the Biodex. The HHD data for dorsiflexors and elbow flexors seemed to be overinflated and this could be explained by the limitations of the device and
testing method. Another explanation for the discrepancies of Biodex results versus HDD is that the Biodex measures muscle torque in Nm, which accounts for the lever arm length (i.e. the point at which the force is applied along the subject’s limb); whereas the HHD only measures muscle force and the lever arm length is not taken into account. As a result, the differences in the recorded muscle force between subjects may be affected by the position that the HHD was placed along the limb segment. There have been a number of studies showing the validity and reliability of HHD\textsuperscript{99,100} but when we compared the results of this study with gold standard measurement (Biodex), inconsistent results can be seen and thus some caution must be taken when interpreting the results.

5.4 Relationships between muscle size and strength

The measures of muscle size obtained from this study were strongly associated with measures of muscle strength but not with functional capacity. We found moderate to high correlations between muscle strength and muscle size in LTx candidates. Seymour 2008\textsuperscript{84,85} have shown a similar correlation between RF CSA and knee extensor strength in COPD patients ($r=0.78$, $p<0.001$)\textsuperscript{84}. Measurements of quadriceps muscle thickness have also been studied in healthy elderly\textsuperscript{101} and COPD patients\textsuperscript{102}, however, only poor to moderate correlations between muscle LT and strength have been reported in both populations\textsuperscript{101,102}. Discrepancies observed between these studies and our study might be due to differences in the measurement of muscle thickness. Menon 2012\textsuperscript{102} measured quadriceps thickness (RF and VI) and Sipila 1991\textsuperscript{101} only included the thickness of RF and VL, not the VI muscle. In our study, we included thickness of RF plus VL and VI all together that might provide a better representation of the quadriceps muscles responsible for knee extension strength. Similarly, the measurement of gastrocnemius lateralis and soleus LT might not have correlated with plantarflexor strength because gastrocnemius medialis was not captured. Another factor that affects the relationship between muscle size and strength is muscle quality, which was not measured in this study. Muscle quality and muscle composition such as intramuscular lipid that has been associated with lower muscle strength\textsuperscript{82} and increased risk for mobility limitation in older adults\textsuperscript{83}. 
5.5 Functional exercise capacity and mobility

In this study, upper limb and lower limb functional exercise capacity were measured using the UULEX and the 6-MWT, respectively. The 6-MWT has been described extensively in LTx candidates and our study sample showed similar impairment in this test (58 % predicted)\textsuperscript{5,51}. Using linear regression analysis, biceps muscle size was a significant predictor of upper limb exercise capacity. Upper limb exercise capacity has not previously been described in LTx candidates and was found to be impaired to a similar level as shown in COPD\textsuperscript{58,73}. We speculate that muscle size might explain upper limb limitation measured by UULEX because this test targets the endurance of the arm muscles, rather than muscle strength or power. Selective atrophy of type 1 muscle fibres (slow-twitch, oxidative fibers) has been reported in individuals with chronic lung disease and LTx\textsuperscript{43}, and may contribute to impaired muscle endurance. Jaunaudis-Ferreira 2013\textsuperscript{73} and Takahashi 2003\textsuperscript{58} reported that patients with COPD were able to perform the UULEX for average total time of 520 ± 80 seconds and 556 ± 116, respectively, which was very similar to our results (554 ± 164 seconds). Arm fatigue seemed to be the limiting factor for upper limb functional capacity in LTx candidates. The majority of the LTx candidates who were not able to finish the test, reported arm fatigue as a limiting factor and also had higher RPE scores for arm fatigue than for shortness of breath. Two studies using the UULEX test in COPD also reported that RPE scores for arm fatigue were higher than for dyspnea\textsuperscript{58,103}. This may indicate a similar mechanism for arm exercise limitation between COPD patients and LTx candidates. It is known that activities of daily living (ADLs) performed with upper limbs, especially with unsupported arms, are poorly tolerated by patients with COPD\textsuperscript{103,104} and may be an area for further investigation in LTx candidates.

Our study is the first to report results on two measures of functional mobility, the TUG and SPPB, in LTx candidates. On the TUG, most of the LTx candidates (85%) finished the task in less than 11 seconds; however, their time was still lower than the healthy control group. Butcher 2004\textsuperscript{55} used the TUG test to assess balance and mobility of COPD patients and concluded that
COPD patients exhibited significant reductions in functional mobility and balance when compared with controls and that may affect their ability to perform activities of daily living\textsuperscript{55}. Our LTx group had a worse mean time on the TUG (9.3 ± 3.7 seconds) compared with the COPD group in Butcher 2004 study\textsuperscript{55} (7.0 ± 0.4 seconds). This difference may be due to our LTx group been more limited than stable COPD patients, with moderate to severe disease, who are not on the transplant waiting list.

On the SPPB test, 23\% of the LTx candidates scored 8 points or less, which is the cut point indicative of risk of disability or frailty in elderly\textsuperscript{53} but had an average score that was 20\% lower than controls. Eisner 2008\textsuperscript{54} reported that COPD patients also had impaired lower limb function (by 1 point mean difference) measured using SPPB when compared with control. Further evidence of frailty in our study sample comes from the PASE scores. We found that LTx candidates PASE scores were not only significantly lower than controls but according to reference cut-off scores for healthy elderly\textsuperscript{61} 56\% of LTx candidates fell within the frail category based on PASE (89.6). Frailty has been suggested by Fried 2001\textsuperscript{105} as clinical syndrome in which three or more of the following criteria are met: unintentional weight loss, self reported exhaustion, weakness, slow walking speed, and low physical activity level. Although the goal of this study was not to assess frailty in LTx candidates, we have found preliminary evidence that characteristics of frailty such as weakness, impaired mobility and low physical activity level may exist in this population.

5.6 Limitations

There are several limitations in this study, which must be considered. Pre-transplant factors that contribute to muscle dysfunction such as pulmonary exacerbations that required steroids or hospitalization were not recorded or controlled. Also, study subjects were assessed during a relatively stable period pre-transplant so any further deterioration during the pre-transplant period was not measured. Regarding the measurement tools used, muscle strength required a voluntary contraction of the participant and therefore may not reflect their maximal tension generating capacity of the muscle. US has been shown to correlate with MRI for muscle size but
is not the gold standard measurement tool therefore, may lack sensitivity in detecting muscle atrophy compared with MRI or CT.

Seventy per cent of the subjects tested in this cohort have ILD and since there are limited studies on muscle dysfunction in this population many of the comparisons were made to the literature in COPD patients who are not on the waiting list for LTx. Muscle dysfunction has been explored extensively in the COPD population and it is the closest reference to make comparisons with LTx candidates. Even though people with COPD have similar diagnoses to some patients on the waiting list for LTx, the studies on muscle dysfunction are conducted in people with moderate to severe COPD who have a stable medical status and may not even be taking supplemental oxygen. On the other hand, LTx candidates are those with severe, end-stage lung disease and individuals in who all other medical and rehabilitation interventions have failed. Therefore, these groups of patient may be quite different in regards to functional status. In addiotion, in this cohort I included only people over 40 years to improve the homogeneity of the study sample, so younger patients and in particular, people with cystic fibrosis were not included in this study. However, cystic fibrosis constitutes about one third of patients going for lung transplantation.
Chapter 6
Conclusion

In summary, we note that compared with age matched control subjects, LTx candidates had muscle weakness of thigh muscles (26%), but distal leg and upper limb muscle size and strength did not appear to be as impaired as the quadriceps muscle. This pattern is similar to what is observed with muscle disuse. This was the first cohort study to measure upper and lower limb muscle size of LTx candidates using US imaging and we found that muscle strength was associated with muscle atrophy of the quadriceps and biceps. We also demonstrated that LTx candidates had lower functional performance on the TUG compared to age-matched controls, but the majority of LTx candidates did not fall in the risk category for impaired mobility based on reference values for the elderly. These measures of functional mobility have not previously been reported in LTx candidates and may provide a clinically applicable method for assessment of lower body function. Upper limb function has not previously been studied in LTx candidates and may have an important role in activities of daily living. We found that upper limb exercise capacity was significantly impaired in LTx candidates and our results are in agreement with the findings in COPD patients. Results from the linear regression analysis showed biceps muscle size as a significant predictor of the UULEX. Upper limb function should be addressed as part of rehabilitation of LTx candidates. In summary, our results confirm the presence of muscle weakness in LTx candidates of the quadriceps and functional capacity impairment as well as the role of muscle disuse as an important factor contributing to muscle dysfunction. These results can be used by rehabilitation professionals to design training programs that can specifically target muscle weakness and low exercise capacity in LTx candidates.
Chapter 7
Directions and Future Research

There are several avenues for future research based on the results of this thesis. Future studies should focus on measuring whether muscle atrophy improves in the post-transplant phase, both with natural recovery and with exercise training. This was the first study to use tests of functional mobility to assess lower extremity function in LTx so it would be interesting to examine if these tests are able to capture changes in function after transplantation. Because this is the first study to show impaired upper limb exercise capacity in LTx candidates, future studies looking at the implementation of specific arm exercise training that involves a combination of unsupported and supported arm training, which has been used in COPD\textsuperscript{106} are needed.
Tables and Figures

Table 2-1: Pre and post-transplant factors contributing to skeletal muscle dysfunction

<table>
<thead>
<tr>
<th>Pre-LTx Factors</th>
<th>Post-LTx Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inactive lifestyle\textsuperscript{5,45}</td>
<td>• Inactive lifestyle\textsuperscript{7,41,107}</td>
</tr>
<tr>
<td>Medications:</td>
<td>Medications:</td>
</tr>
<tr>
<td>• Corticosteroids\textsuperscript{37}</td>
<td>• Corticosteroids\textsuperscript{37,108}</td>
</tr>
<tr>
<td>• Hypoxemia\textsuperscript{58,109}</td>
<td>• Inflammation\textsuperscript{110}</td>
</tr>
<tr>
<td>• Inflammation\textsuperscript{110}</td>
<td>• Malnutrition\textsuperscript{110}</td>
</tr>
<tr>
<td>• Prolonged intensive care admission\textsuperscript{30}</td>
<td>• Immunosuppressants\textsuperscript{31}</td>
</tr>
<tr>
<td>• Primary graft dysfunction\textsuperscript{30}</td>
<td></td>
</tr>
</tbody>
</table>
Table 2-2: Changes in skeletal muscle observed pre and post-transplant

<table>
<thead>
<tr>
<th>Pre-LTx Muscle Changes</th>
<th>Post-LTx Muscle Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ↓ Muscle Strength$^{3,7,13}$</td>
<td>• ↓ Muscle Strength$^{3,7,11,13,30}$</td>
</tr>
<tr>
<td>• Muscle atrophy$^{1,10}$</td>
<td></td>
</tr>
<tr>
<td>• Lower proportion of Type 1 muscle fibres$^{43}$</td>
<td></td>
</tr>
<tr>
<td>• Low mitochondrial oxidative enzyme activity$^{43}$</td>
<td></td>
</tr>
<tr>
<td>• Higher glycolytic enzyme activity$^{43}$</td>
<td></td>
</tr>
<tr>
<td>• Low ATP production rate$^{43}$</td>
<td></td>
</tr>
<tr>
<td>• Impaired oxidative capacity$^{29}$</td>
<td></td>
</tr>
<tr>
<td>• Impaired skeletal muscle calcium and potassium regulation$^{44}$</td>
<td></td>
</tr>
</tbody>
</table>
Table 4-1: Demographics, anthropometrics and pulmonary function

<table>
<thead>
<tr>
<th>Variable</th>
<th>LTx (n=34)</th>
<th>Control (n=12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20 (59%)</td>
<td>6 (50%)</td>
<td>Chi square p=0.281</td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>60 ± 8.3</td>
<td>56 ± 9.5</td>
<td>p=0.143</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>26 ± [24 - 28]</td>
<td>26 ± [24 – 28]</td>
<td>p=0.815</td>
</tr>
<tr>
<td></td>
<td>Median [IQR]**</td>
<td>Median [IQR]**</td>
<td></td>
</tr>
<tr>
<td>PASE</td>
<td>84 ± 53</td>
<td>166 ±122</td>
<td>p=0.001</td>
</tr>
</tbody>
</table>

Lung Transplant Candidates only

<table>
<thead>
<tr>
<th>Variable</th>
<th>LTx (n=34)</th>
<th>Control (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-MWT (m)</td>
<td>380 ± 102</td>
<td></td>
</tr>
<tr>
<td>6-MWT %Pred</td>
<td>58 ± 17</td>
<td></td>
</tr>
</tbody>
</table>
Lung Function

\[
\begin{align*}
\text{FEV}_1 (\text{L}) & \quad 1.4 \pm 0.7 \\
\text{FEV}_1 (\%\text{Pred}) & \quad 43.5 \pm 18.5 \\
\text{FVC (L)} & \quad 2 \pm 0.8 \\
\text{FVC (}\%\text{pred}) & \quad 50 \pm 13 \\
\text{TLC (L)} & \quad 4 \pm 1.7 \\
\text{TLC (}\%\text{pred}) & \quad 67 \pm 30 \\
\text{D}_{\text{LCO}} (\text{ml/min/mmHg}) & \quad 9.7 \pm 3.7 \\
\text{D}_{\text{LCO}} (\% \text{pred}) & \quad 55 \pm 22.3 
\end{align*}
\]

*Significant at the 0.05 level; **Not normally distributed data were reported in median and interquartile range [IQR]; the 6-MWD in LTx subjects was compared to reference values for the Canadian population"
Table 4-2: Comparisons between LTx candidates and control participants for muscle size

<table>
<thead>
<tr>
<th>Muscle size</th>
<th>LTx (n=34)</th>
<th>Control (n=12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF CSA at 50% LT (cm²)</td>
<td>7.4 ± 2.3</td>
<td>9.4 ± 2.4</td>
<td>0.014</td>
</tr>
<tr>
<td>RF+VL+VI at 50% LT (cm)</td>
<td>4.9 ± 1</td>
<td>5.6 ± 0.8</td>
<td>0.029</td>
</tr>
<tr>
<td>Gastroc + Soleus LT (cm)</td>
<td>2.7 ± 0.6</td>
<td>3.4 ± 0.7</td>
<td>0.017</td>
</tr>
<tr>
<td>Biceps LT (cm)</td>
<td>2.5 ± 0.4</td>
<td>2.8 ± 0.3</td>
<td>0.062</td>
</tr>
</tbody>
</table>

*Significant at the 0.012 level; CSA = cross-sectional area; LT = layer thickness; RF = rectus femoris; VL = vastus lateralis; VI = vastus intermedius
Table 4-3: Comparisons between LTx candidates and control participants for muscle strength measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>LTx (n=34)</th>
<th>Control (n=12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Muscle Strength</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee extension peak torque (Nm)</td>
<td>114 ± 33</td>
<td>147 ± 29</td>
<td>0.005*</td>
</tr>
<tr>
<td>Knee extension force (N)</td>
<td>214 ± 67</td>
<td>265 ± 108</td>
<td>0.110</td>
</tr>
<tr>
<td>Ankle dorsiflexion peak torque (Nm)</td>
<td>27 ± 10</td>
<td>30 ± 7</td>
<td>0.353</td>
</tr>
<tr>
<td>Ankle dorsiflexion force (N)</td>
<td>132 ± 41</td>
<td>235 ± 128</td>
<td>0.002*</td>
</tr>
<tr>
<td>Ankle plantarflexion peak torque (Nm)</td>
<td>37 ± 18</td>
<td>50 ± 15</td>
<td>0.032</td>
</tr>
<tr>
<td>Elbow flexion peak torque (Nm)</td>
<td>36 ± 18</td>
<td>42 ± 16</td>
<td>0.295</td>
</tr>
<tr>
<td>Elbow flexion force (N)</td>
<td>177 ± 74</td>
<td>260 ± 79</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*Significant at the 0.012 level; Measurements of torque (Nm) were collected on the Biodex and measurements of force (N) were collected using hand held dynamometry; plantarflexion was collected on the Biodex only
Table 4-4: Comparison between LTx candidates and control participants for functional performance measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>LTx (n=34)</th>
<th>Control (n=12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional Tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TUG (sec)</td>
<td>8.4 [7.6 - 10]</td>
<td>6.4 [5.7 – 7.9]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Median [IQR]**</td>
<td>Median [IQR]**</td>
<td></td>
</tr>
<tr>
<td>SPPB sub scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeated chair stands</td>
<td>3 ± 1</td>
<td>4 ± 0</td>
<td></td>
</tr>
<tr>
<td>Balance Test</td>
<td>4 ± 1</td>
<td>4 ± 0</td>
<td></td>
</tr>
<tr>
<td>8` Walk</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
<td></td>
</tr>
<tr>
<td>Total SPPB score</td>
<td>10 [9 – 11]</td>
<td>12 [10 - 12]</td>
<td>0.137</td>
</tr>
<tr>
<td></td>
<td>Median [IQR]**</td>
<td>Median [IQR]**</td>
<td></td>
</tr>
</tbody>
</table>

*Significant at the 0.016 level. TUG = Timed Up and Go test; SPPB = Short Physical Performance Battery; **Not normally distributed data was reported in median and interquartile range [IQR], other data are reported as mean ± standard deviation
Table 4-5: Summary of Unsupported Upper Limb Exercise test results in LTx candidates and controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre LTx (n=34)</th>
<th>Control (n=12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Time</td>
<td>554 ± 164</td>
<td>702 ± 124</td>
<td>0.009*</td>
</tr>
<tr>
<td>Dyspnea pre-test</td>
<td>1 ± 1</td>
<td>0 ± 1</td>
<td></td>
</tr>
<tr>
<td>Dyspnea post-test</td>
<td>3 ± 2</td>
<td>1 ± 1</td>
<td></td>
</tr>
<tr>
<td>Arm Fatigue pre-test</td>
<td>1 ± 1</td>
<td>0 ± 0</td>
<td></td>
</tr>
<tr>
<td>Arm Fatigue post-test</td>
<td>5 ± 2</td>
<td>4 ± 1</td>
<td></td>
</tr>
</tbody>
</table>

*Significant at the 0.016 level. Dyspnea and arm fatigue measured using the RPE scale
Table 4-6: Correlations between muscle size, muscle strength and function in lung transplant candidates

<table>
<thead>
<tr>
<th>Correlations (n=34)</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroc + Soleus LT vs. Ankle PF</td>
<td>0.12</td>
<td>0.490</td>
</tr>
<tr>
<td>RF CSA 50% vs. Knee extensors strength</td>
<td>0.63</td>
<td>0.000*</td>
</tr>
<tr>
<td>VL+RF+VI LT vs. knee extensor strength</td>
<td>0.56</td>
<td>0.000*</td>
</tr>
<tr>
<td>Knee extensor strength vs. TUG</td>
<td>-0.32</td>
<td>0.058</td>
</tr>
<tr>
<td>Knee extensor strength vs. 6-MWT %Pred</td>
<td>0.30</td>
<td>0.084</td>
</tr>
<tr>
<td>Knee extensor strength vs. SPPB</td>
<td>0.37</td>
<td>0.030</td>
</tr>
<tr>
<td>Dorsiflexion strength vs. TUG</td>
<td>-0.27</td>
<td>0.117</td>
</tr>
<tr>
<td>Dorsiflexion strength vs. SPPB</td>
<td>0.40</td>
<td>0.018</td>
</tr>
<tr>
<td>Dorsiflexion strength vs. 6-MWT %Pred</td>
<td>0.35</td>
<td>0.040</td>
</tr>
<tr>
<td>Plantarflexion strength vs. SPPB**</td>
<td>0.27</td>
<td>0.118</td>
</tr>
<tr>
<td>Plantarflexion strength vs. TUG</td>
<td>-0.21</td>
<td>0.227</td>
</tr>
<tr>
<td>Plantarflexion strength vs. 6-MWT %Pred</td>
<td>0.06</td>
<td>0.699</td>
</tr>
<tr>
<td>Elbow Flexion strength vs. Biceps LT</td>
<td>0.71</td>
<td>0.000*</td>
</tr>
<tr>
<td>Elbow Flexion strength vs. UULEX</td>
<td>0.36</td>
<td>0.035</td>
</tr>
<tr>
<td>Biceps LT vs. UULEX</td>
<td>0.41</td>
<td>0.016</td>
</tr>
</tbody>
</table>

*Significant at the 0.003 level. **Spearman rank correlation LT = layer thickness; PF = plantar flexion; TUG = Timed Up and Go test; SPPB = Short Physical Performance Battery; 6-MWT= 6-Minute walk test; UULEX = Unsupported Upper Limb Exercise Test
**Figure 3-1A:** Trans-axial view of rectus femoris (RF) muscle at 50% of thigh length. B mode Ultrasound imaging F=12MHz, Depth=4.5cm, Gain=78. The cross-sectional area of RF is outlined.

**Figure 3-1B:** Sagittal view of rectus femoris (RF) muscle at 50% length. US B mode imaging F=12MHz, Depth=8cm, Gain=78. The distance between the superficial and deep aponeurosis of RF is outlined – layer thickness (LT).
Figure 3.2: Set-up and subject positioning for the Unsupported Upper Limb Exercise Test
Figure 4-1: Study Flow Chart of lung transplant candidates

- Screened, n=73
- Excluded (n=20)
  - Systemic disease
  - Lupus, scleroderma, RA, fibromyalgia
- Approached, n=53
  - Excluded (n=16)
    - Extra time commitment (n=13)
    - No interest (n=3)
- Informed Consent, n=37
  - Excluded (n=3)
    - Had Tx before test (n=1)
    - Died before test (n=2)
- Tested, n=34
Figure 4-2: Correlation between Biceps LT and elbow flexion muscle strength in LTx candidates (n = 34)
Figure 4-3: Correlation between RF CSA 50% muscle size and knee extension muscle strength in LTx candidates (n = 34)
Figure 4-4: Correlation between quadriceps LT [sum of rectus femoris (RF), vastus lateralis (VL) and intermedius (VI)] and knee extension muscle strength in LTx candidates (n = 34)
Figure 4-5: Correlation between knee extension muscle strength (Biodex) and the Short physical performance battery test (SPPB) in LTx candidates (n = 34)
Figure 4-6: Correlation between ankle dorsiflexion muscle strength (Biodex) and the Short performance physical battery test (SPPB) in LTx candidates (n = 34)
Figure 4-7: Correlation between ankle dorsiflexion muscle strength (Biodex) and the 6-Minute Walk Test (% Pred) in LTx candidates (n = 34)
References


Appendices

Appendix A: Consent Form

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Title
Understanding the progression of skeletal muscle dysfunction in lung transplant recipients

Investigator
Dr. Lianne Singer, 416-340-4800, extn 4996

Co-Investigators
Dr. Sunita Mathur, PT, PhD, 416-978-7761
Dr. Dina Brooks, PT, PhD
Polyana Mendes, BSc(PT)
Lisa Wickerson, BSc(PT), MSc
Denise Helm, BSc(PT)

Sponsor
Ontario Respiratory Care Society

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 doctor or 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 of function after lung transplant. This study will look at skeletal muscle strength, muscle size and functional exercise capacity 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 52 people from the lung transplant program at UHN (Toronto General Hospital) will be included this study.

**Study Design**

This is a longitudinal study. This means that assessments will be take place over a period of time. There will be 5 visits during the study. The testing sessions at each visit will be split into 2 parts 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 twelve months following your lung transplant.

**Study Visits and Procedures**
There will be 5 study visits: before transplant, at hospital discharge after transplant, 3 months after transplant, 6 months after transplant, and 12 months after the transplant. On all five visits, you will undergo two sets of tests, one set at Toronto General Hospital and one set at University of Toronto.

For patients referred to St. John’s Rehab Hospital for an inpatient rehabilitation program, the hospital discharge assessment will be conducted on-site at St John’s Rehab. Follow-up assessments at 3, 6 and 12 months will be conducted at Toronto General Hospital and at the University of Toronto.

**Functional testing at Toronto General Hospital (~2 hours):**

*Short Performance Physical Battery (SPPB)* – this is a test of mobility and balance. You will be asked to stand in one position holding your balance, rise from a chair 5 times and walk for 4 meters while being timed.

*Timed Up and Go* – this is a test of mobility and balance. You will be timed as you rise from a chair, walk 3 meters, turn around and sit back down in the chair.

*Unsupported Upper Limb Exercise Test* – this is a test of your arm endurance. While sitting in a chair, you will be asked to raise a weighted bar (0.5kg) from your lap to a height at shoulder level to a regular beat given by a metronome (a device that produces an audible beat at a regular intervals). If you meet a certain time, the bar will be made heavier to a maximum of 2 kg. You will continue the test until you feel too tired, out of breath or can no longer continue for another reason.

*Muscle testing* – the study investigator will test the strength of your thigh, calf and upper arm muscles using a small hand held device. You will be asked to push against the device as hard as
you can and the force you exert will be recorded. You will repeat the test 3 times to determine your best effort.

6 Minute Walk Test – you will be asked to walk in a hallway for 6 minutes and we will measure how far you walk. You will be able to take a rest if needed. This test is part of the routine care at UHN for people having lung transplants.

Laboratory Testing at University of Toronto (~ 2hours):

Ultrasound – we will use an ultrasound to look at the muscles of your thigh, calf and arm. Gel will be placed on your skin and the ultrasound will be used to capture pictures of your muscles. The pictures will be used to determine the size (thickness) of your muscles.

Strength testing – you will be seated on a machine that is used to test your leg and arm muscle strength. You will be asked to push or pull against a pad as hard as you can to determine your maximal muscle strength.

Calendar of Visits:
Boxes marked with an X show what will happen at each visit:

<table>
<thead>
<tr>
<th>Visit</th>
<th>Pre-transplant</th>
<th>Post-transplant – hospital discharge</th>
<th>3 months post-transplant</th>
<th>6 months post-transplant</th>
<th>12 months post-transplant</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UHN procedures:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPPB</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>20 min</td>
</tr>
<tr>
<td>Timed Up and Go</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>15 min</td>
</tr>
<tr>
<td>6 Minute Walk test</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>30 min</td>
</tr>
<tr>
<td>UULEX</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>30 min</td>
</tr>
<tr>
<td>Muscle testing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>25 min</td>
</tr>
<tr>
<td><strong>U of T procedures:</strong></td>
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<td></td>
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</tr>
<tr>
<td>Ultrasound</td>
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<td>X</td>
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<td>X</td>
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<tr>
<td>Strength testing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>1 hr</td>
</tr>
</tbody>
</table>

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

Wear comfortable clothing suitable for exercise for the study visits.

- Ask your study team about anything that worries you.
- Tell study staff anything about your health that has changed.
- Tell your study team if you change your mind about being in this study.

**Risks Related to Being in the Study**

This study has risks. Some of these risks we know about. The risks we know of are:

Muscle fatigue and soreness - It is common to feel that your muscles are sore or tired after the strength testing and functional testing (occurs in about 20% of people). The tiredness should go away after a few hours and the soreness should go away after a day.

There is also a possibility of risks that we do not know about and have not been seen in study subjects to date. Some can be managed. Please call the study doctor if you have any side effects even if you do not think it has anything to do with this study.

**Benefits to Being in the Study**

You may not receive any direct benefit from being in this study. Information learned from this study may help other people undergoing lung transplants 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, or not answer an interview question by saying “pass”.
Confidentiality

If you agree to join this study, the study doctor 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 doctor 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 leave the study will still be used in order to help answer the research question. 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 Participating in the Study**

You will not have to pay for any of the testing procedures involved with this study. You will be reimbursed $10 per visit to assist with parking costs.

**Conflict of Interest**

The study team has an interest in completing this study. Their interests 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: Dr. Lianne Singer at 416-340-4800 x4996 or Dr. Sunita Mathur at 416-978-7761.
If you have any questions about your rights as a research participant or have concerns about this study, call the Chair of the University Health Network Research Ethics Board (REB) or the Research Ethics office number at 416-581-7849. 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

☐ 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: Reliability and Validity of Muscle Ultrasound

Brightness mode (B-mode) ultrasonography (US) can be used to produce high quality images of muscle morphology and similar to MRI, it shows contrast between muscle and fat tissue. A limitation of US is that it has a relatively limited depth and field of view compared with MRI\(^{62}\). However US is quick to perform, safe, relatively inexpensive and a more widely available technique compared with MRI. Furthermore, US provides adequate information about muscle size and shape and is suitable for laboratory and clinical use.

In this thesis to ensure validity of the US, measures US and MRI were performed in a pilot study in COPD patients and healthy controls. In this pilot, 3 subjects underwent an MRI (gold standard measurement) of their leg muscles and an US scan of the same muscles was performed. To test the intra-rater reliability of the US, measures of muscle size a second pilot study was performed. In this pilot, 3 healthy participants underwent two repeated measures of US within a one-week period.

### MRI Protocol:

Participants underwent an MRI of their thigh at Toronto General Hospital (1.5T whole-body scanner, Signa, GE Medical Systems). Subjects were positioned in supine with their dominant lower limb positioned on a cardiac coil for thigh imaging. Coverage was from knee to proximal thigh to ensure that the maximal cross-sectional area of the quadriceps was covered. Transaxial images were acquired using the spoiled gradient echo (SPGR) sequence, with the following parameters: TR=5.7 ms, TE=2.7 ms, acquisition matrix of 256 x 256 pixels, slice thickness of 7mm and slice gap of 7mm, flip angle=10° and optimized field of view (~40cm\(^2\)). Muscle size data of COPD patients and healthy controls are summarized in Table X. A mean percentage difference of less than 2.5% between MRI and US measurements of CSA was observed.

### US protocol:

The subject’s thigh muscles were imaged. On the test occasion three US images were obtained in each subject by one rater using the US GE Logic E system, using a 5-13 MHz linear
transducer probe. The US measurements were performed after the subject had been lying down for about 20 min to allow fluid shifts to occur\textsuperscript{62,63}. During the measurements, subjects was positioned comfortably with their limb (arm or leg) supported by a pillow and the CSA of the RF muscle accessed was made with a standard transducer location corresponding to the largest diameter of the anatomical sites. The RF muscle was imaged at 50\% femur length with the subject in supine and the knee flexed to \textasciitilde30\textdegree, according to procedures previously described\textsuperscript{67}.

The US images were captured directly on the GE system, and subsequently transferred to a computer for further analysis. Image analysis was done using publicly available computer software (Osirix for Mac, http://www.osirix-viewer.com/) and measurements of muscle RF CSA muscle were manually outlined. Representative images of CSA and LT measurements of the RF muscle are shown in Figure A and Figure B.

Table 1: Comparisons between MRI and US measurement of RF CSA of COPD and control participants

<table>
<thead>
<tr>
<th>Subject</th>
<th>Average CSA from MRI</th>
<th>Average CSA from US</th>
<th>Absolute Difference</th>
<th>Mean percentage difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CON001</td>
<td>9.78</td>
<td>11.62</td>
<td>1.84</td>
<td>17%</td>
</tr>
<tr>
<td>CON009</td>
<td>11.23</td>
<td>9.08</td>
<td>2.15</td>
<td>21%</td>
</tr>
<tr>
<td>COPD009</td>
<td>6.98</td>
<td>5.26</td>
<td>1.72</td>
<td>28%</td>
</tr>
<tr>
<td>Subject</td>
<td>Muscle</td>
<td>Average Day 1</td>
<td>Average Day 2</td>
<td>Absolute Difference</td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>1</td>
<td>RF 50% LT</td>
<td>2.4</td>
<td>2.6</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>RF 50% LT</td>
<td>1.2</td>
<td>1.3</td>
<td>0.1</td>
</tr>
<tr>
<td>3</td>
<td>RF 50% LT</td>
<td>1.6</td>
<td>1.7</td>
<td>0.1</td>
</tr>
<tr>
<td>1</td>
<td>VI 50%LT</td>
<td>1.8</td>
<td>2.0</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>VI 50%LT</td>
<td>1.0</td>
<td>1.3</td>
<td>0.3</td>
</tr>
<tr>
<td>3</td>
<td>VI 50%LT</td>
<td>1.2</td>
<td>1.4</td>
<td>0.2</td>
</tr>
<tr>
<td>1</td>
<td>VL 50%LT</td>
<td>2.6</td>
<td>2.6</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>VL 50%LT</td>
<td>1.1</td>
<td>1.7</td>
<td>0.6</td>
</tr>
<tr>
<td>3</td>
<td>VL 50%LT</td>
<td>1.5</td>
<td>2.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 1 summarizes the validity of the US measure in relation with MRI with mean percentage level average of 22%. Intraclass correlation coefficient for comparison between MRI and US measures was 0.80, indicating good inter methods validity. The results of the intra-rater reliability of the US are summarized in Table 2 with very low absolute differences between methods. Intraclass correlation for intra-rater reliability of the US measures of muscle size was ICC=0.92.
Figure A: Magnetic Resonance Image (1.5T whole-body scanner, Signa, GE Medical Systems) image of mid-thigh, Rectus femoris CSA is outlined

Figure B: Ultrasound (F=12MHz, Depth=4.5cm) image of the quadriceps. Sample scan of a study participant showing RF CSA 50% outlined
Appendix C: Short Physical Performance Battery

Short Physical Performance Battery

Subject Number: ____________ Date: ______________

1-Repeated Chair Stands

Instructions: Do you think it is safe for you to try and stand up from a chair five times without using your arms? Please stand up straight as quickly as you can five times, without stopping in between. After standing up each time, sit down and then stand up again. Keep your arms folded across your chest. Please watch while I demonstrate. I’ll be timing you with a stopwatch. Are you ready? Begin

Time: ____ sec (if five stands are completed)

Number of Stands Completed:
()1 ( )2 ( )3 ( )4 ( )5

Chair Stand Ordinal Score: _____

0 = unable 1 = > 16.7 sec 2 = 16.6-13.7 sec 3 = 13.6-11.2 sec 4 = < 11.1 sec

2-Balance Testing

—–

Begin with a semi tandem stand (heel of one foot placed by the big toe of the other foot). Individuals unable to hold this position should try the side-by-side position. Those able to stand in the semi tandem position should be tested in the full tandem position. Once you have completed time measures, complete ordinal scoring.

**a. Semitandem Stand Instructions:** Now I want you to try to stand with the side of the heel of one foot touching the big toe of the other foot for about 10 seconds. You may put either foot in front, whichever is more comfortable for you. Please watch while I demonstrate.

**Grading:** Stand next to the participant to help him or her into semitandem position. Allow participant to hold onto your arms to get balance. Begin timing when participant has the feet in position and lets go.

**Circle one number**
2. Held for 10 sec
1. Held for less than 10 sec; number of seconds held _____
0. Not attempted

**b. Side-by-Side stand Instructions:** I want you to try to stand with your feet together, side by side, for about 10 sec. Please watch while I demonstrate. You may use your arms, bend your knees, or move your body to maintain your balance, but try not to move your feet. Try to hold this position until I tell you to stop.

**Grading:** Stand next to the participant to help him or her into the side-by-side position. Allow participant to hold onto your arms to get balance. Begin timing when participant has feet together and let’s go.

**Grading**
2. Held of 10 sec
1. Held for less than 10 sec; number of seconds’ held _____
0. Not attempted
c. **Tandem Stand Instructions:** Now I want you to try to stand with the heel of one foot in front of and touching the toes of the other foot for 10 sec. You may put either foot in front, whichever is more comfortable for you. Please watch while I demonstrate.

**Grading:** Stand next to the participant to help him or her into the side-by-side position. Allow participant to hold onto your arms to get balance. Begin timing when participant has feet together and lets go.

**Grading**
2. Held of 10 sec
1. Held for less than 10 sec; number of seconds’ held ____
0. Not attempted

**Balance Ordinal Score:** ____

0 = side by side 0-9 sec or unable
1 = side by side 10, <10 sec sem tandem
2 = sem tandem 10 sec, tandem 0-2 sec
3 = sem tandem 10 sec, tandem 3-9 sec
4 = tandem 10 sec

3. **8’ Walk**

**Instructions:** This is our walking course. If you use a cane or other walking aid when walking outside your home, please use it for this test. I want you to walk at your usual pace to the other end of this course 3M (a distance of 8’). Walk all the way past the other end of the tape before you stop. I will walk with you. Are you ready?

**Grading:** Press the start button to start the stopwatch as the participant begins walking. Measure the time take to walk 8’. Then complete ordinal scoring.
Time________________________ sec

Gait Ordinal Score: ___

0 = could not do
1 = >5.7 sec (<0.43 m/sec)
2 = 4.1-6.5 sec (0.44-0.60 m/sec)
3 = 3.2-4.0 (0.61-0.77 m/sec)
4 = <3.1 sec (>0.78 m/sec)

Summary Ordinal Score: ______

Range: 0 (worst performance) to 12 (best performance)