OXYGENATION DURING EXERCISE IN INDIVIDUALS WITH INTERSTITIAL LUNG DISEASE

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
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Abstract

Individuals with interstitial lung disease (ILD) commonly exhibit exertional hypoxemia. The overall objective of this thesis was to examine aspects of oxygenation during exercise in ILD. The first study (Chapter 2) examined constant load endurance exercise with systemic arterial oxygen saturation monitoring using pulse oximetry. This study found that in a cohort of 375 lung transplant candidates with advanced ILD, high exertional oxygen requirements were required and were increased over time to prevent hypoxemia during exercise. Higher levels of exertional oxygen use were associated with a lower exercise capacity and aerobic training intensity. The second study (Chapter 3) was a cross-over study designed to compare feasibility (participant tolerance and preference) and acute cardiorespiratory responses of a single bout of interval exercise with a bout of continuous exercise on a cycle ergometer in nine lung transplant candidates with ILD. Findings from this study revealed that interval exercise was well tolerated and preferred. Interval exercise resulted in a lower peak heart rate with trends towards less arterial oxygen desaturation, lower leg fatigue and less elevation in blood lactate compared to continuous exercise. The third study (Chapter 4) prospectively examined regional
skeletal muscle oxygenation/ deoxygenation and muscle blood volume using near infrared spectroscopy during upper and lower limb incremental loading in three groups: thirteen lung transplant candidates with oxygen dependent severe ILD, ten individuals with non-oxygen dependent mild/moderate ILD and thirteen healthy persons. This study showed that muscle deoxygenation occurred at a lower level of total work in the two ILD groups. During lower limb loading regional blood volume was attenuated in severe ILD compared to healthy persons. Regional muscle deoxygenation was not associated with systemic arterial oxygen saturation. The findings from these three studies provide insight into oxygen delivery and utilization during exercise in ILD. Individuals with ILD, exertional hypoxemia and high supplemental oxygen use presented with reduced exercise capacity during aerobic and resistance exercise and impairments in systemic and regional muscle oxygenation. Optimal oxygen supplementation and alternative modes of aerobic training may improve peripheral muscle oxygen utilization and capacity, and should be further studied.
Acknowledgments

The important thing is not to stop questioning. Curiosity has its own reason for existing.

Albert Einstein 1879-1955

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I dedicate this thesis to my father, Reverend Peter Wickerson.
Preface

Format of thesis

This thesis is presented in manuscript style. Chapter 1 includes the summary of the research problem, a literature review and the research objectives and hypotheses. A portion of a published scoping review is part of the literature review. Chapter 2 is a published manuscript, and Chapters 3 and 4 are manuscripts in preparation. Chapter 5 is an integration of the research findings and directions for future study.

Summary of contributions related to the thesis (in order of appearance):


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Abbreviations

A-a PO₂ – alveolar-arterial oxygen gradient

ABGs – arterial blood gases

ANOVA- analysis of variance

BMI – body mass index

BP – blood pressure

CI – confidence interval

COP – cryptogenic organizing pneumonia

COPD – chronic obstructive pulmonary disease

CPET – cardiopulmonary exercise test

CTD – connective tissue disease

DIP – desquamative interstitial pneumonia

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

DSP – distance-saturation product

DSP/FiO\textsubscript{2} – distance-saturation product adjusted for fraction of inspired oxygen

ECG – electrocardiogram

EFL – elbow flexor loading

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

FiO\textsubscript{2} – fraction of inspired oxygen
FVC – forced vital capacity

GAP index – gender age pulmonary physiology index

Hb – hemoglobin

Hb-diff – hemoglobin difference

Hct - hematocrit

HHb – deoxyhemoglobin

HMb – deoxymyoglobin

HR – heart rate

HRQOL – health related quality of life

IIP – idiopathic interstitial pneumonia

ILD – interstitial lung disease

IPF- idiopathic pulmonary fibrosis

IQR – interquartile range

KEL – knee extensor loading

LAM- lymphangioleiomyomatosis

MAP – mean arterial pressure

mPAP – mean pulmonary arterial pressure

Mb- myoglobin

MET- metabolic equivalent of the task

MVIC – maximal voluntary isometric contraction
NIRS- near infrared spectroscopy

NSIP – nonspecific interstitial pneumonia

O$_2$Hb – oxyhemoglobin

O$_2$Mb – oxymyoglobin

PAO$_2$ – partial pressure of alveolar oxygen

PaO$_2$ – partial pressure of arterial oxygen

PFT – pulmonary function test

PH – pulmonary hypertension

PiO$_2$ – partial pressure of inspired oxygen

PO$_2$ – partial pressure of oxygen

PR – pulmonary rehabilitation

RA-ILD – rheumatoid arthritis associated interstitial lung disease

RR – respiratory rate

SaO$_2$ – arterial oxygen saturation

SD- standard deviation

SmO$_2$ – skeletal muscle tissue oxygen saturation

SpO$_2$ – oxygen saturation as measured by pulse oximetry

StO$_2$ – tissue oxygen saturation

SvO$_2$ – mixed venous saturation of oxygen

tHb – total hemoglobin
TLC – total lung capacity

TSI – tissue saturation index

UIP – usual interstitial pneumonia

VI – vastus intermedius

VL – vastus lateralis

\( VO_{2\text{max}} \) – maximal oxygen consumption

\( VO_{2\text{peak}} \) – peak oxygen consumption

6MWD – six-minute walk distance

6MWT – six-minute walk test
Chapter 1

1 Introduction

1.1 Statement of the problem

Interstitial lung disease (ILD) is a heterogeneous, progressive, chronic, fibrotic lung disease associated with reduced exercise capacity, dyspnea, lower health-related quality of life (HRQOL) and increased mortality.\textsuperscript{1-3} Exercise limitation in ILD is multifactorial, arising from ventilatory and circulatory limitations, impairments in gas exchange and peripheral muscle dysfunction.\textsuperscript{4-8} These pathological changes affect oxygenation of tissues during exercise by impairing the transport, delivery and utilization of oxygen to the exercising muscles (Figure 1-1). There is emerging evidence of the effectiveness of exercise training in ILD,\textsuperscript{9-12} however optimal training strategies are not known. Individuals with ILD exhibit a rapid and profound hypoxemia (low levels of oxygen in the arterial blood) on exertion, and can require high levels of supplemental oxygen during exercise.\textsuperscript{8,13-15} Although supplemental oxygen is widely used in ILD to prevent exertional hypoxemia and support aerobic exercise and physical activity, there is a lack of evidence supporting the efficacy of ambulatory oxygen therapy in improving exercise capacity, symptoms and survival in this population.\textsuperscript{16}

The overall objective of this thesis was to explore whole body and local skeletal muscle oxygenation during endurance and resistance exercise in people with advanced ILD. The relevance and implications for this research are to contribute to the evidence on safe and effective exercise training and oxygen supplementation to optimize physical function in ILD.
1.2 Literature review

1.2.1 Overview of interstitial lung disease

1.2.1.1 Prevalence, subtypes, clinical progression and prognosis

Interstitial lung disease (ILD) is a heterogeneous group of chronic, fibrotic respiratory disorders comprising over 200 subtypes including idiopathic interstitial pneumonias (IIPs), granulomatous ILDs such as sarcoidosis, and ILDs of known causes including connective tissue diseases, occupational and environmental exposures, radiation therapy and drug side effects (Figure 1-2). A population-based study in the United States reported the prevalence of ILD as 81 per $10^5$ in men and 67 per $10^5$ in women. Interstitial lung diseases are accompanied by reduced exercise capacity, disabling symptoms (dyspnea, fatigue, non-productive cough), decreased HRQOL and increased mortality. The clinical progression and prognosis is dependent on the ILD subtype. Idiopathic pulmonary fibrosis (IPF) is most common idiopathic interstitial pneumonia and has a poor prognosis (median survival of two to three years at the time of diagnosis). The course of IPF can be variable and unpredictable. Pulmonary function testing reveals a restrictive pattern with reduced lung volumes and decreased diffusing capacity for carbon monoxide ($D_{LCO}$). The change in forced vital capacity (FVC) and $D_{LCO}$ are frequently monitored to evaluate the response to treatment and prognosis in ILD. Hypoxemia occurs early in the disease process and worsens with disease progression. Pulmonary hypertension (PH) can complicate ILD. PH is evident in greater than 60% of end-stage ILD and is associated with decreased exercise capacity, increased severity of hypoxemia and worse survival. Mortality risk in IIPs has also been associated with exercise capacity. A higher mortality as been associated with a lower six-minute walk distance (6MWD), desaturation $\leq 88\%$ during the six-minute walk test (6MWT), an
abnormal heart rate recovery of $\leq 13$ beats one minute following the 6MWT and a maximal oxygen uptake from a cardiopulmonary exercise test (CPET) of $< 8.3 \text{ ml kg}^{-1}\text{min}^{-1}$.\textsuperscript{22-27}

1.2.1.2 Treatment interventions

Medical treatment options for IPF are evolving. Treatments include anti-fibrotics (e.g. Pirfenidone) and tyrosine kinase inhibitors (e.g. Nintedanib) to slow the rate of decline in forced vital capacity in individuals with mild to moderate lung impairment, supplemental oxygen and exercise-based pulmonary rehabilitation.\textsuperscript{19,28} However, none reverse the condition and many individuals continue to suffer through progression of their disease. Lung transplantation is an option for a select group of individuals with end-stage disease, and ILD is a leading cause for referral to lung transplantation.\textsuperscript{29}
Figure 1-1:

Pathological changes in interstitial lung disease affecting systemic arterial oxygen delivery and regional muscle oxygen supply and utilization during exercise

Abbreviations: SaO₂: arterial oxygen saturation; SpO₂: arterial oxygen saturation as estimated by pulse oximetry; SmO₂: skeletal muscle tissue oxygen saturation as measured by near infra-red spectroscopy; SvO₂: mixed venous oxygen saturation
* Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial pneumonia
1.2.2 Oxygen transport and utilization during exercise in health

Exercise is a stress that increases the metabolic oxygen demand of contracting skeletal muscles to create energy for biological work. Physiological responses during exercise include central and peripheral changes. Central changes that increase oxygen delivery to working muscles include: increases in minute ventilation, increased diffusion capacity in the lung (recruitment and distension of pulmonary capillaries) and increased pulmonary and systemic blood flow. 31 The increase in blood flow through the lungs during exercise reduces the time available for oxygen to diffuse from the alveoli into the pulmonary capillaries (capillary transit time). 31 Peripheral changes that increase oxygen extraction and utilization of working muscles include: blood flow redistribution to active muscles, a decrease in the affinity of hemoglobin (Hb) for oxygen that facilitates unloading into the muscles, and an increase in the surface area for diffusion though dilatation and recruitment of muscle capillaries to facilitate faster diffusion of oxygen into the mitochondria (Figure 1-3). 31 For oxygen delivery and extraction to work optimally, a well-functioning respiratory, cardiac, vascular and muscular system is required with adequate reserves to allow them to respond to the increased oxygen demands of exercise. In healthy people the primary factor limiting maximal oxygen uptake (VO$_{2\text{max}}$) is maximal cardiac output (estimated to explain 70-85% of the variance in VO$_{2\text{max}}$), with a smaller contribution of peripheral factors such as muscle capillary density. 32

1.2.3 Mechanisms of exercise limitation in ILD

Individuals with ILD have reduced exercise capacity with subsequent hypoxemia, dyspnea and leg fatigue. The following section reviews the key physiological changes that contribute to this exercise limitation.
1.2.3.1 Ventilatory factors and altered respiratory mechanics

An increase in lung elasticity due to a deposition of fibrous tissue results in a restrictive ventilatory defect with low static and dynamic lung compliance, increased recoil pressures and reduced lung volumes.\textsuperscript{33} An increased inspiratory neural drive is also present during exercise.\textsuperscript{33} These changes result in an elevated minute ventilation for a given workload during exercise, failure to decrease ventilatory dead space, and a decrease in inspiratory capacity.\textsuperscript{34,35} Individuals exhibit a rapid, shallow breathing pattern characterized by increased respiratory frequency, low tidal volume and shorter inspiratory time to the total respiratory cycle duration.\textsuperscript{36} Inspiratory muscle strength and diaphragmatic mobility is usually preserved as low lung volumes are thought to place these muscles at a mechanical advantage, however mixed findings have been reported and little is known of the relationship between respiratory muscle performance and functional ability.\textsuperscript{33,37} A fall in twitch gastric pressure suggestive of abdominal muscle fatigue has been reported following a symptom-limited exercise test in ILD, but was not associated with reduced exercise tolerance.\textsuperscript{38}

1.2.3.2 Gas exchange abnormalities

Impairment in oxygen gas exchange is caused mainly from ventilation/perfusion mismatch due to destruction of pulmonary microvasculature and shunt.\textsuperscript{5,8} Oxygen diffusion arising from a thickened alveolar-capillary barrier due to extensive collagen deposition in the alveolar walls is also a limitation to gas exchange, contributing approximately 19% to hypoxemia at rest and 40% during exercise when capillary transit time decreases.\textsuperscript{5,31} The slower rate of oxygen diffusion prevents the partial pressure of alveolar gas (PAO\textsubscript{2}) from equilibrating with the capillary blood
partial pressure of oxygen. A low mixed venous oxygen content also contributes to gas exchange abnormalities. A reduced cardiac output or a decreased oxygen content with proportionally increased oxygen extraction by working muscles when oxygen delivery is reduced will increase venous admixture or relative shunt. The resulting effect is rapid and profound hypoxemia with a widened alveolar-arterial oxygen gradient (A-a PO$_2$) during exercise, even if individuals are normoxic at rest. Despite these reductions in oxygen gas exchange during exercise, hypercapnia is not commonly observed in ILD, as individuals are able to increase their minute and alveolar ventilation to eliminate carbon dioxide in the face of an increase in dead space fraction.

1.2.3.3 Circulatory limitations

Endothelial remodeling and pulmonary capillary destruction in ILD can cause damage to the pulmonary vasculature from an overexpression of cytokines and growth factors, as well as hypoxic pulmonary vasoconstriction. Hypoxic pulmonary vasoconstriction is a mechanism that increases ventilation/perfusion matching by constricting pulmonary arteries supplying poorly ventilated alveoli to divert blood to well ventilated alveoli. The damage to the pulmonary vasculature can lead to an increase in pulmonary vascular resistance and pulmonary arterial pressures (pulmonary hypertension), defined as a mean resting pressure of $\geq 25$ mmHg. The diminished pulmonary vascular bed and increased pulmonary vascular resistance and arterial pressures increase right ventricular afterload, attenuate pulmonary blood flow and subsequently the rise in cardiac output at higher levels of exercise.
Figure 1-3:

Oxygen hemoglobin dissociation curve: changes in hemoglobin’s affinity for oxygen with exercise

Abbreviations: $O_2$Hb: oxygenated hemoglobin; $PO_2$: partial pressure of oxygen
1.2.3.4 Peripheral limitations

Exercise limitation in ILD is often described in the context of changes within the lungs and pulmonary vasculature that lead to poor gas exchange and reduced functional capacity. Less is known about the role of peripheral vascular and muscle factors on exercise limitation, although peripheral skeletal muscle dysfunction is an emerging field of study in chronic lung disease. Peripheral skeletal muscle dysfunction is recognized as an important systemic consequence in COPD that contributes to morbidity and mortality, however less is known in ILD. 39 There is emerging evidence that peripheral muscle dysfunction may contribute to exercise limitation in ILD Figure 1-4. Quadriceps strength has been shown to be lower in ILD than healthy age and sex-matched controls and an independent predictor of VO_{2max} and 6MWD. 40,41 The majority of studies of peripheral muscle function in ILD examine volitional measures of muscle strength and endurance. 30 Several studies reveal a reduction in muscle cross sectional area, reduced muscle thickness and lower amounts of fat free mass in lower limbs. 30 Little is known of the oxidative capacity of peripheral muscles in ILD including muscle fibre type proportion, mitochondrial density, capillarization and metabolic enzymes, and how changes may affect muscle strength, muscle endurance and exercise capacity. 30 Individuals with ILD may present with a number of contributing factors that lead to decreases in muscle oxidative capacity such as deconditioning, chronic hypoxemia, inflammation, infection, malnutrition, physical inactivity, oxidative stress, corticosteroid use, co-morbidities and aging. Therefore further characterization of peripheral muscle function is needed. 4,30
Figure 1-4: Framework for understanding peripheral muscle dysfunction in interstitial lung disease adapted from reference 30.
1.2.4 Non-invasive measurement of oxygenation during exercise

The majority of oxygen (98%) transported within the blood is chemically bound to Hb in the red blood cell, and oxygenation of blood can be measured non-invasively and continuously during exercise using optical technologies such as pulse oximetry and near-infrared spectroscopy (NIRS). Both pulse oximetry and NIRS use non-ionizing electromagnetic radiation (low frequency, long wavelength radiation that does not carry enough energy to completely remove an electron from an atom or molecule), and measurement theory is based on 1) the biological optical window existing at wavelengths between 660 nm and 940 nm where light can penetrate into tissues and be absorbed by chromophores such as Hb and 2) the different light absorption properties of Hb in its’ various forms [oxyhemoglobin (O$_2$Hb) and deoxyhemoglobin (HHb)].

1.2.4.1 Pulse oximetry

Pulse oximetry transmits two wavelengths of light [red (660 nm) and infrared (940 nm)] through a blood sample to a photo detector to estimate the percentage of Hb in circulating arterial blood that is saturated with oxygen (SpO$_2$). It recognizes pulsatile arterial blood by detecting the variation in light transmission during each heart beat when a surge of blood increases the blood volume across the monitoring site, thus isolating it from venous and capillary blood, and tissue (skin, subcutaneous fat, muscle, bone). A normal SpO$_2$ value of 95-100% is calculated by the ratio of the concentration of O$_2$Hb to total Hb concentration in the arterial blood, reflecting oxygen supply or delivery:

$$\text{SpO}_2 = \frac{\text{O}_2\text{Hb}_{\text{arterial blood}}}{\text{O}_2\text{Hb}_{\text{arterial blood}} + \text{HHb}_{\text{arterial blood}}} \times 100$$
Accuracy is generally reported to be ± 2% compared against arterial blood gases when SpO$_2$ is greater than 80%, however accuracy does vary between different pulse oximetry models.

Sources of error in pulse oximetry readings include intravenous dyes, dark skin pigment, high levels of carboxyhemoglobin, extraneous light, severe hypoxemia (SpO$_2$ < 70%) and signal quality. Signal quality is reduced if there is poor peripheral perfusion, anemia and motion artifact from a loose or unstable probe placement or fit or excessive movement (e.g. hand tremors). A delayed response time of pulse oximeters during acute hypoxic challenges is affected by the oximetry monitoring site (finger, forehead, ear, toe) and perfusion status (vasoconstriction, hypothermia, vasoreactive drugs). A two to three-fold greater delay in response time during normothermic conditions have been observed using finger oximetry compared with forehead and ear monitoring as the blood vessels in the fingers undergo greater vasoconstriction during exercise than vessels in the forehead or ear.

### 1.2.4.2 Near-infrared spectroscopy

Local tissue oxygenation can be estimated using NIRS. Conversion of the amount of near infrared light absorption to reflect changes in oxygenation are based on the Beer-Lambert Law which states that absorbance of a substance at particular wavelength is proportional to both concentration of the substance and the distance (or path length) between the light entry and exit point of a medium. As biological tissue is a heterogeneous medium that scatters light, this law is modified by incorporating a path-length correction factor, with assumptions made about the light-tissue interaction (how much is scattered, absorbed or reflected). The NIRS technology used in this thesis to measure skeletal muscle oxygenation was spatially-resolved spectroscopy. This method uses devices containing three transmitter optodes that each emit two different
wavelengths of light (around 760 and 850 nm), some of which are absorbed by O$_2$Hb and HHb and reflected in a shallow arc back to one receiver to be measured. The three distances between the transmitters and the receiver (the inter-optode distances) provide information on different depths of penetration (the depth of penetration into the underlying tissue is approximately half of the inter-optode distance). Real time, absolute changes in concentration of O$_2$Hb, HHb and their sum, total hemoglobin (tHb) that estimates blood volume underneath the probe, can be measured (Figure 1-5). Myoglobin (Mb) is also an oxygen dependent chromophore located within the muscle cell that absorbs infrared light. Due to similar spectral characteristics, NIRS cannot differentiate between Hb and Mb, although Hb is believed to contribute to the majority of the signal. The majority of the signal is believed to arise from small vessels < 1mm in diameter (arterioles, capillaries, venules) as the small heme concentrations in these vessels do not absorb all the light and thus some light can be reflected back to a receiver to be measured. Spatially resolved NIRS uses the three transmitter optodes to calculate an absolute percentage of skeletal muscle oxygen saturation of the microcirculation reflecting the dynamic balance between tissue oxygen delivery and utilization at the intracellular level. The terminology for skeletal muscle oxygenation has been described as the tissue saturation index (TSI), tissue oxygen saturation (StO$_2$) or skeletal muscle oxygen saturation (SmO$_2$), and the latter term will be used throughout this thesis. The SmO$_2$ under normal conditions is 60-80%, and is quantified by the ratio of the concentration of O$_2$Hb/Mb to total Hb/Mb concentration in the muscle microcirculation:

$$\text{SmO}_2 = \frac{O_2\text{Hb/Mb}_{\text{muscle}}}{O_2\text{Hb/Mb}_{\text{muscle}} + \text{HHb/Mb}_{\text{muscle}}} \times 100$$
Figure 1-5:

Spatially-resolved near-infrared technology to measure skeletal muscle oxygenation
Studies examining tissue oxygenation and hemodynamics have used venous occlusion, arterial occlusion and measurements during exercise to calculate blood flow, oxygen consumption, venous saturation, reoxygenation rate and half recovery time of O$_2$Hb, HHb tHb and SmO$_2$. Exercise can include static muscle contractions (isometric exercise over a certain percentage of maximal force that constricts blood vessels serving the muscles and muscle capillaries) and dynamic muscle contractions (isotonic or isokinetic rhythmic or repetitive contractions with periods of muscle relaxation allowing blood flow to muscles during relaxation and assisting venous return through the intermittent squeezing action of the muscle contraction). Muscle blood flow has been reported to be impaired due to small vessel compression when exercise exceeds 25-30% maximal isometric voluntary contraction (MIVC) of the elbow flexors. Near infrared spectroscopy measures have been shown to reliably measure blood volume and oxygenation during exercise, and show good agreement with gold standard techniques of oxidative capacity. The accuracy of the NIRS signal is impacted by light absorbance and scattering properties of overlying skin (perfusion, temperature, melanin) and subcutaneous fat (thickness). Subcutaneous fat absorbs less light than muscle, increasing the light intensity at the detector site and resulting in higher NIRS measurements. The optical density of tissue sample is inversely related to amount of light transmitted through, and as the depth sensitivity of NIRS is up to two centimetres, measurements are limited to superficial muscles.
1.2.5 Oxygen administration during exercise

1.2.5.1 Effect of oxygen on hypoxemia

Hypoxemia is a state of low oxygen levels in the arterial blood. Oxygen enriched air can reverse hypoxemia providing there is no significant cardiopulmonary shunt between the heart and lungs. Supplemental oxygen raises the fraction of inspired oxygen (FiO₂) above that of room air (0.21), subsequently increasing the partial pressure of inspired oxygen (PiO₂). This raises the alveolar partial pressure of oxygen (PAO₂), increases the difference in partial pressures between the alveoli and pulmonary capillary (A-a gradient), increases the rate of oxygen diffusion across the alveolar-capillary membrane and raises the partial pressure of arterial oxygen (PaO₂) increasing the pressure gradient for oxygen that favours binding to Hb and increases the affinity of oxygen to Hb to improve oxygen delivery to the tissues.¹³,³¹ At the tissue level, muscles can extract large amounts of oxygen with only a small drop in capillary partial pressure of oxygen, maintaining a pressure gradient to assist oxygen diffusion into the muscle cell ³¹ (Figure 1-3). Therefore, an individual who is hypoxemic on room air due to respiratory, circulatory, and/or peripheral limitations to exercise can benefit from a higher FiO₂ supplied by supplemental oxygen to increase the driving force for oxygen diffusion (partial pressure of oxygen) at the alveolar/capillary and capillary/myofibre interfaces.

Long-term home oxygen criteria aim to maintain a resting PaO₂ ≥ 55mmHg (corresponding to a SpO₂ 88%) to prevent resting hypoxemia. ⁵³ A partial pressure of oxygen 55mmHg is located on the steep slope of the oxygen dissociation curve, where Hb has less affinity for oxygen, and small decreases in PaO₂ result in large decreases in SpO₂ (Figure 1-3). ³¹ As previously described, exercise can further stress the gas exchange system in chronic lung disease as exercise increases the demand for oxygen, decreases the time for oxygen diffusion from the alveoli to the
pulmonary capillary, and produces acidic and hot exercising muscles that shift the oxygen
dissociation curve to the right to facilitate unloading of oxygen from Hb leading to hypoxemia
(Figures 1-1 and 1-3). 31

1.2.5.2 Recommendations for long-term oxygen therapy in ILD

There is a strong recommendation (based on both evidence and expert consensus) for oxygen
therapy in IPF to treat resting hypoxemia (SpO2 <88%). However this recommendation is based
on very low level evidence and is primarily extrapolated from the reduced mortality seen in the
COPD population with significant resting hypoxemia. 2,54,55 In individuals with ILD who
experience isolated exertional hypoxemia, the impact of oxygen therapy on mortality is not
known. 2 Although oxygen therapy is commonly prescribed in ILD, there is a lack of evidence
for the effectiveness of oxygen on short and long-term clinical outcomes such as exercise
capacity, quality of life and survival. 2,56 Mechanisms by which oxygen may increase exercise
capacity include a reduction in ventilatory workload, decreased dyspnea, improved cardiac
function, more balanced pulmonary and systemic hemodynamics, an increase in oxygen
transport to metabolically active tissues, increased oxygen utilization, energy metabolism and
muscle function, and a delay in the onset of muscle fatigue, metabolic acidosis, time to anaerobic
threshold and lactate production. 56 There is a lack of guidance for administration and titration of
oxygen during exercise training. 2,13,16 56,57 Individuals with ILD who exhibit a significant degree
of gas exchange limitation may require high levels of supplemental oxygen, which can impact
the intensity and duration of training and physiological adaptations to exercise, especially if
oxygen supplementation is not standardized or optimized. The role of hyperoxia during aerobic
training is currently being investigated in IPF. 58
1.2.6 Exercise in ILD

1.2.6.1 Acute responses to exercise

Compared to healthy people, characteristic acute responses to maximal aerobic exercise testing in ILD include: a high minute ventilation characterized by a rapid respiratory rate and reduced tidal volume due to reduced lung volumes and compliance, increased work of breathing to overcome the high elastic load of the lungs, reduced maximal heart rate, increases in pulmonary arterial pressure to maintain cardiac output if pulmonary vascular resistance is increased, hypoxemia due to ventilation/perfusion mismatch and diffusion limitation, significant dyspnea and leg fatigue resulting in a reduced VO$_{2peak}$, low levels of maximal work, reduced anaerobic threshold. $^{13,33,34}$ These acute responses differ from a healthy population where increases in tidal volume support increased minute ventilation, oxygen saturation is maintained, pulmonary vascular resistance does not substantially increase and the primary factor limiting maximal exercise is cardiac output. $^{32}$

1.2.6.2 Chronic responses to exercise training

Although there are a number of respiratory, cardiovascular and peripheral physiological adaptations to exercise training in the healthy population, the mechanisms underlying the modest improvements in exercise capacity (VO$_{2peak}$ and 6MWD) in ILD are not well understood. Potential adaptations include increased cardiac function and contractility, improved respiratory and peripheral muscle strength, increased chest wall expansion and improved peripheral muscle oxygen extraction and oxidative capacity. $^{59,60}$
1.2.6.3 Effects of rehabilitation in ILD

Systematic reviews of physical rehabilitation in ILD report moderate quality evidence for an increase in 6MWD, low quality evidence for an increase in VO2max and quality of life, and a decrease in dyspnea scores, with no reported adverse effects. \(^9\)-\(^12\) A meta-analysis of five randomized and quasi-randomized controlled trials found a weighted mean difference of 44 metres in 6MWD (95% confidence interval (CI) 26-63 metres), and 36 metres (95% CI 16-55 metres) in a subgroup with IPF, \(^9\) both which exceed the minimally clinically important difference of 28m in ILD. \(^61\) Immediately following rehabilitation, improvements in 6MWD in individuals with advanced ILD or those who desaturate during exercise testing are smaller and do not always reach statistical significance. \(^9\)-\(^11\),\(^62\) A recent randomized controlled trial comparing eight weeks of exercise to usual care in 142 people with various ILD etiologies reported an increase in 6MWD of 25 metres (95% CI 2-47 metres). \(^11\) The largest gains were observed in the asbestosis ILD subgroup, followed by IPF. The smallest gains were observed in the connective-tissue related ILD subgroup. Greater benefit in 6MWD and dyspnea symptoms were seen in those with a lower 6MWD and worse baseline symptoms. Both the exercise and control groups had a decline in 6MWD at six months, however the improvements in the 6MWD were better sustained in people with better baseline lung function and no pulmonary hypertension. Although the primary outcome of pulmonary rehabilitation is typically the 6MWD, some studies using resistance training have measured and demonstrated improvements in quadriceps strength, \(^63\)-\(^65\) change in one-repetition maximum of upper and lower limb muscles \(^66\) and increased mid-thigh cross sectional area in ILD. \(^67\)
1.2.6.4 Exercise prescription in ILD

There is variability in the format and exercise prescription used in the pulmonary rehabilitation studies in ILD. Exercise training often utilizes the same exercise principles as those applied to the COPD population and typically occurs for eight to twelve weeks with at least two supervised sessions a week. Endurance training has been prescribed initially at 50-80% of peak work rate from a cardiopulmonary exercise test or 70-80% 6MWT speed, however the exercise duration, modes of training and progression of training loads differ. Aerobic training is usually prescribed as continuous exercise using walking or cycling as an exercise mode, and time is typically increased up to 30 minutes before intensity is increased (walking speed or cycle workload). Aerobic training typically aims for continuous exercise for 15-30 minutes at a constant work rate, although intermittent bouts might be needed secondary to symptoms and cardiorespiratory response. Progression may be at the discretion of the supervising therapist or follow a standardized protocol, but often is not clearly described in the research studies. One study described initial aerobic training duration as five minutes of exercise and one minute of rest repeated five times, and progressed one minute of duration to the exercise bout until 15 minutes of continuous exercise was achieved. Resistance training is typically done in conjunction with endurance training and prescribed initially as one to three sets of 10 to 15 repetitions, however the method of determining exercise intensity (e.g. percentage of one repetition maximum) is usually not specified.

The ideal timing of rehabilitation in the ILD trajectory is unclear. Some studies have found that individuals with the lowest 6MWD benefit the most, whereas other studies demonstrate that individuals who are less functionally impaired had a greater response. Individuals with better baseline lung function and no pulmonary hypertension have shown greater maintenance of long
term functional benefits. The increased rate of disease progression in ILD, specifically IPF, may impact the evolution of exercise limitation, physical inactivity and peripheral muscle dysfunction differently than chronic lung conditions characterized by a slower disease progression and longer life expectancy. There is a lack of information on alternative modes of training that have been studied in COPD such as high intensity interval aerobic exercise, muscle partitioning (single legged cycling) or eccentric exercise. In summary, individuals with ILD benefit from exercise training in terms of increased exercise capacity, strength, symptoms and HRQOL, however optimal and disease-specific exercise prescription and program delivery are not known.
1.3 Thesis objectives and hypotheses

The overall aim of this thesis is to examine exertional hypoxemia and changes in muscle oxygenation in people with ILD (Figure 1-6). The overall hypothesis is that exertional hypoxemia reduces exercise capacity, peripheral muscle function, endurance training intensities and tolerance in ILD, and supplemental oxygen can attenuate some of these responses.

**Figure 1-6:** Framework for thesis objectives

Oxygen therapy was delivered as per current clinical administration practice.
Specific objectives and hypotheses:

Study 1 - Constant load endurance exercise with arterial oxygen saturation monitoring (Chapter 2)

Objectives:

1. Describe the oxygen requirements of individuals with advanced ILD during short-term and long-term exercise training.
2. Examine the relationship between exertional oxygen use, exercise capacity and aerobic training parameters.
3. Examine predictors of the change in oxygen requirements during exercise training.

Hypotheses:

1. The majority of individuals with advanced ILD will require exertional oxygen at baseline using a variety of oxygen delivery systems and flow rates, and this requirement will increase over four weeks and six months to reflect either a higher oxygen flow rate or a progression to a reservoir or high flow oxygen system.

2. Higher exertional oxygen requirements will be associated with a reduced 6MWD and decreased aerobic training parameters (reduced treadmill training speed and duration, % 6MWT intensity, estimated metabolic equivalents).
3. Predictors of the change in exertional oxygen requirements during exercise training will include a worse or deteriorating disease severity (IPF diagnosis, presence of pulmonary hypertension, lower $D_{LCO}$ and FVC, lower 6MWD).

**Study 2 - Interval and constant load endurance exercise with arterial oxygen saturation monitoring (Chapter 3)**

Objectives:

1. Compare feasibility (participant tolerance and preference) between a single bout of interval and continuous exercise on a cycle ergometer.

2. Compare acute cardiorespiratory responses ($SpO_2$, heart rate, respiratory rate, blood pressure, blood lactate) during a single bout of continuous exercise versus interval exercise in individuals with advanced ILD.

Hypotheses:

1. Compared to continuous training, interval exercise will result in a lower level of dyspnea and leg fatigue, less unintended breaks and similar patient preference.

2. Compared to continuous exercise, interval exercise will result in a lower $SpO_2$, higher peak heart rate and lower blood lactate concentration levels.
Study 3- Incremental resistance exercise with arterial oxygen saturation and regional skeletal muscle oxygen saturation monitoring (Chapter 4)

Objectives:
1. Examine if and when recruited muscles deoxygenate during upper (biceps) and lower (quadriceps) limb incremental loading.
2. Examine if blood volume is preferentially redistributed to the active muscle during incremental exercise.
3. Examine if arterial oxygen saturation (SpO₂) reflects the regional muscle oxygen saturation (SmO₂) during incremental exercise.

Hypotheses:
1. Skeletal muscle oxygen saturation (SmO₂) will decrease to a greater extent in exercising muscles of people with ILD compared to healthy controls during incremental limb loading at task failure.
2. The magnitude of the increase in total hemoglobin, a marker of regional blood volume, will be attenuated in the exercising muscles in ILD compared to healthy people during incremental limb loading at maximal workloads.
3. Systemic arterial oxygen saturation measured by pulse oximetry (SpO₂) will not be correlated to regional skeletal muscle oxygen saturation (SmO₂) during incremental limb loading.
Chapter 2

Exertional oxygen requirements during exercise training in advanced interstitial lung disease

1.3 Abstract

Little is known about the oxygen requirements during physical exertion or exercise in individuals with interstitial lung disease (ILD). This study examined: 1) exertional oxygen requirements, 2) the relationships between; exertional oxygen use, exercise capacity and aerobic training parameters (treadmill walking), and 3) predictors of change in exertional oxygen requirements during pulmonary rehabilitation (PR). A retrospective study of lung transplant candidates with advanced ILD who underwent at least four weeks of outpatient PR between 2004 and 2014 was undertaken. Data were extracted at baseline, four weeks and six months. Exertional oxygen was prescribed during PR to support continuous, moderate intensity aerobic training. Our cohort had a median age of 61 (55 to 66) years, were 57% male and most were diagnosed with idiopathic pulmonary fibrosis [n=214 (57%)]. A variety of oxygen delivery systems were used. Exertional oxygen requirements increased after four weeks [0.5 (0.4-0.6) vs. 0.5 (0.4-0.73), p<0.001, n=375] and six months [0.44 (0.36-0.5) vs. 0.5 (0.4-0.55), p<0.001, n=196] of PR. Higher exertional oxygen requirement was associated with lower six-minute walk distance (6MWD) and lower aerobic training intensity at all time-points. There were no identified predictors of the change in exertional oxygen requirements. Individuals with advanced ILD had high exertional oxygen requirements to participate in moderate intensity aerobic training, which increased over time. Exertional oxygen needs may inform exercise prescription and response during PR in ILD.
2.2 Introduction

Interstitial lung disease comprises a heterogeneous group of chronic respiratory disorders characterized by progressive parenchymal fibrosis leading to a restrictive ventilatory defect, circulatory limitations, gas exchange abnormalities and peripheral muscle dysfunction. Individuals with ILD experience exertional dyspnea, fatigue, exercise intolerance and decreased HRQOL. Although there is emerging evidence that pulmonary rehabilitation (PR) is effective in ILD, a lower functional benefit and lack of long term benefits are observed in certain groups including IPF and individuals who present with severe disease, exhibit exercise-induced oxygen desaturation and/or use supplemental oxygen. The evaluation and management of severe exercise-induced hypoxemia is not well defined, and can present a challenge for safe and effective exercise training for individuals with ILD.

Supplemental oxygen has been shown to improve exercise capacity acutely in ILD, however there is limited information on the impact of exertional hypoxemia and oxygen supplementation on exercise training intensity and response during PR. The aims of this study were to describe the exertional oxygen requirements of individuals with advanced ILD during short-term and long-term PR, examine the relationship between exertional oxygen use, exercise capacity and aerobic training parameters, and examine predictors of the change in exertional oxygen requirements during PR.

2.3 Methods

2.3.1 Participants
We conducted a retrospective, single centre study (REB 15-9293-BE and 31935) that included individuals over the age of 18 years, diagnosed with ILD, listed for a first lung transplant and participated in outpatient PR for at least four weeks between January 2004 and December 2014. Individuals who had a non-ILD diagnosis, listed for a re-transplant or multi-organ transplant, or did not participate in outpatient PR during the pre-transplant period were excluded.

2.3.2 Chart abstraction

Demographic, medical, oxygen and exercise data was collected from electronic medical records and outpatient rehabilitation charts for the following three time periods: baseline (start of PR), at four weeks and six months of PR. Baseline exertional oxygen requirements (peak FiO₂) and aerobic training parameters were taken by the second or third exercise training session to allow for oxygen titration to achieve an appropriate FiO₂ to support 10 to 20 minutes of continuous aerobic exercise, familiarity with exercise equipment, training expectations and guidelines for increasing or decreasing exercise intensity and duration.

2.3.3 Exercise training and prescription

Individuals underwent an outpatient, supervised exercise training session three times a week for the duration of the waiting period for transplant. The exercise program was prescribed with the goals to increase and/or maintain aerobic and musculoskeletal fitness for surgery. Each training session was 90 minutes long and included stretching, functional exercises (squats, stair stepping), resistance training of the upper and lower limbs and aerobic training on the treadmill and cycle.

The intensity of aerobic training was adjusted weekly, in an effort to increase the intensity while maintaining an adequate oxygen saturation (SpO₂) of typically ≥ 88%, not exceeding 85% of
age-predicted maximal heart rate, eliciting a modified Borg dympnea score of between 3-4 (moderate to somewhat severe on a 10-point scale) and attaining a treadmill walking speed of at least 70-80% of the six minute walk test (6MWT) speed. Exertional oxygen use was increased by the physiotherapist to support 20 minutes of continuous, moderate intensity aerobic training as tolerated while maintaining the oxygen saturation prescribed by the respirologist. However, if individuals could not maintain an appropriate SpO₂, heart rate or dyspnea rating for 20 consecutive minutes despite an increase in the exertional oxygen requirement, intermittent aerobic exercise was prescribed by breaking up the exercise duration into two or more bouts interspersed with rest periods, or bouts of decreased exercise intensity.

2.3.4 Supplemental oxygen administration

In the majority of cases oxygen was supplied via bulk liquid oxygen delivered through oxygen wall outlets during aerobic training. A variety of oxygen interfaces were used. Appendix 3

2.3.5 Outcomes

2.3.5.1 Exertional oxygen requirement

Exertional oxygen requirement during aerobic training was recorded from the exercise training logs. Oxygen requirement was categorized (oxygen flow rate and delivery system) and converted to the estimated fraction of inspired oxygen (FiO₂). Appendix 3.

2.3.5.2 Exercise capacity
The 6MWT was conducted using standard procedures using the level of oxygen the individual was using for aerobic training at each time point and was not kept constant for repeated tests. The 6MWT was stopped at the individual’s request or by the physiotherapist if there were signs and symptoms of significant respiratory distress, however a lower limit of SpO₂ was not strictly defined for test termination.

2.3.5.3 Aerobic training parameters

The main outcome was the intensity of treadmill training, as cycle workload in Watts was not consistently recorded during the study period. The following information regarding treadmill training was calculated: percentage of the 6MWD walking speed achieved during treadmill walking, the percentage of age-predicted maximum heart rate during treadmill walking and the estimated metabolic equivalent for the task (MET)-minutes.⁸²,⁸³

Walking speed \( \text{m/min} = \text{walking speed} \times 26.83 \)

\[
\text{VO}_2 \text{ml/kg/min} = \text{VO}_2 \text{rest} + \text{VO}_2 \text{horizontal} + \text{VO}_2 \text{vertical}
\]

\[
= 3.5 + (0.1 \times \text{walking speed} \text{m/min}) + (1.8 \times \text{walking speed} \text{m/min} \times \% \text{grade})
\]

\[
\text{MET} = \text{VO}_2 \text{ml.kg}^{-1} \text{min}^{-1} / 3.5
\]

Abbrevations: m: metre; mph: miles per hour; VO₂: maximal oxygen consumption
2.3.6 Statistical analysis

Normality was checked using the Shapiro-Wilk test and due to non-normally distributed variables, non-parametric statistics were used for analysis. Continuous variables were described using median [interquartile range (IQR)], and categorical variables as count frequencies and percentages. Change in exertional oxygen requirement over time was tested using a Wilcoxon signed rank test (baseline to four weeks and baseline to six months). Bivariate correlational analyses was performed using Spearman rank correlation coefficients for continuous variables and Goodman and Kruskal’s lambda for categorical variables to examine the relationship between exertional oxygen requirement with 6MWD and aerobic training intensity at baseline, four weeks and six months. Multivariable linear regression analysis was performed to examine predictors of change in exertional FiO\textsubscript{2} from baseline to four weeks and six months. A post-hoc analysis of exertional oxygen requirements and aerobic training intensities was performed on three sub-groups who underwent six months of PR according to their 6MWT response [increased their 6MWD above the minimally clinical important difference for ILD populations\textsuperscript{84} of $\geq$ 24m, maintained their 6MWD (between -24 and 24m) and decreased their 6MWD $\leq$ 24m] between baseline and six months using a Kruskal-Wallis test. Statistical significance was defined as $p < 0.05$ for all analyses. Statistical analysis was performed on SAS statistical software University Edition.

Statistical power was estimated a priori. Anticipating that 80% of the individuals with ILD listed for a first transplant for at least four weeks between January 2004 and December 2014 (n=511) attended outpatient PR for at least four weeks resulted in an available subject pool of n=409. There was no available information on the change in FiO\textsubscript{2} during exercise in ILD, therefore a correlational coefficient based on the objective of examining the relationship of exertional
oxygen use, exercise capacity and aerobic training parameters was used to determine the power of our sample of convenience. The estimated effect size that could be detected at 90% power assuming a two-tailed alpha of 0.05 was $r=0.15$.

### 2.4 Results

#### 2.4.1 Demographic characteristics and clinical outcomes

A total of 375 individuals with ILD who underwent at least four weeks of outpatient PR prior to lung transplantation and had available exercise training data were included. A post hoc analysis was performed to compute achieved power based on the mean differences. Using a 2 tailed test, an effect size of 0.45 and $\alpha=0.01$, the sample of 375 resulted in an achieved $\beta$ of 0.99. Data was collected up to six months on the lung transplant waiting list (Figure 2-1).

Baseline demographics are described in (Table 2-1). The most prevalent diagnosis was IPF specified as usual interstitial pneumonia (UIP). There were 212 men and 163 women, with a median age of 61 (55-66) years and evidence of severe restrictive lung disease with a median forced vital capacity (FVC) of 49 (38 to 60)% predicted. In 251 individuals who underwent repeated pulmonary function testing between the time of transplant assessment and at any point up to six months on the wait list, there was evidence of disease progression (FVC decreased a median of 0.1 (0 to 0.3) L, $p<0.0001$). Baseline exercise capacity and aerobic training on the treadmill are described in Table 2-2. Baseline 6MWD varied considerably from 52m to 574m (8-84% predicted), with a median of 318 (234 to 385) m or 47 (34 to 57)% predicted. The proportion of people with co-morbid conditions included: 42% with cardiovascular disease (hypertension, coronary artery disease, congestive heart failure, atrial fibrillation, peripheral
vascular disease, dyslipidemia), 26% with gastroesophageal reflux disease, 14% with diabetes or glucose intolerance, 10% with osteoarthritis, 7% with psychological disturbances (depression or anxiety disorder) and 6% with osteoporosis. Ten percent had three or more co-morbid conditions. At the six-month time point, 196 individuals were still waiting for a transplant, 141 had undergone a transplant and 38 had died on the waiting list (Table 2-3).

2.4.2 Changes in exercise capacity and aerobic training during pulmonary rehabilitation

The 6MWD was maintained from baseline to four weeks [318 (234 to 385) m vs. 328 (242 to 391) m, median change 0 (-32 to 26) m, p=0.29; n=225]. There was wide variability in the change in 6MWD ranging from a maximal increase of 150m to a maximal drop of 224m from baseline to four weeks. In those individuals still awaiting a transplant at six months, the 6MWD decreased slightly from baseline to six months [348 (271-405) m vs. 338 (258 to 384) m, median change -18 (-61 to 17) m, p<0.0001; n=175]. There was a maximal increase of 185m, and a maximal drop of 356m from baseline to six months.

Aerobic training METS increased from baseline to four weeks [(1.9 (1.7 to 2.3) vs. 2.2 (1.8 to 2.6), median change 0.15(0-0.3), p<0.0001; n=323). The percentage of 6MWT speed used for training (calculated from the closest 6MWT at each study time-point) increased from 65 (50-79)% to 80 (66-93)% (median change 12 (1-23)%, p<0.0001). Aerobic training METS increased from baseline to six months [2.1 (1.8-2.5) vs. 2.4 (2.0-2.8), median change 0.23 (0-0.5), p<0.0001; n=180]. The percentage of 6MWT speed used for training increased from 67 (54-82)% to 92 (80-105)% (median change 21 (6-38)%, p<0.0001).
2.4.3 Exertional oxygen requirements

At baseline, 70% of individuals used supplemental oxygen at rest, whereas 95% wore oxygen on exertion with a higher FiO$_2$ than resting levels [0.50 (0.40 to 0.60) during exertion vs. 0.32 (0.28 to 0.40) at rest, p<0.0001, n=375] (Table 2-4). Nasal cannulae were the most common oxygen delivery system used on rest and exertion at a wide variety of flow rates (1-15 litres/minute), almost exclusively at continuous flow. During exertion there was a greater use of reservoir (e.g. oxymizers, non-rebreather masks) and high flow oxygen (e.g. Venturi masks) delivery systems [n=181 (48%)] on exertion vs. rest n=36 (10%)] (Table 2-4). Baseline oxygen titration orders ranged from maintaining a SpO$_2$ ≥75-92% with exertion, with the more common orders requiring a SpO$_2$ for exertion of ≥ 88% [n= 150 (40%)] or ≥ 90% [(n= 130 (35%)]. There was an increase in exertional FiO$_2$ from baseline to four weeks [median (IQR) 0.50 (0.4-0.6) vs. 0.50 (0.4-0.73), p<0.001, n=375] and from baseline to six months [median (IQR) 0.44 (0.36-0.5) vs. 0.50 (0.4-0.55), p<0.001, n=196], with a higher proportion requiring high flow or reservoir oxygen mask delivery devices [baseline to four weeks 46% vs. 58%, (n=375) and baseline to six months 36% vs. 60%, (n=196)]. Changes in the use of oxygen delivery systems during exertion at baseline, four weeks, and six months PR is shown in Figure 2-2. Further detail on the measures of central tendency and dispersion of FiO$_2$, resting and exertional delivery systems and estimated FiO$_2$ at baseline, four weeks and six months are provided in Appendices 4 to 6. The proportion of people who had a change in their FiO$_2$ vs. no change is reported in Appendix 11.

There were differences between the groups who increased their 6MWD (n=34), maintained their 6MWD (n=54) and decreased their 6MWD (n=75) between baseline and six months in terms of the change in exertional FiO$_2$ (F=4.46, p=0.01), baseline 6MWD (F=3.35, p=0.03) and the change in treadmill METS (F=5.05, p=0.007). Specifically, the group who increased their
6MWD had a lower 6MWD at baseline. The group who decreased their 6MWD over six months had a greater increase in exertional FiO₂ and less of an increase their treadmill training METS.

2.4.4 Relationship between exertional oxygen use, exercise capacity and aerobic training parameters

A higher baseline exertional FiO₂ showed a low to moderate negative association with the baseline 6MWD [r= -0.4, p<0.0001 (n=375)] and training METS [r= -0.24, p<0.001 (n=375)], Appendix 7. Similarly, at four weeks a higher FiO₂ was associated with a lower four week 6MWD [r= -0.42, p<0.0001 (n=375)] and lower training METS at four weeks [r= -0.31, p<0.0001 (n=375)], Appendix 8 and at six months a higher FiO₂ was associated with a lower six month 6MWD [r= -0.36, p<0.0001 (n=196)] and lower training METS at six months [r= -0.35, p<0.0001 (n=196)] Appendix 9. There were no correlations between the change in FiO₂ and 1) the change in 6MWD or 2) the change in training METS at four weeks. There was a correlation between the change in FiO₂ and change in 6MWD at six months (r = -0.26, p=0.0008), and no correlation between change in FiO₂ and change in training METS. Appendix 10.

2.4.5 Predictors of change in exertional oxygen use

The following variables were included in a multivariable regression model to predict change in exertional FiO₂: age, sex, diagnosis (IPF vs. other), Canadian urgency list status (stable vs. deteriorating/rapidly deteriorating), baseline exertional FiO₂, baseline 6MWD, baseline training METS, DLCO (% predicted), FVC (% predicted) and mean PAP. No predictive factors were
identified for the change in exertional FiO₂ after four weeks ($R^2 = 0.034$, $p > 0.05$ for all variables) or at six months of PR ($R^2 = 0.03$, $p > 0.05$ for all variables).
**Figure 2-1:**

Study flow chart
Figure 2-2:
Change in oxygen delivery devices during six months of pulmonary rehabilitation (n=196).

Abbreviations: non-rebreather: non-rebreather mask; Venturi: Venturi mask; nasal: nasal cannulae; room: room air
Table 2-1: Baseline characteristics (n=375)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (IQR) or n (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>212 (57%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 (55-66)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>UIP</td>
<td>214 (57%)</td>
</tr>
<tr>
<td>CTD</td>
<td>48 (13%)</td>
</tr>
<tr>
<td>NSIP</td>
<td>37 (10%)</td>
</tr>
<tr>
<td>Other</td>
<td>30 (8%)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>26 (7%)</td>
</tr>
<tr>
<td>NYD</td>
<td>17 (4%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>3 (1%)</td>
</tr>
<tr>
<td><strong>PFTs</strong></td>
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</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (L)</td>
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<tr>
<td>% pred</td>
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<tr>
<td>FVC (L)</td>
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</tr>
<tr>
<td>% pred</td>
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<tr>
<td>TLC (L)</td>
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<tr>
<td>% pred</td>
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</tr>
<tr>
<td>DLCO (ml/mmHg)</td>
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<td>% pred</td>
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</tr>
<tr>
<td>*<em>ABGs</em></td>
<td></td>
</tr>
<tr>
<td>PaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>66 (57-78)</td>
</tr>
<tr>
<td>SaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>94 (91-96)</td>
</tr>
<tr>
<td><strong>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</strong></td>
<td>27.6 (24-30)</td>
</tr>
<tr>
<td><strong>mPAP (mmHg)</strong>**</td>
<td>22 (17-28)</td>
</tr>
<tr>
<td><strong>Wait list status</strong>*</td>
<td></td>
</tr>
<tr>
<td>(time of listing)</td>
<td></td>
</tr>
<tr>
<td>1 Stable</td>
<td>191 (51%)</td>
</tr>
<tr>
<td>2 Deteriorating</td>
<td>172 (46%)</td>
</tr>
<tr>
<td>3 Rapidly deteriorating</td>
<td>12 (3%)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR: interquartile range; UIP: usual interstitial pneumonia, CTD: connective tissue disease, NSIP: non-specific interstitial pneumonia, NYD: not yet diagnosed, PFTs: pulmonary function tests, BMI: body mass index; mPAP: mean pulmonary artery pressure; FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity, TLC: total lung capacity DLCO: diffusing capacity of carbon monoxide; PaO<sub>2</sub>: partial pressure of arterial oxygen; ABGs: arterial blood gases; SaO<sub>2</sub>: arterial oxygen saturation

* n=313 on room air (FiO<sub>2</sub> 0.21) at time of transplant assessment
** n=303 at time of transplant assessment
*** Based on Canadian listing urgency
Table 2-2: Baseline exercise capacity (n=367) and aerobic training parameters (n=329)

<table>
<thead>
<tr>
<th>Six minute walk test</th>
<th>Median (IQR) or N (%) or range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distance:</strong></td>
<td></td>
</tr>
<tr>
<td>metres</td>
<td>318 (234-385)</td>
</tr>
<tr>
<td>% pred *</td>
<td>47 (34-57)</td>
</tr>
<tr>
<td>Pre SpO₂ (%)</td>
<td>98 (96-99)</td>
</tr>
<tr>
<td>End SpO₂ (%)</td>
<td>87 (81-91)</td>
</tr>
<tr>
<td>Pre HR bpm</td>
<td>93 (82-104)</td>
</tr>
<tr>
<td>End HR bpm</td>
<td>116 (103-127)</td>
</tr>
<tr>
<td>% max HR</td>
<td>73 (62-82)</td>
</tr>
<tr>
<td>End RR</td>
<td>36 (30-43)</td>
</tr>
<tr>
<td>Pre Borg dyspnea</td>
<td>1 (0.5-2)</td>
</tr>
<tr>
<td>End Borg dyspnea</td>
<td>4 (3-5)</td>
</tr>
<tr>
<td>Pre Borg leg fatigue</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>End Borg leg fatigue</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td><strong>Rests:</strong></td>
<td></td>
</tr>
<tr>
<td>Number needing a rest</td>
<td>72 (20%)</td>
</tr>
<tr>
<td>Length of rests (seconds)</td>
<td>61 (30-91)</td>
</tr>
<tr>
<td>Number of rests</td>
<td>1-3</td>
</tr>
<tr>
<td><strong>Gait aids used:</strong></td>
<td></td>
</tr>
<tr>
<td>Rollator</td>
<td>139 (38%)</td>
</tr>
<tr>
<td>High wheeled walker</td>
<td>6 (1.6%)</td>
</tr>
<tr>
<td>Cane</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td><strong>FiO₂</strong></td>
<td>0.44 (0.4-0.59)</td>
</tr>
<tr>
<td><strong>DSP (m%)</strong></td>
<td>268 (190-333)</td>
</tr>
<tr>
<td><strong>DSP/FiO₂</strong>*</td>
<td>5.6 (3.6-7.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aerobic training <strong>a</strong></th>
<th>Median (IQR) or N (%) or range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed (mph)</td>
<td>1.2 (1-1.7)</td>
</tr>
<tr>
<td>Time (minutes)</td>
<td>20 (15-20)</td>
</tr>
<tr>
<td>% 6MWT speed</td>
<td>67 (55-82)</td>
</tr>
<tr>
<td>METS</td>
<td>1.9 (1.7-2.3)</td>
</tr>
<tr>
<td>---------</td>
<td>--------------</td>
</tr>
<tr>
<td>End SpO&lt;sub&gt;2&lt;/sub&gt; (%)</td>
<td>93 (91-95)</td>
</tr>
<tr>
<td>End Borg dyspnea</td>
<td>3 (3-4)</td>
</tr>
<tr>
<td>FiO&lt;sub&gt;2&lt;/sub&gt;*</td>
<td>0.44 (0.4-0.55)</td>
</tr>
<tr>
<td>Rests</td>
<td></td>
</tr>
<tr>
<td>Number needing a rest</td>
<td>14 (4%)</td>
</tr>
<tr>
<td>Incline</td>
<td></td>
</tr>
<tr>
<td>Number using an incline</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Degree of incline (%)</td>
<td>2-5</td>
</tr>
<tr>
<td>Intermittent training&lt;sup&gt;β&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Number training</td>
<td>14 (4%)</td>
</tr>
</tbody>
</table>

**Abbreviations:** SpO<sub>2</sub>: oxygen saturation measured by pulse oximetry; HR: heart rate; bpm: beats per minute; RR: respiratory rate; DSP: distance-saturation product<sup>86</sup>; DSP/FiO<sub>2</sub>: distance-saturation product adjusted for fraction of inspired oxygen<sup>87</sup>; 6MWT: six minute walk test; METS: metabolic equivalent for the task; FiO<sub>2</sub>: fraction of inspired oxygen; mph: miles per hour.

* from reference 85
** using a pulsed oxygen flow for the 6MWT (n=6) and during aerobic training (n=1)
*** adjusted for oxygen use<sup>87</sup>
<sup>α</sup> performed on the treadmill
<sup>β</sup> breaking up the exercise duration into two or more bouts interspersed with rest periods
**Table 2-3:** Characteristics of participants according to status at six months (reported as median (IQR) or n (proportion)).

<table>
<thead>
<tr>
<th></th>
<th>Still on wait list (n=196)</th>
<th>Underwent transplant (n=141)</th>
<th>Died pre-transplant (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>61 (11)</td>
<td>61 (11)</td>
<td>64 (12)</td>
</tr>
<tr>
<td><strong>Female gender</strong></td>
<td>97 (49%)</td>
<td>41 (29%)</td>
<td>25 (66%)</td>
</tr>
<tr>
<td><strong>IPF diagnosis</strong></td>
<td>100 (51%)</td>
<td>94 (67%)</td>
<td>20 (53%)</td>
</tr>
<tr>
<td><strong>FVC (% predicted)</strong></td>
<td>47 (21)</td>
<td>51 (23)</td>
<td>54 (22)</td>
</tr>
<tr>
<td><strong>mPAP * (mmHg)</strong></td>
<td>22 (10)</td>
<td>21 (10)</td>
<td>24 (10)</td>
</tr>
<tr>
<td>**Wait list status 2 or 3 **</td>
<td>60 (31%)</td>
<td>98 (70%)</td>
<td>26 (68%)</td>
</tr>
<tr>
<td><strong>Baseline FiO₂</strong></td>
<td>0.44 (0.14)</td>
<td>0.5 (0.31)</td>
<td>0.63 (0.31)</td>
</tr>
<tr>
<td><strong>Baseline 6MWD (m)</strong></td>
<td>348 (134)</td>
<td>276 (184)</td>
<td>240 (140)</td>
</tr>
<tr>
<td><strong>Baseline training METS</strong></td>
<td>2.1 (0.8)</td>
<td>1.9 (0.4)</td>
<td>1.8 (0.2)</td>
</tr>
</tbody>
</table>

**Abbreviations:** IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity; mPAP: mean pulmonary artery pressure; 6MWD: six-minute walk distance; METS: metabolic equivalent for the task

* measured at time of transplant assessment and available in 156 of individuals still on wait list, 114 of individuals who underwent transplant and 33 of individuals who died at the six month time point.

**Wait list status 2 (deteriorating) and wait list status 3 (rapidly deteriorating) based on Canadian listing urgency*
Table 2-4: Baseline resting and exertional oxygen requirements (n=375)

<table>
<thead>
<tr>
<th>Resting oxygen requirement *</th>
<th>N (%), median (IQR) or range</th>
<th>Exertional oxygen requirement*</th>
<th>N (%), median (IQR) or range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery system:</td>
<td></td>
<td>Delivery system:</td>
<td></td>
</tr>
<tr>
<td>Room air</td>
<td>114 (30%)</td>
<td>Room air</td>
<td>19 (5%)</td>
</tr>
<tr>
<td>Nasal cannulae</td>
<td>225 (60%)</td>
<td>Nasal cannulae</td>
<td>175 (47%)</td>
</tr>
<tr>
<td>Oxymizer</td>
<td>28 (8%)</td>
<td>Oxymizer</td>
<td>26 (7%)</td>
</tr>
<tr>
<td>Venturi mask</td>
<td>1 (0.2%)</td>
<td>Venturi mask</td>
<td>55 (14.5%)</td>
</tr>
<tr>
<td>Oxymask</td>
<td>5 (1.3%)</td>
<td>Oxymask</td>
<td>23 (6%)</td>
</tr>
<tr>
<td>Non-rebreather mask</td>
<td>2 (0.5%)</td>
<td>Non-rebreather mask</td>
<td>77 (20.5%)</td>
</tr>
<tr>
<td>Flow rate (LPM)</td>
<td>1-12</td>
<td>Flow rate (LPM)</td>
<td>1-15</td>
</tr>
<tr>
<td>Estimated FiO₂</td>
<td>0.32 (0.28-0.40)</td>
<td>Estimated FiO₂</td>
<td>0.5 (0.40-0.60)</td>
</tr>
</tbody>
</table>

**Abbreviations**: IQR: interquartile range; LPM: litres per minute; FiO₂: fraction of inspired oxygen

* pulsed oxygen flow for exercise training (n= 1)
2.5 Discussion

Individuals with advanced ILD in this study required high levels of supplemental oxygen during exercise training. The estimated FiO$_2$ at baseline was variable and increased over time either through higher oxygen flow rates and/or a change in oxygen delivery devices to high flow or reservoir systems. There were no identified predictors of the change in exertional FiO$_2$ after four weeks and six months of PR. A higher exertional FiO$_2$ was associated with a lower exercise capacity and aerobic training intensity at baseline and after four weeks and six months of PR. Exertional oxygen was increased over time to support moderate intensity continuous aerobic training while maintaining the oxygen saturation guidelines prescribed for exertion.

The majority of individuals in this study cohort (95%) required oxygen up to an estimated FiO$_2$ of 0.75 during the 6MWT and for exercise training. Individuals in this study with higher exertional FiO$_2$ had lower exercise capacity and trained at a lower aerobic intensity. Previously we found that lung transplant candidates using six litres/minute by nasal cannulae were able to train at a higher percentage of their average 6MWT speed than individuals using greater than six litres/minute by nasal cannulae or reservoir or high flow oxygen delivery devices. 88 A recent systematic review of oxygen therapy in ILD reported that acute bouts of oxygen resulted in increased peak work capacity, VO$_{2\text{max}}$, cycle endurance time and in some studies an increased 6MWD. However they also concluded that evidence is lacking on the effect of long-term oxygen therapy on exercise capacity in ILD. 57,89 A few studies have reported on supplemental oxygen during PR in ILD with oxygen resulting in either an increase or no change in exercise capacity during PR, 57,89,90 and a lower incremental shuttle walk test improvement in individuals with ILD who used oxygen compared to non-oxygen users. 72 High oxygen delivery in ILD may
provide additional benefits to exercise capacity during PR in ILD and is currently being investigated.  

The majority of oxygen delivery devices were low flow, variable FiO₂ performance devices, which may deliver a lower FiO₂ than what is estimated due to a rapid, shallow respiratory rate common in ILD, and the inability of these devices to meet or exceed peak inspiratory flow. Clinical practice guidelines for oxygen titration during exercise need to consider the PR setting, available oxygen equipment and expertise to deliver high flow oxygen. Although current oxygen prescription guidelines recommend that ambulatory oxygen should be offered to patients for use during PR or exercise training following a formal assessment, to increase oxygen saturation and increase oxygen delivery to working muscles, and prevent potential complications of hypoxemia such as increased myocardial work and pulmonary vasoconstriction leading to worsening pulmonary hypertension, there are currently no clinical practice guidelines for the evaluation and management of exercise-induced hypoxemia to ensure both safe and effective exercise training during PR. This is a particular challenge in individuals with advanced, progressive ILD who may experience severe exercise induced hypoxemia, previously described as a SpO₂ < 89% despite an oxygen use of up to 6L/min. If PR programs do not have an oxygen titration policy to support moderate to high levels of exercise intensity, individuals with ILD who experience severe hypoxemia and may be stopped prematurely or only exercise at a low intensity that in turn may not lead to beneficial physiological adaptations (such as peripheral muscle adaptations).

Although the 6MWD was maintained at four weeks and showed a small decrease at six months, training intensity was increased at both time points. Baseline training intensity was guided by
ratings of dyspnea. Aerobic training may have led individuals to become desensitized to dyspnea allowing for greater training intensity. Individuals may also have been placed on opioids to manage severe dyspnea following referral to the palliative care team, which may have also facilitated higher training intensities. In addition, potential improvements in peripheral muscle function may have led to increased training intensity. Cardiorespiratory responses to moderate intensity exercise in a controlled training environment may differ from a 6MWT where individuals are expected to walk as far as possible in a specified time, and may experience significant oxygen desaturation. Other clinical outcomes such as muscle strength, functional mobility, balance and physical activity may be less dependent on gas exchange limitations and show more response to PR than the 6MWT. Such improvements may have important implications to HRQOL and independence in activities of daily living.

Oxygen use may be a surrogate marker of disease severity, as desaturation on the 6MWT has been reported as a prognostic marker of mortality in ILD.\textsuperscript{24} In this study we did not find any predictors of change in exertional oxygen over a six month period despite including markers of disease severity such as lung function, demographics and functional limitation. However oxygen use may have been prescribed at a higher level at baseline to support and optimize exercise training, leaving less room for a further increase in oxygen, therefore the change in oxygen requirements may not have been a true representation of disease progression.

\textbf{2.5.1 Limitations}

This was a retrospective study over an eleven year period, and changes in drug therapy may have had an impact on disease progression. As the majority of individuals used low flow variable performance oxygen delivery devices, only estimates of FiO\textsubscript{2} were available rather than an
accurate measure of FiO₂. As there are no standardized oxygen administration guidelines for PR, oxygen titration was dependent on the discretion of physiotherapists at a single centre. Individuals who were hospital inpatients while waiting for lung transplantation who often have very high oxygen requirements and a limited ability to participate in aerobic training were excluded from this study, however, these individuals are not typical of those participating in structured PR programs. Lastly, this study examined lung transplant candidates, who are carefully selected and may be younger and have fewer co-morbidities than the general ILD population.

2.6 Conclusions

Individuals with advanced ILD required high exertional oxygen requirements to participate in continuous moderate intensity aerobic training. Exertional oxygen requirements were increased over time to support exercise training, however no predictors of change were identified. Higher levels of exertional oxygen use were associated with a lower exercise capacity and aerobic training intensity, which can inform training expectations during PR. Further research is needed to examine the effects of oxygen on exercise training, understand the potential risks of higher oxygen prescription and examine how to optimally combine PR with oxygen supplementation.
Chapter 3

3 Feasibility of interval aerobic exercise in individuals with advanced interstitial lung disease

3.1 Abstract
Little is known about interval exercise in interstitial lung disease (ILD). This study compared feasibility (participant tolerance, preference and acute cardiorespiratory responses) of a single bout of interval exercise with a bout of continuous exercise on a cycle ergometer. A randomized cross-over study of individuals with advanced ILD participating in rehabilitation was performed. A cardiopulmonary exercise test (CPET) was first conducted on a cycle ergometer to obtain peak work (Wpeak: Watts). Total workload was matched between a bout of interval exercise (alternating 30 seconds at 100% of Wpeak: 30 seconds total rest x 20 min) and continuous exercise (50% of Wpeak x 20 min). Tests were separated by one hour. Nine lung transplant candidates with ILD were included (4 men, 62 (6) years, forced vital capacity (FVC) 60 (10)% predicted, all using supplemental oxygen). Mean Wpeak from CPET was 80 (15) Watts. Eight (89%) of participants reported a preference for interval exercise and one reported no preference (p=0.01). One participant required two unintended breaks during continuous exercise. There were no large differences between interval and continuous exercise although some trends emerged. Interval exercise resulted in a lower peak heart rate (124 (12) vs. 132 (15), p=0.04) and a trend towards less oxygen desaturation (drop of 8 (4)% vs. 11 (5)%, p=0.05) and lower end-exercise Borg leg fatigue (3.8 (2) vs. 4.4 (2), p=0.05). The quantity and quality of end-exercise
dyspnea was similar between both exercise modes. Interval exercise was well tolerated and preferred by individuals with advanced ILD.

### 3.2 Introduction

Interstitial lung disease (ILD) is a heterogeneous group of chronic respiratory disorders accompanied by reduced exercise capacity, disabling symptoms and decreased health-related quality of life (HRQOL). \(^1\,^9^2\) Mechanisms of exercise limitation are multifactorial and include ventilatory and circulatory limitations, impairments in gas exchange and peripheral muscle dysfunction. \(^4\,-\,^6\) Professional international society guidelines and statements support exercise training in ILD, however the strength of recommendations vary \(^6^8\) and optimal training strategies are not known.

During aerobic exercise, acute responses in ILD include tachypnea, ventilation/perfusion mismatching, diffusion limitation, hypoxemia, increased pulmonary arterial pressure and reliance on anaerobic metabolism. \(^5\,-\,^6\) These cardiorespiratory responses and accompanying symptoms (dyspnea, leg fatigue) may impact the feasibility of exercise in terms of a decreased ability to exercise at a prescribed workload, unintended breaks and early termination of exercise. Traditionally, aerobic exercise has been prescribed using constant load endurance training in chronic lung disease. Interval exercise, defined as repeated bouts of higher intensity exercise interspersed with pre-defined recovery periods of rest or lighter intensity exercise, has been suggested as an alternative exercise strategy. Interval exercise can impose a high load to the peripheral muscles with a reduced reliance on anaerobic metabolism and lower blood lactate accumulation. \(^9^3\,^9^4\) This metabolic shift may permit an increased training intensity and/or
duration and lead to greater physiological adaptations in oxygen uptake, delivery, extraction and utilization.

In chronic obstructive pulmonary disease (COPD), studies have examined between three to sixteen weeks of interval exercise matched for the same total work as continuous exercise. Both exercise modes have resulted in similar physiological training adaptations in exercise capacity (peak oxygen consumption (VO_{2peak}), 6-minute walk distance (6MWD), peak power), skeletal muscle adaptations (increased muscle capillary-to-fibre ratio, muscle fibre oxidative capacity and cross-sectional area of type I and IIa fibres) and HRQOL, but interval exercise is accompanied with reduced symptoms of dyspnea and leg fatigue during training. A randomized non-inferiority trial showed that interval exercise was no less effective than high intensity continuous exercise (matched for workload) in severe COPD for improving HRQOL and exercise capacity, and was better tolerated with less unintended breaks and better protocol adherence. One study evaluated how long people with severe COPD could tolerate high intensity exercise by comparing two symptom-limited exercise tests: a constant load exercise test at 80% Wpeak and an interval exercise test of alternating 30 seconds of 100% Wpeak: unloaded cycling. Participants were able exercise longer during interval cycling compared to constant load cycling, and demonstrated lower metabolic and ventilatory responses during interval exercise.

Compared to COPD, little is known about the responses to interval exercise in people with ILD. Rapid and profound exertional hypoxemia is common in advanced ILD. High intensity intervals may lead to significant demands on oxygen transport that could result in greater hypoxemia and accompanying dyspnea compared with continuous exercise, limiting the feasibility of this exercise mode in people with severe gas exchange limitations. There is no
consensus on the optimal protocol for interval exercise in terms of percentages of Wpeak and duration of the work:recovery ratios. One published abstract compared the effects and feasibility of interval training in eight lung transplant candidates with ILD alternating between 100% Wpeak for 30 seconds and rest for 30 seconds, for 12 minutes duration initially and progressing up to 36 minutes. This interval training five days a week for three weeks was associated with an increase in 6MWD of 64 metres and Wpeak of 13 watts. Interval training was reported to be feasible as there were a low number of unintended breaks taken during the exercise sessions. Interval exercise was not compared with continuous exercise in this study and there was no information provided on nadir oxygen saturation (SpO₂) during or after the exercise sessions to determine if this mode of exercise worsens hypoxemia.

Before examining the effectiveness of interval exercise compared with continuous exercise, the feasibility of the protocol needs to be established. Thus, the purpose of this study was to examine the feasibility in terms of unintended breaks, symptoms, perceived overall effort, participant preference and acute cardiorespiratory responses of a single bout of interval exercise as compared to continuous exercise in oxygen-dependent individuals with advanced ILD awaiting lung transplantation.

3.3 Methods

3.3.1 Study design

A cross-over study with participants acting as their own controls was conducted. Participants underwent a resting electrocardiogram (ECG) followed by a maximal incremental cardiopulmonary exercise test to determine Wpeak. One-week later, participants underwent an
interval and continuous cycle exercise bout. Both exercise bouts were conducted on the same day. Subjects were stratified by sex and the test order was alternated to ensure balance. There was a one-hour rest between the tests to allow vital signs and symptoms to return to baseline. The study protocol is shown in Figure 3-1.

3.3.2 Participants

The study was approved by the University Health Network (REB #16-6345) and the University of Toronto, Toronto, Canada (Protocol ID 34951). All participants provided written informed consent.

3.3.2.1 Inclusion criteria

Individuals (age ≥ 18 years) with advanced ILD listed for a first lung transplant in the Toronto Lung Transplant Program, University Health Network (UHN) and attending outpatient rehabilitation.

3.3.2.2 Exclusion criteria

Individuals awaiting a re-transplant or multi-organ transplant, hospitalized for respiratory distress, presence of disease exacerbation or significant deterioration, listed for transplant as rapidly deteriorating, presence of significant coronary artery disease and scheduled for intraoperative coronary artery bypass surgery at the time of transplant, mean pulmonary arterial pressure > 35mmHg on right heart catheterization, and existing neuromuscular and/or orthopedic issues that interfere with cycling exercise.
3.3.3 Measures

3.3.3.1 Cardiopulmonary exercise test

A maximal, symptom-limited incremental cycle ergometry test was performed by a pulmonary function technician on an electromagnetically braked cycle ergometer (Lode, B.V. Medical Technology, Groningen, The Netherlands) according to published guidelines. Three lead ECG and oximetry were measured continuously. Three minutes of rest was followed by three minutes of unloaded pedaling. The workload was then increased using a continuous ramp protocol of ten watts per minute while maintaining a pedaling frequency of 50 revolutions per minute (rpm). The test continued until the participant could not maintain a pedaling frequency of 50 rpm for 30 seconds or reached volitional exhaustion. Additional test termination criteria included: abnormal ECG rhythm or ischemia, chest pain, dizziness or faintness, nausea, severe hypoxemia (SpO₂ < 80%) accompanied by signs and symptoms of respiratory or cardiovascular distress and extreme dyspnea. Recovery included three minutes of unloaded pedaling. Peak workload in watts was recorded and the peak oxygen uptake (VO₂peak) was estimated from the final completed workload using a reference equation. Pre- and post test blood pressure, respiratory rate, symptoms of dyspnea and leg fatigue using the modified 0-10 Borg scale and descriptors of dyspnea were recorded. The test was performed using the level of supplemental oxygen that was prescribed for aerobic training during pre-transplant rehabilitation. Direct measures of gas exchange parameters and ventilation were not performed using a metabolic cart as participants required high levels of supplemental oxygen during the test that affect the validity of the metabolic measures.
3.3.4 Exercise protocols

The cycling protocols were administered by a physiotherapist and a research assistant. The total amount of work (time x workload) of both protocols was matched (Appendix 12). The interval exercise bout included a one minute warm up at 25% Wpeak, followed by alternating intervals of 100% Wpeak for 30 seconds and 30 seconds of rest for a total of 20 minutes. (Figure 3-1) The continuous exercise bout included a one minute warm up at 25% Wpeak followed by 19 minutes at 50% Wpeak for a total of 20 minutes. Individuals were asked to maintain a pedaling frequency of 50 rpm, which was externally paced with a metronome. Exercise was performed on a calibrated cycle ergometer (Monark Ergomedic 828E, Vansbro, Sweden). Exercise was performed on the same level of oxygen used during the CPET. Oxygen saturation (SpO₂) and heart rate were measured continuously during the exercise with pulse oximetry (Nellcor Puritan Bennett N-595 Oximeter, USMed-Equip, Houston, Texas) using a forehead sensor (Covidien Nellcor Maxfast, Medtronic, Minneapolis, USA) with readings recorded every 30 seconds. Pre-and post-exercise measures included blood pressure, respiratory rate, symptoms of Borg dyspnea and leg fatigue, and three descriptors of dyspnea (Appendix 13) that best described their breathing. Blood lactate was measured before and immediately after each exercise protocol using finger-prick capillary blood from the palmer surface of the non-dominant middle or ring finger using a hand-held electronic blood lactate analyzer (Lactate Scout+ EKF Diagnostics, Germany). After both exercise bouts were completed, in addition to the Borg scale, participants were asked which protocol resulted in more overall dyspnea, leg fatigue, and exertion as well as which exercise mode they preferred.
3.3.5 Clinical characteristics

The most recent six-minute walk test (6MWT) was recorded from the rehabilitation chart if it was completed within four weeks of the study procedures, otherwise an updated 6MWT was performed. The most recent pulmonary function test (within 3 months) and current use of opioids for dyspnea\textsuperscript{105} were recorded from the electronic medical record.

3.3.6 Statistical analysis

Normality of the data was checked using the Shapiro Wilk test. Paired t-tests were performed to compare the mean change in SpO\textsubscript{2}, heart rate, blood lactate, respiratory rate, Borg dyspnea and Borg leg fatigue from resting values. A Wilcoxon signed rank test was performed for non-normally distributed variables. Fisher exact tests were performed to compare categorical variables (dyspnea descriptors, overall perceived effort, dyspnea, leg fatigue and preference). Data were described as mean (SD) unless otherwise indicated. A p-value of \(< 0.05\) was considered statistically significant. Statistical analyses were performed using SAS University Edition.

The sample size was calculated using a paired 2-sided t. test, a mean difference in SpO\textsubscript{2} of 4\% (considered a clinically significant drop),\textsuperscript{106} a standard deviation of the SpO\textsubscript{2} after cycle training (3.65) from lung transplant candidates with ILD in Study 1 (SAS University Edition). Using an alpha of 0.05 and a power of 0.8, 12 participants were needed.
Figure 3-1:

Experimental Protocol

**Abbreviations**: SpO₂: saturation of oxygen in arterial blood measured by pulse oximetry; HR: heart rate; BP: blood pressure; RR: respiratory rate.
3.4 Results

3.4.1 Participants

Recruitment occurred between October 2017 and March 2018 (Figure 3-2). Nine participants (4 men) aged 62 (6) years with a variety of ILD were included. Pulmonary function, exercise capacity and oxygen requirements are listed in Table 3-1. Two participants were taking oral opioids (1 mg hydromorphone as needed and 5 mg of morphine once to two times per day). The proportion of individuals with co-morbid conditions included 55% (n=5) with gastroesophageal reflex disease, 33% (n=3) with cardiovascular disease, 33% (n=3) with osteoarthritis, 22% (n=2) with diabetes or glucose intolerance, 11% (n=1) with osteoporosis and 11% (n=1) with three or more co-morbidities.

3.4.2 Participant tolerance and preference

Every participant completed both exercise bouts. One participant required two unintended breaks during continuous exercise; no unintended breaks were taken during interval exercise by any of the participants. Following both exercise bouts, seven of the participants (78%) reported that their leg fatigue was greater with continuous compared to interval exercise (p=0.02). When asked which exercise resulted in more overall dyspnea, six participants (67%) reported more overall dyspnea with continuous exercise compared with interval exercise, and one reported similar dyspnea between the two types of exercise (p=0.02). Six participants (67%) described more overall effort with continuous exercise compared with interval exercise, and two
participants reported equal effort (p=0.01). Eight participants (89%) conveyed a preference for interval exercise (p=0.01) and one participant had no preference.

3.4.3 Acute cardiorespiratory responses

There were no differences in baseline values for SpO₂, heart rate, respiratory rate, mean arterial pressure, Borg dyspnea, Borg leg fatigue or lactate before interval and continuous exercise. Interval exercise resulted in a lower peak heart rate than continuous exercise (124 (12) vs. 132 (15), respectively, p=0.04) (Table 3-2). There was a clinically relevant drop in SpO₂ of ≥ 4% during both exercise bouts, with a trend towards less desaturation during interval exercise compared to continuous exercise (drop in SpO₂ 8 (4)% vs. 11 (5)%), respectively, p=0.05) (Table 3-2). There were also trends towards lower end-exercise Borg leg fatigue (3.8 (2) vs. 4.4 (2), respectively p=0.05) and less elevation in blood lactate (1.6 (3) vs. 4 (2) mmol, respectively p=0.07) compared to continuous exercise, although this did not reach significance (Table 3-2). There were no differences between the interval and continuous exercise in end-exercise Borg dyspnea, mean arterial pressure, respiratory rate, or blood lactate (Table 3-2). The heart rate and SpO₂ fluctuated up and down during the interval exercise compared to a steady increase (heart rate) or decrease (SpO₂) during continuous exercise (Figure 3-3, n=1). The change and nadir SpO₂, peak heart rate, leg fatigue, change in lactate and overall effort/dyspnea between the interval and continuous exercise in those who performed the interval exercise first (n=5) and second (n=4) is shown in Appendix 14. No adverse effects were observed either during the testing sessions or over the following week.
3.4.4 Descriptors of dyspnea

There were a variety of dyspnea descriptors reported at rest and end exercise. There were no differences in the frequency of different dyspnea descriptors between interval and continuous exercise. The two most common descriptors after both types of exercise were heavy breathing and increased work/effort (Figure 3-4, Appendix 13).
**Figure 3-2**: Participant recruitment

Abbreviations: mPAP: mean pulmonary arterial pressure; MSK: musculoskeletal; CPET: cardiopulmonary exercise test
Table 3-1: Participant characteristics (n=9)

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) or n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Male:female</td>
<td>4:5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 (6)</td>
</tr>
<tr>
<td>FVC (L) (% predicted)</td>
<td>2.1 (0.5)</td>
</tr>
<tr>
<td></td>
<td>60 (10)</td>
</tr>
<tr>
<td>DLCO (% predicted)</td>
<td>51 (10)</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>23 (8)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>IPF</td>
<td>4</td>
</tr>
<tr>
<td>Other IIP</td>
<td>3</td>
</tr>
<tr>
<td>CTD</td>
<td>1</td>
</tr>
<tr>
<td>LAM</td>
<td>1</td>
</tr>
<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td>29 (2)</td>
</tr>
<tr>
<td><strong>Exercise capacity</strong></td>
<td></td>
</tr>
<tr>
<td>6-minute walk test</td>
<td></td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>423 (50)</td>
</tr>
<tr>
<td>(% predicted)</td>
<td>66 (10)</td>
</tr>
<tr>
<td>End test SpO2 (%)</td>
<td>85 (6)</td>
</tr>
<tr>
<td><strong>Cardiopulmonary exercise test</strong></td>
<td></td>
</tr>
<tr>
<td>Peak work (W)</td>
<td>80 (15)</td>
</tr>
<tr>
<td>(% predicted)</td>
<td>65 (14)</td>
</tr>
<tr>
<td>End heart rate (% predicted)</td>
<td>87 (11)</td>
</tr>
<tr>
<td>End SpO2 (%)</td>
<td>89 (6)</td>
</tr>
<tr>
<td>Estimated VO2peak (L/min)*</td>
<td>1.79 (0.69)</td>
</tr>
<tr>
<td>(ml/kg/min)</td>
<td>21.8 (6)</td>
</tr>
<tr>
<td><strong>Exertional oxygen requirements</strong></td>
<td></td>
</tr>
<tr>
<td>Oxygen flow/ delivery system</td>
<td></td>
</tr>
<tr>
<td>6L/min nasal cannulae</td>
<td>3</td>
</tr>
<tr>
<td>6L oxymask</td>
<td>1</td>
</tr>
<tr>
<td>10L/min nasal cannulae</td>
<td>2</td>
</tr>
<tr>
<td>15L/min nasal cannulae</td>
<td>1</td>
</tr>
<tr>
<td>10L/min oxymask</td>
<td>2</td>
</tr>
<tr>
<td>Estimated FiO$_2$**</td>
<td>0.5 (0.04)</td>
</tr>
</tbody>
</table>

Abbreviations: FVC: forced vital capacity; D$_{LCO}$: diffusing capacity for carbon monoxide; mPAP: mean pulmonary arterial pressure; IPF: idiopathic pulmonary fibrosis; IIP: idiopathic interstitial pneumonia; CTD: connective tissue disease; LAM: lymphangioleiomyomatosis; BMI: body mass index; 6MWD: six-minute walk distance; SpO$_2$: oxygen saturation measured by pulse oximetry; VO$_{2peak}$: peak oxygen consumption; FiO$_2$: fraction of inspired oxygen

* from reference 103
** from reference 107
**Figure 3-3:**

Heart rate and oxygen saturation in one participant* during continuous and interval exercise

* 60 year old male with IPF using 6L oxymask. Continuous exercise at 45W, interval exercise at 90 W.

Abbreviations: \( \text{SpO}_2 \): oxygen saturation measured by pulse oximetry

Note: Dashed lines during interval exercise used to better illustrate the fluctuations in heart rate and \( \text{SpO}_2 \), however readings were recorded every 30 seconds rather than continuously
Table 3-2: Physiological responses to cycling bouts (n=9), mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Interval</th>
<th>Continuous</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadir SpO₂ (%)</td>
<td>92 (4)</td>
<td>89 (5)</td>
<td>0.06</td>
</tr>
<tr>
<td>Change in SpO₂ (%) *</td>
<td>- 8 (4)</td>
<td>- 11 (5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Peak HR</td>
<td>124 (12)</td>
<td>132 (15)</td>
<td>0.04</td>
</tr>
<tr>
<td>Change in HR **</td>
<td>+ 37 (12)</td>
<td>+ 47 (16)</td>
<td>0.12</td>
</tr>
<tr>
<td>End MAP</td>
<td>110 (16)</td>
<td>112 (17)</td>
<td>0.36</td>
</tr>
<tr>
<td>Change in MAP</td>
<td>+ 18 (13)</td>
<td>+ 21 (15)</td>
<td>0.82</td>
</tr>
<tr>
<td>End RR</td>
<td>37 (5)</td>
<td>37 (8)</td>
<td>0.85</td>
</tr>
<tr>
<td>Change in RR</td>
<td>+ 15 (5)</td>
<td>+ 14 (8)</td>
<td>0.49</td>
</tr>
<tr>
<td>End Borg dyspnea</td>
<td>4.3 (2)</td>
<td>4.9 (2)</td>
<td>0.21</td>
</tr>
<tr>
<td>Change in Borg dyspnea</td>
<td>+ 3.7 (2)</td>
<td>+ 4.1 (2)</td>
<td>0.42</td>
</tr>
<tr>
<td>End Borg leg fatigue</td>
<td>3.8 (2)</td>
<td>4.4 (2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Change in Borg leg fatigue</td>
<td>+ 3.4 (2)</td>
<td>+ 3.7 (12)</td>
<td>0.19</td>
</tr>
<tr>
<td>End lactate (mmol)</td>
<td>5.3 (2)</td>
<td>7.3 (5)</td>
<td>0.12</td>
</tr>
<tr>
<td>Change in lactate (mmol)</td>
<td>+ 1.6 (3)</td>
<td>+ 4 (2)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Abbreviations: SpO₂: oxygen saturation by pulse oximetry; HR: heart rate; MAP: mean arterial pressure; RR: respiratory rate

* change from rest to nadir SpO₂
** change from rest to peak HR

Change in MAP, RR and Borg dyspnea and leg fatigue are from rest to end-test
Figure 3-4:
Dyspnea descriptors\textsuperscript{104, Appendix 13} at rest and during continuous and interval cycling

Participants picked up to three descriptors to describe their dyspnea
3.5 Discussion

The interval exercise protocol was feasible in people with advanced ILD. Most participants preferred a single bout interval exercise over continuous exercise. No participants took any unintended breaks during interval exercise whereas one participant required two unintended breaks during continuous exercise. Matched to continuous exercise for total work, interval exercise resulted in lower peak heart rate and trends towards less oxygen desaturation, lower end-exercise leg fatigue and less elevation in blood lactate. Overall, this protocol of interval exercise was feasible and should be tested for effectiveness during an exercise program performed over several weeks. Interval exercise may be a valuable training strategy in individuals who cannot sustain continuous exercise due to severe oxygen desaturation, dyspnea and fatigue. It can provide an intense training load that may lead to greater physiological adaptations to training and improved functional outcomes as seen in the healthy population.\(^{93,94}\)

Peak heart rate was higher during continuous exercise than interval exercise. In fact, continuous exercise at 50% Wpeak for 20 minutes resulted in individuals reaching 84% of their age-predicted maximal heart rate. During interval exercise, individuals reached 79% of their age-predicted maximal heart rate despite interval workloads of 100% Wpeak. As the protocols were matched for total work, a higher heart rate during continuous exercise may have been needed to respond to a lower \(\text{SpO}_2\)/ acute hypoxemia.\(^{108}\) In addition, the interval exercise may have allowed partial recovery of heart rate during the rest periods that prevented the heart rate from reaching the same peak levels (Figure 3-3). Although previous studies in advanced COPD have used 60% of peak work rate for continuous exercise,\(^{97}\) a lower percentage (50% of Wpeak) was chosen for this study considering the ILD diagnosis, severity of lung disease, high oxygen requirement and potential presence of moderate pulmonary hypertension that might have
prevented participants from safely completing 20 minutes of continuous cycling at that intensity. If 60% of Wpeak had been used for continuous exercise intensity in this study, higher peak heart rates may have been observed and more unintended breaks may have occurred.

Individuals in this study had severe gas exchange abnormalities as evidenced by oxygen desaturation during the 6MWT and CPET despite using between six to fifteen litres per minute of supplemental oxygen (Tables 3-1 and 3-2). Hypoxemia that is not fully corrected with supplemental oxygen in ILD can limit the intensity and duration of exercise training prescribed. There was a trend towards less desaturation during interval compared to continuous exercise. The rest intervals during interval exercise may have allowed the SpO2 to partially recover preserving a higher SpO2 (Figure 3-3). Oxygen diffusion is limited in ILD due to a thickened alveolar-capillary barrier from extensive collagen deposition in the alveolar walls, and diffusion becomes a greater contributor to gas exchange abnormalities during exercise when capillary transit time decreases. The reduced peak heart rate observed during interval exercise could have preserved capillary transit time through the lungs, allowing more time for oxygen diffusion and better preservation of SpO2.

There was also a trend towards lower blood lactate accumulation during interval exercise. Exercise performed at a high intensity (e.g. >85% VO2peak) relies on anaerobic metabolism due to depletion of intramuscular phosphocreatine and myoglobin oxygen stores, leading to accumulation blood lactate, which is a metabolic byproduct of glycolysis. The interspersed rest intervals during interval exercise decreases muscle oxygen consumption, and can assist in re-phosphorylation of phosphocreatine, reloading myoglobin oxygen stores and facilitate lactate removal. Less blood lactate accumulation during interval training has been shown to reduce
ventilatory demand in COPD and lead to less symptoms of dyspnea and leg discomfort.\textsuperscript{95,96,98} The participants in this study also reported less leg fatigue after interval exercise. At anaerobic threshold, there is a steep increase in both ventilation and blood lactate concentration.\textsuperscript{109} An increase in ventilation is stimulated by non-metabolic carbon dioxide released in a buffering reaction of excess lactic acid generation.\textsuperscript{109} Lower leg fatigue and blood lactate elevation may permit a longer duration of exercise training and greater physiological muscle adaptations. Despite higher blood lactate after continuous exercise in this study, there was no difference in end respiratory rate between continuous and interval exercise. Anaerobic threshold may not have been reached after each exercise bout. In addition, tachypnea may have been needed during both interval and continuous exercise to increase minute ventilation to support the workloads.\textsuperscript{36}

There was no mean difference in Borg dyspnea score (quantity) or frequency of dyspnea descriptors (quality) after exercise reported by the participants in this study. However, once both exercise bouts were completed and participants were asked which exercise they experienced more overall dyspnea, more participants indicated continuous exercise. Although less dyspnea has been reported with interval exercise compared with continuous exercise in COPD, mechanisms of dyspnea differ in ILD which may affect the quantity and quality of dyspnea experienced.\textsuperscript{33,103} Specifically, individuals with ILD have a low lung compliance and reduced lung volumes contributing to decreased inspiratory capacity and a rapid, shallow breathing pattern.\textsuperscript{31} At rest, study participants did report mild dyspnea as indicated on the Borg scale, and half of the participants described various dyspnea descriptors (shallow, heavy, unsatisfied inspiration and increased effort). In addition, all participants were enrolled in a pre-transplant rehabilitation program that involved continuous exercise training on a cycle for 20 minutes, and therefore may have been more accustomed to dyspnea during this type of exercise compared
with interval exercise. Two of the participants were also taking opioids to manage dyspnea, which may have affected their perception of dyspnea.

There are a variety of interval exercise protocols with different work: recovery intensities of $W_{peak}$ or $VO_2\text{peak}$, interval durations and work: recovery ratios. ⁹³ This study used the same interval exercise protocol that has been previously used in lung transplant candidates without reported adverse effects, ⁹⁷,¹⁰¹ however it may not be the best protocol to maximize physiological benefits of endurance training. Intervals done at a higher percentage of $W_{peak}$ may provide greater benefits. In healthy populations the work: recovery duration of high intensity interval training is varied depending on the training goal, with shorter intervals (15 seconds) targeting speed and longer intervals (one to four minutes) targeting endurance to enhance maximal oxygen uptake. ⁹³ Individuals with cardiorespiratory disease may not be able to tolerate high intensities for longer intervals. Men with mild to moderate congestive heart failure reported a higher preference and lower perceived exertion when using 30 second work intervals compared with 90 second intervals of 100% $W_{peak}$, and work intervals > 90 seconds at 100% $W_{peak}$ were reported to be unsustainable. ¹¹⁰

Individuals with advanced ILD often have group 3 pulmonary hypertension that can worsen exercise capacity, hypoxemia and dyspnea, and may be an additional factor to consider when choosing an interval exercise protocol. ²¹ Study participants had evidence of mild to moderate pulmonary hypertension, however we excluded participants who had significant pulmonary hypertension. Traditionally, individuals with severe pulmonary hypertension were advised against physical activity and exercise, as it was thought that the increased blood flow during exercise would increase right ventricular afterload and enhance right ventricular wall shear stress
that could worsen right heart failure and potentially lead to cardiovascular collapse. Exercise training studies over the past 12 years have demonstrated that supervised exercise is safe and effective in improving exercise capacity in various types of pulmonary hypertension, and may have a role in improving pulmonary hemodynamics. However the studies have included low to moderate intensity constant and/or interval training, and there is a lack of evidence on the optimal intensity or duration of training. In professional statements on pulmonary rehabilitation, it is recommended to avoid high intensity interval exercise in people with pulmonary hypertension due to the associated rapid changes in pulmonary hemodynamics and risk of syncope that have been observed during exercise testing. Participants in this study did not experience any pre-syncope during the interval exercise. However, recovery intervals at a lower percentage of \( W_{\text{peak}} \) (e.g. 25% \( W_{\text{peak}} \)) may be an alternative to complete rest to potentially attenuate these potential hemodynamic changes, increase the safety of interval exercise and permit its use in individuals with severe pulmonary hypertension.

3.5.1 Limitations

Both tests were performed on the same day and one hour between tests may not have allowed sufficient time for muscle glycogen stores to recover. This may have resulted in decreased muscular performance for the second exercise bout, although the order of the tests was alternated for each sex to help account for this. The participants in this study did not have significant cardiac or musculoskeletal comorbidities and were not experiencing any acute exacerbations, and therefore may not fully represent all people with advanced lung disease. The sample size of this study was small, however the aim was to examine exercise feasibility and not effect. A post hoc power calculation revealed that a sample size of 29 would be required to determine differences in
the SpO2 response: the oxygen saturation dropped significantly during both exercise bouts, and the mean difference in the degree of oxygen saturation between the bouts was less than anticipated (mean 2.3% vs. 4%), and the standard deviation in end-exercise SpO2 was also larger than anticipated (5 vs. 3.65).

3.6 Conclusions

Interval exercise was feasible and a preferred mode of exercise that did not result in greater hypoxemia compared with continuous exercise in individuals with advanced ILD who required high levels of supplemental oxygen. A rigorous, longer term training study is needed to determine the effectiveness of cumulative doses of interval exercise on cardiorespiratory and musculoskeletal systems compared to continuous exercise.
4. Skeletal muscle oxygenation and regional blood volume during incremental limb loading in interstitial lung disease

4.1 Abstract

It is not known to what extent regional skeletal muscle oxygen saturation (SmO$_2$) decreases during exercise in interstitial lung disease (ILD). This study compared SmO$_2$ and regional blood volume of the knee extensors and elbow flexors during incremental limb loading in healthy people and people with varying severity of ILD. This was a prospective cross-sectional study. Incremental, isotonic, concentric exercise was performed on an isokinetic dynamometer. Loading started at 10% of maximal voluntary isometric contraction (MVIC) and increased by 10% MVIC every two minutes until task failure. SmO$_2$ and regional blood volume were measured by near infrared spectroscopy (NIRS) over the vastus lateralis and bicep muscles. Thirteen lung transplant candidates with severe ILD requiring supplemental oxygen (8 men, 65 (5) years, FVC 59 (20)% predicted), ten non-oxygen dependent people with mild/moderate ILD (6 men, 60 (9) years, FVC 81 (17)% predicted) and thirteen healthy people (8 men, 60 (9) years, FVC 101 (14)% predicted) were included. At task failure for both knee extensor loading (KEL) and elbow flexor loading (EFL), SmO$_2$ was decreased to similar levels across all groups, but occurred at lower total workloads in the ILD groups (all p<0.01). During incremental loading there was a change over time for SmO$_2$, oxygenated and deoxygenated hemoglobin (O$_2$Hb and HHb) and hemoglobin difference (Hb-diff) (all p< 0.001), but no between-group differences.
Total hemoglobin, a marker of regional blood volume, was lower in the knee extensors in severe ILD compared with healthy participants at KEL task failure (p=0.05). The decrease in SmO_2 in active muscles during incremental loading may reflect increased muscle oxygen extraction or reduced oxygen supply during exercise. People with severe ILD had lower levels of total work and experienced less increase in blood volume in the knee extensors after KEL compared with healthy people. Peripheral muscle dysfunction in severe ILD may have contributed to muscle deoxygenation at lower workloads.

4.2 Introduction

Interstitial lung disease (ILD) is a heterogeneous chronic lung condition associated with disabling symptoms of dyspnea and fatigue, reduced exercise capacity, lower levels of physical activity and impaired health-related quality of life (HRQOL). Exercise training is recommended in ILD to improve symptoms, exercise capacity and HRQOL. Impairment of gas exchange leading to exertional hypoxemia is commonly observed in many ILDs and contributes to exercise limitation. The intensity of exercise prescription is often determined by an adequate arterial blood oxygen saturation measured by pulse oximetry (SpO_2); however, SpO_2 does not provide information about regional oxygenation of exercising muscle.

There is emerging evidence of peripheral muscle dysfunction in ILD such as muscle atrophy and reduced skeletal muscle strength and endurance. The underlying skeletal muscle pathophysiology contributing to exercise intolerance in ILD is not well studied to date. Reduced arterial oxygen content in people with ILD may result in muscle deoxygenation that limits exercise capacity and performance.
Near infrared spectroscopy (NIRS) is a non-invasive, optical technique that uses differential absorption properties of infrared light to evaluate skeletal muscle oxygen saturation (SmO$_2$) and regional blood volume of the microcirculation (arterioles, capillaries and venules). NIRS can provide insight into the state of oxygen utilization at the level of the tissues and local blood redistribution during exercise. Changes in muscle oxygenation during local resistance loading has not been previously examined in ILD.

The overall aim of this study was to examine changes in skeletal limb muscle oxygen saturation during localized exercise in people with varying severity of ILD as well as healthy people. The specific objectives were to: 1) examine between and within-group differences in active muscle oxygen saturation during incremental loading and at task failure, ii) examine between and within-group differences in regional blood volume redistribution to active muscles during incremental loading and at task failure and iii) examine whether systemic arterial oxygen saturation measured by pulse oximetry (SpO$_2$) is associated with regional muscle oxygen saturation (SmO$_2$). Muscle oxygen saturation was measured with NIRS during incremental isotonic knee extensor loading (KEL) and elbow flexor loading (EFL).

### 4.3 Methods

#### 4.3.1 Participants

Three groups of people were recruited for the study: adults with mild/moderate ILD, adult lung transplant candidates who were oxygen-dependent with severe ILD and healthy controls. Lung
transplant candidates were recruited from the lung transplant program at the University Health Network, Toronto, Canada. All were participating in the pre-transplant rehabilitation program for less than four weeks at the time of study recruitment. Participants with mild/moderate ILD (not listed for lung transplant or prescribed long term oxygen therapy) were recruited from the ILD clinic at the same facility. Healthy, non-smoking, aged and sex-matched people were recruited from a university community and screened with spirometry and the American Heart Association and American College of Sports Medicine health/fitness facility pre-participation screening questionnaire, (Appendix 15). Study recruitment occurred between November 2016 and June 2017 for all groups. Exclusion criteria for all study subjects were: (1) adipose tissue thickness > 10mm at the NIRS monitoring sites (mid-femur and mid-humerus), (2) < 45 or > 75 years of age, (3) active myositis and (4) muscle or joint issues including metabolic, cardiovascular, neurological or musculoskeletal conditions that would interfere with or cause undue risk during testing. In addition, lung transplant candidates were excluded if they were listed as rapidly deteriorating, were hospitalized or were awaiting a re-transplantation or multi-organ transplantation (heart-lung or lung-liver). The study was approved by the University Health Network (REB 16-5088-DE) and the University of Toronto, Toronto, Canada (Protocol ID 33251). All participants provided written informed consent.

4.3.2 Study Protocol

Testing was conducted in a single session. Ultrasound measures of adipose tissue and muscle layer thickness were taken, followed by a measurement of isometric peak torque and subsequent incremental, isotonic, concentric loading. Details of the testing protocols are provided below.
4.3.2.1 Adipose tissue and muscle layer thickness using ultrasound

Thickness of the knee extensor and elbow flexor muscles (the active muscles) of the dominant limb was measured using B-mode ultrasound imaging (5-13 MHz linear transducer, GE Logic E system, GE Medical Systems, Milwaukee, WI, USA). The placement of the NIRS probes were chosen based on anatomical landmarks. Specifically, the lateral quadriceps (vastus lateralis and vastus intermedius) were landmarked by measuring a third of the distance between the midpoint of the superior border of the patella to the anterior superior iliac spine and eight centimetres lateral to this midpoint. The elbow flexors were landmarked by measuring a third of the distance between the midpoint between the epicondyles of the humerus to the acromion process. Muscle layer thickness was measured directly on the ultrasound monitor between the borders of the superficial and deep aponeurosis. Skin and adipose thickness was measured from the outer most layer of the skin to the superficial aponeurosis over the muscles. The thenar eminence of non-dominant hand was designated as a control muscle to provide information on blood volume redistribution, with skin, adipose and muscle layer thickness measured over the thickest part of the muscle belly.

4.3.2.2. Muscle oxygenation and regional blood volume using NIRS

Muscle oxygenation and regional blood volume were measured using spatially resolved NIRS (PortaMon and PortaLite, Artinis Medical Systems, BV, The Netherlands). Each of these wireless devices uses three light emitting transmitters (optodes) and a photon receiver to measure
the relative change in the concentration of oxygenated \((O_2Hb/Mb)\) and deoxygenated hemoglobin/myoglobin (HHb/Mb). The sum of these chromophores provides the total hemoglobin/myoglobin (tHb/Mb), an estimate of regional blood volume beneath the probe. \(^{43}\) Although NIRS cannot differentiate between hemoglobin and myoglobin, hemoglobin is believed to contribute to the majority of the signal. \(^{43}\) Therefore the chromophores in this study were described as oxygenated hemoglobin \((O_2Hb)\), deoxygenated hemoglobin \((HHb)\), total hemoglobin \((tHb)\) calculated as \(O_2Hb + HHb\), and the hemoglobin difference \((Hb-diff)\) calculated as \(O_2Hb - HHb\). The ratio of \(O_2Hb\) to \(tHb\) was used as an absolute measure of tissue oxygen saturation \((SmO_2)\). \(^{48}\)

To set-up NIRS, the subjects’ skin was cleaned with alcohol and the optodes were placed directly over the ultrasound landmarks of the mid-femur, mid-humerus and thenar eminence with double sided tape and secured with hypafix tape. All NIRS values excluding \(SmO_2\) were zeroed at the start point of each incremental test. A data sampling rate of 10Hz was used and collected using NIRS software (Oxysoft, Artinis Medical Systems, BV, The Netherlands). The three transmitters optodes and one receiver of each NIRS device placed over the active muscles provided three inter-optode distances (30, 35 and 40mm). \(^{48}\) The depth of light penetration is estimated to be half the inter-optode distance. The ultrasound measures of adipose and muscle layer thicknesses were used to determine the depth needed to reach halfway through the muscle (vastus lateralis and elbow flexors), and the appropriate transmitter optode was then chosen based on this depth for later data analysis using NIRS software.
4.3.2.3 Isometric peak torque testing

Participants were stratified by sex, age and diagnostic category (healthy, mild ILD and severe ILD) and the assignment of which incremental test to start with was alternated to ensure balance secondary to a small sample size. Isometric peak torque of the knee extensors and elbow flexors were measured on an isokinetic dynamometer (Biodex System 4, Shirley, NY, USA) on the dominant limbs (arm used to write with and leg used to kick a ball with) using a standard protocol (see Figure 4-1 for Biodex set-up). For the knee extensors the participant was seated upright with shoulder and hip straps and the axis of the dynamometer was aligned to the knee joint. An isometric test at 90° of knee flexion was performed for five seconds using standardized verbal encouragement followed by a one-minute rest. For the elbow flexors, the participant was seated upright with shoulder, hip and elbow straps, and the axis of the dynamometer aligned to the elbow joint. Their forearm rested on an arm support as they gripped a handle. An isometric test at 60 degrees elbow flexion was performed for five seconds using standardized verbal encouragement. The highest torque of five repetitions was designated as 100% maximal voluntary isometric contraction (MVIC) for both muscle groups.

4.3.2.4 Incremental loading of knee extensors and elbow flexors

Five minutes after completing the isometric testing, the incremental protocol was performed using an isotonic (constant load) concentric testing mode of the isokinetic dynamometer. The initial load was set to 10% of MVIC and increased by 10% MVIC every two minutes until task
failure. For the KEL protocol participants were required to contract the knee extensors from 90° to 10° of knee flexion, and for the EFL protocol participants were required to contract the elbow flexors from 60° to 140° of flexion. A duty cycle of one-second contraction to five seconds rest was used resulting in 20 contractions over each two-minute increment. A metronome was used to standardize the timing of the contractions. The torque, position and velocity data from the isokinetic dynamometer was sampled at 100Hz and collected using a real-time, data acquisition system (Biopac Systems Canada Inc. and Acqknowledge software, version 4). Task failure was defined when the participant failed to meet the required range of motion (80°) or contraction velocity (80° /second) for three successive contractions. Task failure was also defined if the participant requested to stop due to fatigue, discomfort or significant cardiorespiratory symptoms (SpO₂ < 80%, severe dyspnea or respiratory distress), or if the tester observed excessive muscle compensation. The incremental loading tasks were separated by a rest time of 30 minutes.

4.3.2.5 Cardiorespiratory responses

Dyspnea sensation and rating of perceived exertion for arm and leg fatigue were quantified using a modified Borg 0-10 scale before, during and immediately after KEL or EFL tests. Throughout the incremental loading, SpO₂ and heart rate were measured continuously using pulse oximetry (Nonin 4000, Roxon Medi-Tech Inc, Saint-Leonard, QC, Canada). Blood pressure was measured before and after each of the incremental loading protocols. The participants with severe ILD used the same level of supplemental oxygen they were prescribed for resistance training during their pre-transplant rehabilitation program.
4.3.3 Statistical analysis

All data were tested for normality using the Shapiro-Wilk test and reported as means (standard deviations) unless otherwise described. Between-group differences in functional characteristics, cardiorespiratory responses to loading, SmO$_2$, SmO$_2$/total workload and chromophore (O$_2$Hb, HHb, tHb, Hb-diff) concentration changes at end exercise (task failure) were examined using one-way ANOVA with a subsequent Tukey’s post-hoc test if significant. Within-group differences in SmO$_2$, O$_2$Hb, HHb, tHb and Hb-diff at task failure compared to rest were examined using a paired t-test or Wilcoxon signed rank test. To examine the change in SmO$_2$, O$_2$Hb, HHb, tHb and Hb-diff during incremental loading, the task duration was divided into quintiles. Between and within-group differences were examined using repeated measures ANOVA with a subsequent Tukey’s for between-group differences or Dunnett’s post hoc test for within-group differences, with the reference point being the baseline (resting) measure. To examine the relationship between SmO$_2$ and SpO$_2$ at KEL and EFL task failure, a Spearman rank correlation analysis was performed including all participants. The level of significance for all analyses was $p \leq 0.05$. Statistical analysis was performed on SAS statistical software University Edition. For the sample size calculation, we based the effect size on the mean change in biceps O$_2$Hb during elbow flexor loading in a COPD population (-15.5) since there was no previous data in ILD. The estimated effect size for 3 groups was $f=0.25$ with 6 measures and correlation between repeated measures of 0.8, alpha 0.05 and power 0.9 resulted in an estimated sample size calculation of 15 individuals per group.
4.4 RESULTS

4.4.1 Participant characteristics

Thirteen healthy participants, ten individuals with mild/moderate ILD (FVC 81 (17)% predicted) and thirteen oxygen-dependent lung transplant candidates with severe ILD (FVC 59 (20)% predicted) participated. The flow of recruitment for the ILD populations can be found in Appendices 16 and 17. There were an equal proportion of women in each group. Participant characteristics are described in (Table 4-1). In regards to the sample size, the mean change in O$_2$Hb during elbow flexor loading was less in the ILD populations than what was observed in the previously studied COPD population $^{116}$ used to determine the effect size (mild ILD -4 and severe ILD -3 vs. COPD -15.5).

4.4.2 Incremental loading

There was a difference in total work performed during KEL (p=0.006) with a lower total work performed in the mild and severe ILD groups compared to the healthy group (Table 4-2 and Figure 4-2). There was a difference in total work performed during the EFL (p=0.001) with a lower total work performed in the severe ILD group compared with the healthy and mild ILD groups (Table 4-3 and Figure 4-2). No adverse events occurred during the testing, and there were no reported adverse effects reported to the study investigator the following week.
4.4.3 Muscle oxygenation and regional blood volume at task failure within-group differences

SmO$_2$ decreased in the knee extensors from rest to task failure in the healthy and severe ILD groups (p<0.001) but not in the mild ILD group (p= 0.09) (Figure 4-3, panel A). HHb increased in the knee extensors of the healthy group only (p<0.01) (Figure 4-3, panel C). Blood volume (tHb) of the knee extensors increased in the healthy and mild ILD groups (p=0.03 and p=0.01) but not in the severe ILD group (p=0.71) (Figure 4-5). There was no difference in O$_2$Hb or Hb-diff in the knee extensors from rest to task failure in any group. SmO$_2$ decreased in the elbow flexors from rest to task failure in the mild and severe ILD groups (all p<0.01) but not in the healthy group (p=0.70) (Figure 4-4, panel A). Hb-diff decreased from rest to task failure in the mild ILD group (p=0.006) and the severe ILD group (Figure 4-4, panel D). There were no other significant changes in the elbow flexors O$_2$Hb, HHb or tHb. There were no within-group differences in SmO$_2$, O$_2$Hb, HHb or tHb in the control muscle (thenar eminence) from rest to KEL or EFL task failure (all p> 0.05) in any of the groups.

4.4.4 Between-group differences

There was no difference in end exercise SmO$_2$ among the three groups after KEL (p=0.13) and EFL (p=0.49), or in O$_2$Hb, HHb or Hb-diff at KEL task failure (p=0.55, p=0.31, 0.85 respectively) or EFL task failure (p=0.13, p=0.23, 0.09 respectively), (Figures 4-3 and 4-4). A ratio of SmO$_2$/ total workload was used to represent the data. There was a difference in SmO$_2$/total workload at EFL task failure (p=0.01), and post-hoc testing revealed that the SmO$_2$/total workload was higher in the severe ILD group compared to the healthy group (p=0.01;
Figure 4-2, lower panel). This was due to the lower total workload in the severe ILD group. There was no difference in SmO$_2$/total workload at KEL task failure (p=0.06; Figure 4-2, upper panel). There was a difference among groups in blood volume (tHb) at KEL task failure (p=0.05), with post-hoc testing revealing a lower tHb in the severe ILD group compared to the healthy group (Figure 4-5). There was no difference among the three groups in tHb at EFL task failure (p=0.29), (Figure 4-5). There were no between-group differences in SmO$_2$, O$_2$Hb, HHb or tHb in the control muscle (thenar eminence) in rest or end-exercise values (all p> 0.05).

4.4.5 Muscle oxygenation and regional blood volume during incremental loading within-group differences

During KEL and EFL there were within-group differences over time for SmO$_2$, O$_2$Hb, HHb, Hb-diff and tHb in the active muscles (all p< 0.001; Figures 4-3, 4-4 and 4-5). During KEL, post-hoc testing revealed that the severe ILD group had a lower O$_2$Hb at the 20th percentile of task duration compared to rest (p=0.02; Figure 4-3, panel B). The mild ILD group had a lower Hb-diff at the 20$^{th}$ percentile of task duration compared to rest (p= 0.001; Figure 4-3, panel D). The healthy and mild ILD groups had a higher tHb at the task failure compared to rest (p=0.03 and p=0.01; Figure 4-5). During EFL both mild and severe ILD had a lower SmO$_2$ at the 20th percentile compared to rest (all p=0.04; Figure 4-4, panel A). O$_2$Hb was lower during EFL at 20$^{th}$ percentile in all groups compared to rest (all p<0.01, Figure 4-4, panel B), and also at the 40$^{th}$ percentile in both ILD groups (all p=0.01, Figure 4-4, panel B). Hb-diff was lower in all groups at the 20$^{th}$ percentile (all p<0.05), lower in the severe ILD group at the 40$^{th}$ percentile and at all time points in the mild ILD group (Figure 4-4, panel D).
4.4.6 Between-group differences

During KEL and EFL there were no differences among the three groups for SmO$_2$, O$_2$Hb, HHb or Hb-diff (Figures 4-3 and 4-4). There was a difference in tHb during KEL (p=0.05; Figure 4-5, left panel) with post-hoc testing showing a lower tHb in the severe ILD group compared to the healthy group. There was no difference for tHb during EFL (p=0.50; Figure 4-5).

4.4.7 Cardiopulmonary responses to the incremental loading protocols

With KEL there were differences in baseline heart rate (p=0.0004), end exercise heart rate (p=0.03) and end exercise dyspnea (p=0.005) among the groups (Table 4-2). Post-hoc testing revealed that the severe ILD group had a higher baseline heart rate than the healthy and mild ILD groups, and a higher end-exercise heart rate than the healthy group. The severe ILD group also had a higher end-exercise dyspnea than the healthy and mild ILD groups. With EFL there were differences in baseline heart rate (p=0.002) and end exercise dyspnea (p=0.01) among groups (Table 4-3). Post-hoc testing revealed a higher baseline heart rate in both ILD groups compared to the healthy group and a higher end-exercise dyspnea in the severe ILD groups compared with the healthy and mild ILD groups. No participants reported dyspnea as a reason for test termination.
4.4.8 Relationship between whole body and local muscle oxygenation at task failure

As shown in Figure 4-6, there were no correlations between SmO₂ and SpO₂ at task failure following KEL and EFL in any of the groups.
Table 4-1: Participant characteristics (n=36), mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Healthy (n=13)</th>
<th>Mild ILD (n=10)</th>
<th>Severe ILD (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: female (% female)</td>
<td>8:5 (38.5%)</td>
<td>6:4 (40%)</td>
<td>8:5 (38.5%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60 (9)</td>
<td>60 (9)</td>
<td>65 (5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25 (3)</td>
<td>27 (4)</td>
<td>26 (3)</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>101 (14)</td>
<td>81 (17)</td>
<td>59 (20) *</td>
</tr>
<tr>
<td>D\textsubscript{LCO} (% predicted)</td>
<td>69 (14)</td>
<td>48 (15) *</td>
<td></td>
</tr>
<tr>
<td>GAP index</td>
<td>1.5 (1)</td>
<td>4.2 (1) *</td>
<td></td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>558 (107)</td>
<td>397 (71) *</td>
<td></td>
</tr>
<tr>
<td>6MWD (% predicted)</td>
<td>83 (15)</td>
<td>62 (13) *</td>
<td></td>
</tr>
<tr>
<td>Hbg (g/L)</td>
<td>148 (11)</td>
<td>136 (19)</td>
<td></td>
</tr>
<tr>
<td>Hct (L/L)</td>
<td>0.43 (0.02)</td>
<td>0.41 (0.05)</td>
<td></td>
</tr>
<tr>
<td>Estimated FiO\textsubscript{2}</td>
<td></td>
<td></td>
<td>0.45 (0.1)**</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPF</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>NSIP</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>IPF/COPD</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>DIP</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COP</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYD</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity pneumonia</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>LAM</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Sjogren’s</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA-ILD</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table: Muscle layer thickness (mm)

<table>
<thead>
<tr>
<th></th>
<th>Vastus lateralis and intermedius ***</th>
<th>Elbow flexors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle layer thickness (mm)</td>
<td>36.3 (6)</td>
<td>36.9 (5)</td>
</tr>
<tr>
<td></td>
<td>30.5 (6)</td>
<td>28 (4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Skin and adipose thickness (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over vastus lateralis</td>
<td>7.9 (3)</td>
</tr>
<tr>
<td>Over elbow flexors</td>
<td>5.1 (2)</td>
</tr>
</tbody>
</table>

* p ≤0.05 for differences between groups.

** during testing, determined from reference [107] [Nasal cannulae regular 3-4 litres/minute (n=5), nasal cannulae high flow 6-15 litres/minute (n=5), oxymizer 4-10 litres/minute (n=3)]

*** Muscle thickness was measured a third of the distance between the midpoint of the superior border of the patella to the anterior superior iliac spine and eight centimetres lateral to this midpoint in all participants, and may not represent the thickest part of the vastus lateralis or vastus intermedius in every participant.

Proportion of co-morbid conditions:

Mild ILD- 60% cardiovascular disease, 30% gastroesophageal reflux disease, 20% psychological disturbances, 10% diabetes or glucose intolerance, 10% osteoporosis, 10% with 3 or more co-morbidities

Severe ILD- 77% cardiovascular disease, 38% gastroesophageal reflux disease, 38% diabetes or glucose intolerance, 15% osteoporosis, 15% osteoarthritis, 8% psychological disturbances, 15% with 3 or more co-morbidities

**Abbreviations:** BMI: body mass index; FVC: forced vital capacity; D\textsubscript{LCO}: diffusing capacity for carbon monoxide; GAP index: gender, age and pulmonary physiology index for mortality in idiopathic pulmonary fibrosis; 6MWD: six-minute walk distance; Hbg: hemoglobin; Hct: hematocrit; FiO\textsubscript{2}: fraction of inspired oxygen, IPF: idiopathic pulmonary fibrosis; NSIP: non-specific interstitial pneumonia; IPF/COPD: idiopathic pulmonary fibrosis/ chronic obstructive pulmonary disease; DIP: desquamative interstitial pneumonia; COP: cryptogenic organizing pneumonia; NYD: not yet diagnosed; LAM: lymphangioleiomyomatosis; RA-ILD: rheumatoid arthritis –associated interstitial lung disease
Table 4-2: Incremental knee extensor loading characteristics (n=36), mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Healthy (n=13)</th>
<th>Mild ILD (n=10)</th>
<th>Severe ILD (n=13)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Muscle function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee extensor peak torque (Nm)</td>
<td>162 (50)</td>
<td>137 (44)</td>
<td>104 (32)</td>
<td>N.S</td>
</tr>
<tr>
<td>Maximal % MVIC achieved (%)</td>
<td>58.5 (12)</td>
<td>52.5 (15)</td>
<td>50 (10)</td>
<td>N.S</td>
</tr>
<tr>
<td>Protocol length (minutes)</td>
<td>11.7 (2)</td>
<td>10 (3)</td>
<td>10 (2)</td>
<td>N.S</td>
</tr>
<tr>
<td>Total work performed (J)</td>
<td>6328 (2515)</td>
<td>4911 (2211)</td>
<td>3368 (1330)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Cardiorespiratory responses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start SpO₂ (%)</td>
<td>97 (1)</td>
<td>97 (2)</td>
<td>98 (2)</td>
<td>N.S</td>
</tr>
<tr>
<td>End SpO₂ (%)</td>
<td>97 (1)</td>
<td>95 (3)</td>
<td>95 (4)</td>
<td>N.S</td>
</tr>
<tr>
<td>Start HR (bpm)</td>
<td>67 (9)</td>
<td>74 (7)</td>
<td>84 (11)</td>
<td>0.0004</td>
</tr>
<tr>
<td>End HR (bpm)</td>
<td>90 (12)</td>
<td>92 (9)</td>
<td>101 (14)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age-predicted max end HR (%)</td>
<td>56 (0.1)</td>
<td>58 (0.1)</td>
<td>65 (0.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Start dyspnea</td>
<td>0 (0)</td>
<td>0.2 (0.3)</td>
<td>0.6 (1)</td>
<td>N.S</td>
</tr>
<tr>
<td>End dyspnea</td>
<td>1.6 (1)</td>
<td>1.5 (1)</td>
<td>3.3 (1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Start leg fatigue</td>
<td>0 (0)</td>
<td>0.3 (1)</td>
<td>0.1 (0.3)</td>
<td>N.S</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td><em>End leg fatigue</em></td>
<td>4 (2)</td>
<td>3 (1)</td>
<td>3.5 (1)</td>
<td>N.S</td>
</tr>
<tr>
<td><em>Start MAP (mmHg)</em></td>
<td>99 (9)</td>
<td>96 (13)</td>
<td>93 (7)</td>
<td>N.S</td>
</tr>
<tr>
<td><em>End MAP (mmHg)</em></td>
<td>104 (9)</td>
<td>102 (17)</td>
<td>97 (9)</td>
<td>N.S</td>
</tr>
</tbody>
</table>

**Abbreviations**: VL: vastus lateralis; VI: vastus intermedius; Nm: Newton-metres; MVIC: maximal voluntary isometric contraction; J: joules; SpO₂: saturation of oxygen as measured by pulse oximetry; HR: heart rate; bpm: beats per minute; MAP: mean arterial pressure.
<table>
<thead>
<tr>
<th>Muscle function</th>
<th>Healthy (n=13)</th>
<th>Mild ILD (n=10)</th>
<th>Severe ILD (n=13)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbow flexor peak torque (Nm)</td>
<td>60 (19)</td>
<td>57 (18)</td>
<td>40 (18)</td>
<td>N.S</td>
</tr>
<tr>
<td>Maximal % MVIC achieved (%)</td>
<td>52 (7)</td>
<td>44 (10)</td>
<td>36 (10)</td>
<td>N.S</td>
</tr>
<tr>
<td>Protocol length (minutes)</td>
<td>10.5 (1)</td>
<td>8.8 (2)</td>
<td>7.2 (2)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Total work performed (J)</td>
<td>3003 (1212)</td>
<td>2514 (911)</td>
<td>1446 (811)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiorespiratory responses</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Start SpO\textsubscript{2} (%)</td>
<td>97 (2)</td>
<td>97 (2)</td>
<td>98 (2)</td>
<td>N.S</td>
</tr>
<tr>
<td>End SpO\textsubscript{2} (%)</td>
<td>97 (1)</td>
<td>96 (2)</td>
<td>97 (2)</td>
<td>N.S</td>
</tr>
<tr>
<td>Start HR (bpm)</td>
<td>68 (9)</td>
<td>78 (6)</td>
<td>82 (12)</td>
<td>0.002</td>
</tr>
<tr>
<td>End HR (bpm)</td>
<td>85 (11)</td>
<td>88 (8)</td>
<td>94 (11)</td>
<td>N.S</td>
</tr>
<tr>
<td>Age-predicted max end HR (%)</td>
<td>53 (0.1)</td>
<td>55 (0.1)</td>
<td>61 (0.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Start dyspnea</td>
<td>0 (0)</td>
<td>0.3 (0.5)</td>
<td>0.4 (1)</td>
<td>N.S</td>
</tr>
<tr>
<td>End dyspnea</td>
<td>1.5 (1)</td>
<td>1.5 (1)</td>
<td>3 (1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Start arm fatigue</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.1 (0.2)</td>
<td>N.S</td>
</tr>
<tr>
<td>End arm fatigue</td>
<td>4 (2)</td>
<td>2.5 (2)</td>
<td>3.5 (1)</td>
<td>N.S</td>
</tr>
<tr>
<td>Start MAP (mmHg)</td>
<td>99 (6)</td>
<td>97 (13)</td>
<td>92 (6)</td>
<td>N.S</td>
</tr>
<tr>
<td>End MAP (mmHg)</td>
<td>104 (9)</td>
<td>99 (13)</td>
<td>95 (8)</td>
<td>N.S</td>
</tr>
</tbody>
</table>

**Abbreviations:** Nm: newton-metres; MVIC: maximal voluntary isometric contraction; J: joules; SpO\textsubscript{2}: saturation of oxygen as measured by pulse oximetry; HR: heart rate; MAP: mean arterial pressure

N.S non-significant
Figure 4-1:

Experimental set-up for near infrared spectroscopy monitoring of vastus lateralis during knee extensor loading (left) and biceps during elbow flexor loading (right). Isotonic loading was done using a Biodex dynamometer.
**Figure 4-2**: End exercise (task failure) SmO$_2$ over total workload (n=36)

p. value represents between-group differences. During EFL post-hoc testing revealed a higher SmO$_2$/workload in the severe ILD group compared to the healthy group.

Abbreviations: KEL: knee extensor loading, EFL: elbow flexor loading; SmO$_2$: muscle oxygenation; ILD: interstitial lung disease
Figure 4-3: Change in A) SmO$_2$, B) O$_2$Hb, C) HHb and D) Hb-diff during incremental knee extensor limb loading

* Healthy, α Mild ILD, β Severe ILD

Panel A: SmO$_2$

Task failure: within-group differences (healthy and severe ILD p<0.001, mild ILD p=0.09), between-group differences (p=0.13)

During loading: within-group differences (all p<0.001), between-group differences (p=0.53)

Panel B: O$_2$Hb

Task failure: within-group differences (all p>0.05), between-group differences (p=0.55)

During loading: within-group differences (all p<0.001), between-group differences (p=0.21)

Panel C: HHb
Task failure: within-group differences (healthy $p<0.01$, mild and severe ILD $p>0.05$), between-group differences ($p=0.31$)

During loading: within-group differences (all $p<0.001$), between-group differences ($p=0.49$)

Panel D: Hb-diff

Task failure: within-group differences (all $p>0.05$), between-group differences ($p=0.85$)

During loading: within-group differences (all $p<0.001$), between-group differences ($p=0.84$)

Abbreviations: SmO$_2$: muscle oxygenation; O$_2$Hb: oxygenated hemoglobin, HHb: deoxygenated hemoglobin, Hb-diff: hemoglobin difference
Figure 4-4: Change in A) SmO$_2$, B) O$_2$Hb, C) HHb and D) Hb-diff during incremental elbow flexor limb loading

* Healthy, α Mild ILD, β Severe ILD

Panel A: SmO$_2$

Task failure: within-group differences (mild and severe ILD p<0.01, healthy p=0.70), between-group differences (p=0.49)

During loading: within-group differences (all p<0.001), between-group differences (p=0.34)

Panel B: O$_2$Hb

Task failure: within-group differences (all p>0.05), between-group differences (p=0.13)

During loading: within-group differences (all p<0.001), between-group differences (p=0.23)

Panel C: HHb
Task failure: within-group differences (all $p>0.05$), between-group differences ($p=0.23$)

During loading: within-group differences (all $p<0.001$), between-group differences ($p=0.29$)

Panel D: Hb-diff

Task failure: within-group differences (Healthy $p=0.80$, mild ILD $p=0.006$, severe ILD $p=0.01$), between-group differences ($p=0.09$)

During loading: within-group differences (all $p<0.001$), between-group differences ($p=0.09$)

Abbreviations: $\text{SmO}_2$: muscle oxygenation; $O_2\text{Hb}$: oxygenated hemoglobin, HHb: deoxygenated hemoglobin, Hb-diff: hemoglobin difference
Figure 4-5: Change in total hemoglobin (tHb), an estimate of regional blood volume during incremental limb loading

* Healthy, α Mild ILD, β Severe ILD

Knee extensor loading

Task failure: within-group differences (healthy p=0.03, mild ILD p=0.01, severe ILD 0.71), between-group differences (p=0.05)

During loading: within-group differences (all p<0.001), between-group differences (p=0.05)

Elbow flexor loading

Task failure: within-group differences (all p>0.05), between-group differences (p=0.49)
During loading: within-group differences (all $p<0.001$), between-group differences ($p=0.50$)
**Figure 4-6**: Relationship between muscle oxygen saturation (SmO$_2$) and arterial oxygen saturation (SpO$_2$) at task failure following incremental limb loading

Abbreviations: KEL: knee extensor loading, EFL: elbow flexor loading; SpO$_2$: oxygen saturation as measured by pulse oximetry; ILD: interstitial lung disease
4.5 DISCUSSION

This is the first study to evaluate muscle oxygenation and regional blood volume during incremental loading in ILD. Following upper and lower limb loading there was a similar level of muscle oxygenation (SmO$_2$, O$_2$Hb, HHb, Hb-diff) in active muscles in participants with mild/moderate ILD, oxygen-dependent severe ILD and healthy people, however deoxygenation occurred at a lower total workload in the ILD groups. Total hemoglobin, reflecting regional blood volume, was lower in the severe ILD group compared to healthy people during lower limb incremental loading.

Muscle oxygenation measured using NIRS reflects the dynamic balance between local oxygen supply by the microcirculation and oxygen consumption by the mitochondria. $^{43}$ SmO$_2$ can decrease due to increased muscle oxygen extraction to support increased workloads, or can decrease from a reduction in local oxygen supply/delivery. The increase in deoxygenated hemoglobin (HHb) after KEL in the healthy group suggests increased muscle oxygen extraction during the incremental loading protocol. Although there was a cardiorespiratory response during incremental loading in all groups, it was not a rate-limiting response as only 53-65% of age-predicted maximal heart rate was reached and dyspnea scores were low to moderate. The mean oxygen saturation (SpO$_2$) was $\geq$ 95% at task failure in both ILD groups, and only two individuals dropped to a SpO$_2$ < 90% during KEL (Tables 4-2 and 4-3, Figure 4-5). Although arterial oxygen saturation was not significantly reduced, individuals with ILD may have been less able to extract the available oxygen due to poor peripheral muscle oxidative capacity due to low capillarization, reduced mitochondrial enzyme activity, lower proportion of type I muscle fibers, as has been identified in COPD using muscle biopsy studies. $^{39}$ People with ILD share many of the risk factors for skeletal muscle dysfunction and reduced oxidative capacity as the COPD
population such as chronic hypoxemia, inflammatory and oxidative stress, corticosteroid use, malnutrition, aging and physical activity. Some ILD sub-types such as sarcoidosis and connective tissue associated-ILD may also have primary muscle involvement. A reduced ability of the peripheral muscle to extract oxygen with a relatively preserved SmO₂ may have contributed to the earlier termination in exercise at lower workloads in people with ILD in this study.

Two studies have examined muscle oxygenation in people with ILD during high intensity aerobic exercise. McNarry et al examined HHb of the vastus lateralis as an indicator of oxygen extraction during cycling. They found that both pulmonary oxygen uptake and HHb kinetics were slower in people with idiopathic pulmonary fibrosis compared to healthy participants. Keyser et al examined muscle oxygenation of the gastrocnemius during ten weeks of high intensity aerobic training and found improved muscle oxygen extraction (increased HHb and difference of O₂Hb-HHb) following training without an increase in central oxygen delivery or muscle oxygen availability. In our study, seated isotonic resistance exercise was examined which likely places less demand on gas exchange compared with aerobic exercise. Reid et al examined muscle oxygenation of the elbow flexors during seated incremental EFL in 12 people with moderate to severe chronic obstructive lung disease (COPD) and found a decreased O₂Hb at all time points during loading. An isokinetic loading protocol with set load increments (as compared to a percentage of MVIC) and a greater range of motion and test duration was used, and study participants did not use supplemental oxygen, which may have led to a greater decrease in O₂Hb than observed in this study. Mechanisms and degree of peripheral muscle dysfunction may also differ in COPD compared with ILD. The prolonged disease trajectory of COPD may result in greater muscle dysfunction and subsequent impairment in muscle oxygen utilization.
Blood volume in active muscles was lower in the severe ILD group during lower limb incremental loading but not in upper limb loading. The knee extensors are a larger muscle group than elbow flexors and a higher total workload (in Joules) was reached during KEL than EFL. This may have led to higher cardiorespiratory responses during KEL and more blood volume may have been distributed to the respiratory muscles in the severe ILD group. Although there were no changes in tHb in the control muscle (thenar eminence of the non-dominant hand), blood flow may have been redistributed from other muscles such as those in the lower limb during KEL or other organs. Alternatively, the seated, resistance loading protocol may not have been high enough intensity to require blood flow redistribution. Alterations in vascular response to exercise may have attenuated blood flow redistribution to contracting muscles in ILD. Total hemoglobin was not different during EFL. This may have resulted from compression of small vessels in all muscle groups of the upper limb during an isometric muscle contraction of the forearm and hand to grip the dynanometer handle during EFL. The skeletal muscles of individuals with ILD may be inefficient in terms of metabolic activity, physiological reserve, antioxidant load and vasoreactivity. A reduction in local blood volume during KEL in severe ILD may have contributed to a lower Hb-diff. This may result in less oxygen extraction at the level of the muscle, and limit the total work performed. Little is known about the structural and metabolic characteristics of skeletal muscle and its’ relationship to function in ILD.  

Muscle oxygenation was not significantly correlated to whole body oxygenation. Whereas SpO₂ is an indication of oxygen delivery and calculated from pulsatile arterial blood, the NIRS signal arises from small vessels (arterioles, capillaries and venules) in the local tissue being monitored, thereby providing additional information on tissue oxygen supply and extraction.  Both
measures (SpO₂ and SmO₂) are important to determine oxygen status. Near infrared spectroscopy provides an indication of what is occurring at the level of the muscle such as if muscle oxygenation drops to very low levels that may cause muscle injury or other adverse effects, and if exercise training results in improved oxygen extraction. The SpO₂ provides important information on the oxygen status of the whole body, providing an indication of a decreased affinity of oxygen to hemoglobin which will affect hypoxia in other body organs and tissues, leading to an increased work of breathing and cardiac strain.

4.5.1 Limitations

There were more men recruited, as women tended to have more subcutaneous adipose thickness in the thigh region and were excluded due to the limitations of NIRS. Sex differences were not explored due to the small sample and the women recruited had lower mid thigh adipose tissue and may not have been representative of the general female population (healthy and ILD). Only a few centimetres of superficial muscle can be sampled using NIRS. The vastus lateralis is only one muscle involved in knee extension, and as electromyography was not used, we could not measure to what extent the vastus lateralis was recruited compared to the other muscles of the quadriceps. The variability of muscle oxygenation and blood volume was large, and post-hoc testing revealed a lack of statistical power based on the sample size (based on the standard deviation of O₂Hb observed, a total of 25 per group would be needed to show a difference in O₂Hb during EFL). As the isotonic workloads were based on an individual’s MVIC and not matched for workload, we were unable to examine differences in muscle oxygenation and changes in blood volume among groups at isowork.
4.6 CONCLUSIONS

This exploratory study demonstrated that muscle deoxygenation occurred at a lower level of total work in severe ILD and regional blood volume was attenuated compared to healthy persons during lower limb incremental loading. This provides insight into possible exercise limitations in ILD. A future study examining if resistance training improves muscle oxygen saturation at higher isotonic workloads in ILD is warranted.
Chapter 5

5 Discussion and conclusion

5.1 Overview of findings

The studies included in this thesis utilized different modes of exercise (constant endurance, interval endurance and incremental resistance exercise) and non-invasive measures of systemic arterial oxygen saturation and regional skeletal muscle oxygen saturation (pulse oximetry and near infra-red spectroscopy) to gain greater insight into the interactions between exertional hypoxemia and muscle hypoxia with exercise capacity and parameters in individuals with advanced interstitial lung disease who required oxygen supplementation (ILD). The novel findings of this thesis are presented in Figure 5-1.
INTERSTITIAL LUNG DISEASE

Exercise  oxygen therapy  Oxygen delivery & utilization

**Constant load endurance**
- High $O_2$ required to support moderate intensity training, increased over time
- Increased $O_2$ associated with lower exercise capacity and training **Study 1**

**Interval endurance**
- Interval exercise was well tolerated & preferred over constant load **Study 2**
- Lower peak HR & trend to less desaturation/leg fatigue/blood lactate

**Incremental resistance**
- Same level of muscle deoxygenation at lower workloads compared to healthy
- Regional blood volume attenuated with lower limb loading **Study 3**

**Arterial oxygen saturation**
- Significant hypoxemia during constant load and interval endurance exercise **Studies 1 & 2**
- Preserved $SpO_2$ with incremental resistance exercise **Study 3**

**Muscle oxygen saturation**
- Arterial oxygen saturation ($SpO_2$) not associated with local muscle oxygen saturation ($SmO_2$) during resistance loading **Study 3**

**Figure 5-1:** Thesis framework with main study findings

Oxygen therapy was delivered as per current clinical administration practice
A summary of the main findings from each study of this thesis include:

**Study 1 - Constant load endurance exercise with arterial oxygen saturation monitoring**

(Chapter 2)

This retrospective study of 375 lung transplant candidates with ILD undergoing rehabilitation examined oxygen requirements with constant load endurance exercise (treadmill walking) using pulse oximetry to measure exertional hypoxemia (Figure 5-1). Results showed that supplemental oxygen requirements for exercise were variable and ubiquitous in advanced ILD. The prescribed fraction of inspired oxygen was increased over time through increased oxygen flow rates and/or changes in oxygen delivery systems to support constant load endurance training and maintain arterial oxygen saturation (typically $\text{SpO}_2 \geq 88\%$). A higher exertional oxygen requirement was negatively associated with both six-minute walk distance and endurance training intensities. There were no predictive factors identified for the change in exertional oxygen requirements over four weeks and six months of pre-transplant rehabilitation.

**Study 2 - Interval and constant load endurance exercise with arterial oxygen saturation monitoring**

(Chapter 3)

This randomized cross-over study examined feasibility and acute cardiorespiratory responses of a single bout of interval and continuous exercise on a cycle ergometer in nine lung transplant candidates with ILD (Figure 5-1). Matched for total work, interval exercise (alternating 30
second bouts of 100% Wpeak for 30 seconds: rest for a total of 20 minutes) was the preferred mode of exercise compared to constant load exercise (50% Wpeak for 20 minutes). Interval exercise did not result in any unintended breaks. Peak heart rate was lower with interval exercise. There was a clinically relevant drop in oxygen saturation during both exercise bouts, however there was a trend towards less oxygen desaturation with interval exercise (drop in SpO₂ of 8% vs. 11%, p=0.05). There were trends towards reduced Borg leg fatigue and less elevation in blood lactate with interval exercise. There were no differences in quantity or quality of dyspnea between an acute bout of interval and constant load exercise.

**Study 3- Incremental resistance exercise with systemic arterial oxygen saturation and regional skeletal muscle oxygen saturation monitoring (Chapter 4)**

Regional skeletal muscle oxygenation and blood volume was examined prospectively during incremental upper and lower limb resistance loading using near infrared spectroscopy (NIRS) in 13 oxygen-dependent lung transplant candidates with severe ILD, ten people with non-oxygen dependent mild/moderate ILD and 13 healthy persons (Figure 5-1). There were similar decreases in skeletal muscle oxygenation in active upper and lower limb muscles in people with mild/moderate ILD, severe ILD and healthy persons, however muscle deoxygenation occurred at a lower total workload in both ILD groups. Total hemoglobin (an estimate of regional blood volume) was attenuated in the active knee extensors in individuals with severe ILD compared with healthy persons during lower limb incremental loading. Systemic arterial oxygen saturation measured by pulse oximetry was not associated with regional skeletal muscle oxygen saturation as measured by NIRS during incremental limb loading in healthy or ILD groups.
Taken together, these findings highlight that impairments in oxygen delivery can impact exercise capacity, tolerance and response to exercise in individuals with ILD, which have implications for exercise training strategies and oxygen supplementation. As pharmacological and surgical treatment options are limited for many people with ILD, exercise training and supplemental oxygen are recommended to increase function and HRQOL. 28 Guidelines for both exercise training and oxygen supplementation are extrapolated largely from the COPD population, despite differences in the pathophysiology of exercise limitation and mechanism and degree of gas exchange abnormalities. 69,118 Oxygen has been shown to increase exercise capacity in ILD, however oxygen is not always prescribed to a level that fully corrects hypoxemia. 6,57 Exercise prescription that is not supported by adequate oxygen supplementation may lead to either significant hypoxemia/hypoxia and symptoms that impact the safety, compliance and adherence to exercise, or result in exercise that is prescribed at low levels of intensity/duration limiting physiological adaptations to training. We did not manipulate oxygen administration in any of the three studies, and oxygen was administered according to current clinical oxygen practices (study 1) and delivered at the same oxygen prescription that the individual was using during pre-lung transplant rehabilitation (studies 2 and 3). To optimize functional outcomes, oxygen supplementation (mode, flow rate, delivery system) and exercise prescription (intensity, duration, mode) should be examined together.
5.2 Oxygen delivery and utilization

5.2.1 Measurement of arterial and muscle oxygen saturation

Non-invasive, continuous measures of arterial oxygen saturation and regional muscle oxygen saturation provide valuable, real-time assessment during exercise that can guide exercise and oxygen prescription. Pulse oximetry estimates oxygen saturation in the circulating arterial blood and is used widely clinically to determine an appropriate dose of exercise (intensity and/or duration) as well as an appropriate dose of supplemental oxygen to maintain a certain arterial oxygen saturation level (e.g. SpO$_2$ $\geq$ 88%).\textsuperscript{56} Pulse oximetry was used in all three studies, and in studies 1 and 2 exertional hypoxemia was evident in oxygen-dependent lung transplant candidates with ILD during endurance exercise. Rapid and profound exertional hypoxemia is common in ILD despite high flow rates of oxygen due to respiratory and circulatory factors limiting gas exchange, with gas exchange further exacerbated by a decreased capillary transit time due to increased cardiac output during exercise.\textsuperscript{5} In study 3, arterial oxygen saturation was fairly well preserved in individuals with ILD during seated, resistance exercise of upper and lower limbs indicating adequate systemic oxygen delivery.

A limitation of using pulse oximetry to adjust exercise intensity and/or duration is that it does not provide information about regional oxygenation of the exercising muscle. Near infrared spectroscopy (NIRS) provides information on both oxygen delivery and oxygen extraction/utilization at the level of the skeletal muscle. In study 3 we did not find a correlation between arterial oxygen saturation measured by pulse oximetry and regional skeletal muscle
oxygen saturation (SmO$_2$) measured by NIRS in healthy or ILD populations. There was arterial oxygen desaturation in studies 1 and 2, however as only pulse oximetry was used, it is not known if and to what extent regional muscle oxygenation occurred during interval and constant load endurance exercise. The reasons for the reduction in SmO$_2$ during exercise may differ in health and respiratory disease. Skeletal muscles are regularly exposed to hypoxia during exercise as a consequence of rapid oxygen consumption to meet the metabolic needs of the working tissues.\textsuperscript{119,120} Thus healthy people may experience a drop on SmO$_2$ due to increased oxygen extraction to meet the oxygen needs of a high exercise workload. Individuals with ILD may have a lower SmO$_2$ during exercise due to reduced oxygen supply/delivery (from a lower partial pressure of oxygen that would decrease oxygen diffusion into the muscle cells). There were a few participants with mild and severe ILD who did desaturate to < 90% during incremental resistance loading. However, intrinsic structural and metabolic changes in the skeletal muscle such as loss of type 1 muscle fibres, reduced capillary to fibre ratio, decreased mitochondrial density, reduced oxidative enzyme activity, decreased vasoreactivity and a shift to anaerobic energy production that have been observed in chronic respiratory disease\textsuperscript{39} may have impacted oxygen extraction due to a lower oxygen demand by the muscle, thus preserving SmO$_2$ but contributing to a lower workloads achieved in the ILD groups. Compensatory mechanisms of the skeletal muscles to acute hypoxia induced by exercise include vasodilation to maintain oxygen delivery.\textsuperscript{119} In study 3 regional blood volume (measured by tHb) was attenuated in individuals with severe ILD compared with healthy persons during lower limb incremental loading, which may have also contributed a similar drop in SmO$_2$ at lower workloads.
5.3 Peripheral skeletal muscle dysfunction and muscle hypoxia in ILD

In study 3, people with ILD performed less upper and lower limb resistance work during an incremental exercise to task failure than healthy people, which may have been related to reduced muscle strength. Results from a scoping review on peripheral skeletal muscle dysfunction in ILD found reduced volitional muscle strength, preferentially in the lower limbs was the most commonly measured impairment, however other determinants may have contributed to the reduced workload achieved.  

Several studies have revealed a reduction in muscle cross sectional area, reduced muscle thickness and lower amounts of fat free mass in lower limbs. A small but not significant decrease in muscle layer thickness of the knee extensors and biceps was found in study 3, more so in severe ILD. Muscle endurance and metabolic characteristics of muscles such as muscle capillarization and oxidative capacity are not well described in ILD, but play an integral role in local skeletal muscle oxygenation, specifically in oxygen utilization. In study 2 we observed high levels of blood lactate after acute bouts of endurance exercise indicating an earlier shift and greater reliance on anaerobic sources of energy. People with ILD may also have a reduced ability to clear lactate, leading to increased accumulation.

Hypoxia is one factor that can lead to peripheral muscle dysfunction. In study 3 we observed a similar level of skeletal muscle oxygen desaturation in ILD compared to healthy persons, however this occurred at lower workloads and may indicate a reduced muscle oxidative capacity. Individuals with ILD demonstrate marked arterial oxygen desaturation or hypoxemia during exercise, which may lead to a hypoxic muscle environment. Muscle hypoxia can inhibit protein
synthesis and increase muscle degradation, inducing structural changes such as reduced muscle fibre area to improve oxygen diffusion into the muscle cells and reduced muscle mass to decrease oxygen demand. While these structural adaptations may help the muscle to become better oxygenated in situations of low circulating oxygen, it may impact exercise capacity. Hypoxia increases reactive oxygen species production and may increase oxidative stress leading to peripheral skeletal muscle atrophy and compromising muscle capillarization and muscle oxidative capacity resulting in functional consequences of muscle weakness and greater fatigability. Hypoxia can inhibit cellular oxygen consumption and mitochondrial metabolism leading to a rapid shift from aerobic to anaerobic metabolism for energy production during exercise, which may explain higher lactate levels. Potential exposure to more prolonged and severe hypoxemia in people with severe ILD may lead to peripheral skeletal muscle dysfunction, and in study 3 lung transplant candidates did present with lower knee and elbow peak torque and reduced muscle layer thickness than healthy controls. Oxidant stress has been shown in individuals with idiopathic pulmonary fibrosis. Peripheral skeletal muscle dysfunction may be a potentially modifiable factor in ILD, and a further understanding of the role of hypoxemia and oxidative stress in skeletal muscle dysfunction can help to target strategies for exercise training and oxygen supplementation.

### 5.4 Exercise in ILD

Due to altered respiratory mechanics, ventilation inefficiency, circulatory impairments, gas exchange abnormalities and peripheral muscle limitations, individuals with ILD experience dyspnea and fatigue with acute exercise leading to reduced maximal and functional exercise
capacity and performance. In all three studies included in this thesis lung transplant candidates had a reduced 6-minute walk distance (47-66% predicted). In study 2 lung transplant candidates had a reached a lower peak work rate (65% predicted) on maximal exercise testing and a low estimated VO$_{2peak}$ (21.8 ml/kg/min). In study 3, the total work performed during incremental resistance limb loading was reduced 23-47% after upper and lower limb loading in the mild and severe ILD groups compared to healthy persons.

Supplemental oxygen has been shown to increase endurance time, maximal workload, maximal oxygen uptake and exercise capacity acutely in ILD. In study 1, oxygen requirements for exercise were increased over time to maintain oxygen saturation during treadmill walking as disease progression occurred (Figure 5-1). This supports the importance of continual reassessment of exertional oxygen needs in people with advanced ILD. In COPD, individuals demonstrate greater oxygen desaturation during walking as compared with cycling, and in study 2 participants had a lower arterial oxygen saturation after the 6MWT than the CPET on a cycle ergometer. However, participants still demonstrated clinically significant oxygen desaturation during cycling in study 2 despite high oxygen flows during both constant load and interval exercise, accompanied by moderately-severe symptoms of dyspnea and leg fatigue. Seated, incremental resistance loading in study 3 was not associated with significant hypoxemia, and resulted in moderate symptoms of dyspnea and limb fatigue, and therefore may be an important training strategy to improve peripheral muscle function and potentially exercise capacity without the same constraints from cardiorespiratory limitations.

There is emerging evidence of the efficacy of exercise training in ILD in improving exercise capacity, with research studies and clinical pulmonary rehabilitation practice utilizing constant
load endurance exercise as a primary training mode. The research studies have reported less functional benefit (e.g. change in 6-minute walk distance) in certain ILD subgroups including people with idiopathic pulmonary fibrosis (IPF), people with severe disease, people who exhibit exercise-induced oxygen desaturation and people requiring supplemental oxygen for exercise. All participants in studies 1 and 2 and the lung transplant candidates in study 3 had severe lung disease, experienced exertional hypoxemia, were oxygen dependent and a majority were diagnosed with IPF, and thus represented a group with significant gas exchange abnormalities and reduced oxygen delivery that could limit exercise intensity/duration/volume and physiological adaptations to training.

Individuals with advanced lung disease may have difficulty maintaining constant load exercise for prolonged periods due to hypoxemia, dyspnea and/or leg fatigue. Exercise training intensity and duration is often guided by the level of oxygen saturation and symptoms, with general pulmonary rehabilitation guidelines to maintain an oxygen saturation ≥88% and target moderate symptom scores. In study 1, relatively low aerobic training intensities were prescribed to maintain an acceptable oxygen saturation and symptom burden during constant load endurance exercise. High training intensities are recommended to obtain physiological benefits, and interval exercise has shown to provide similar benefits to constant load training (matched for total work) but is accompanied with less dyspnea in COPD. In study 2, interval exercise was shown to be feasible and preferred to constant load exercise, with a trend towards less oxygen desaturation and leg fatigue during interval exercise. Professional respiratory society statements on pulmonary rehabilitation recommend interval endurance training as an alternative strategy to traditional constant load endurance training that may increase the functional benefit.
we matched work between the interval and continuous modes. If interval exercise is not matched to constant load exercise for total work and individuals are able to perform more work with interval exercise at a tolerable level of hypoxemia and symptoms, it may be a beneficial training strategy to increase the exercise dose and maximize training adaptations at the muscle level.

5.5 Limitations

There are several limitations that should be considered when interpreting and applying the results of these studies. For all three studies, oxygen prescription was not standardized between patients: the choice of oxygen flow rate and delivery device varied based on participant tolerance, preference and response. Oxygen prescription for exertion was dependent on the discretion of physiotherapists at a single the transplant centre, where the goals of optimizing fitness for surgery by progressing exercise intensity and duration may have lead to higher supplemental oxygen use compared to pulmonary rehabilitation programs that enroll individuals with ILD who are not surgical candidates. As the oxygen prescription order is often to maintain oxygen saturation $\geq 88\%$ rather than within a tight oxygen saturation range, some participants may have been maintaining a higher oxygen saturation of $> 92\%$ with exertion while others had lower oxygen saturations, which may have impacted oxygen delivery. The majority of study participants were lung transplant candidates who are carefully screened for significant co-morbidities and frailty, are younger, have sufficient social support and motivation and are undergoing regular rehabilitation, and therefore may not be fully representative of the overall ILD population. All studies used non-invasive measures of oxygenation and therefore could not provide specific information intrinsic muscle properties that may limit exercise capacity.
including oxidative capacity, mitochondrial function, muscle fibre type, capillarity and other factors involved in signaling pathways for protein synthesis and degradation.

5.6 Future directions

This thesis has identified several areas for future research:

5.6.1 Exercise training in ILD

Interval exercise appears to be a feasible mode of exercise that does not lead to greater oxygen desaturation compared with constant load exercise in oxygen dependent individuals with advanced ILD. A non-inferiority study of interval and continuous exercise training should be done to examine the feasibility and cardiorespiratory responses of chronic bouts of training as well as the effects on VO_{2peak}, muscle metabolism, systemic inflammation and immune function.

An initial interval work intensity of 100% W_{peak} of 30 seconds duration appears feasible, however using active recovery such as 25% of W_{peak} rather than complete rest may be more tolerable and safer for individuals with ILD and significant pulmonary hypertension to reduce changes in pulmonary hemodynamics and to be able to generalize to a broader ILD population. It would be interesting to examine if individuals could perform more total work with interval exercise if the duration of exercise was determined by symptoms of leg fatigue and/or dyspnea rather than matched to constant load exercise work, and if this leads to greater protocol adherence and physiological adaptations.
In addition to further examining the feasibility and effects of interval exercise in ILD (study 2) on exercise capacity and peripheral muscle function, examining SmO$_2$ during other training strategies that may have a lower oxygen demand such as muscle partitioning$^{123}$ and eccentric cycling$^{124}$ should be studied.

5.6.2 Oxygen Supplementation

Current oxygen administration and titration practices during exercise testing, exercise training, physical activity and activities of daily living are based on general guidelines for COPD, which may not meet the specific needs of the ILD population. As seen in Study 1, high levels of supplemental oxygen were required, and increased over time. Specific ILD recommendations for oxygen administration during physical activity and exercise training are needed. The role of hyperoxia in permitting higher levels of endurance training (along with the hypothetical risks of oxygen toxicity and excessive cardiac stress) should also be examined.

5.6.3 Hypoxemia as a mechanism of peripheral muscle dysfunction in ILD

Considering the many causes of ILD and the variable rate of disease progression, more information on the natural history of the development of peripheral skeletal muscle dysfunction (muscle strength and muscle endurance) is needed, as well as mechanistic studies examining the contribution of hypoxemia to the development and progression of peripheral skeletal muscle dysfunction.
5.7 Conclusions

This thesis examined exertional hypoxemia, muscle oxygenation, exercise capacity and aerobic and resistance exercise using measures of systemic arterial oxygen saturation and regional skeletal muscle oxygen saturation. Exertional hypoxemia can be challenging to manage during exercise training in the ILD population due to significant arterial oxygen desaturation, and we described high oxygen requirements that increased over time with disease progression. An acute bout of interval endurance exercise at 100% of peak work rate for 30-second intervals was found to be feasible and preferred in individuals with advanced ILD, leading to less oxygen desaturation; and may be an alternate to constant load endurance exercise training in advanced ILD. Regional skeletal muscle deoxygenation occurred at low workloads of incremental resistance limb loading, however this was not reflected in measurements of systemic arterial oxygen saturation. Attenuated local blood volume redistribution to active muscles during lower limb resistance exercise was found and may be indicative of peripheral muscle dysfunction. Further research on the effects of hypoxemia and exercise on oxygen delivery and utilization of peripheral skeletal muscle function is warranted to optimize function and provide guidelines for safe, feasible and effective exercise and supplemental oxygen prescription in the ILD population.
References


Appendix 1: Ethics approval letters for studies 1-3

Notification of REB Approval for Access to Retrospective Data for Research Purposes

Date: July 3rd, 2015
To: [Redacted]

Re: 15-9293-BE
Relationship of Oxygen Requirements to Exercise Capacity and Training in Interstitial Lung Disease

REB Review Type: Expedited
REB Initial Approval Date: July 3rd, 2015
REB Expiry Date: July 3rd, 2016

Documents Approved:
Protocol Version date: June 25th, 2015
Data Collection Form Version date: June 25th, 2015

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada. The approval and the views of the REB have been documented in writing.

Furthermore, members of the Research Ethics Board who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

Best wishes on the successful completion of your project.

Sincerely,

[Redacted]

Co-Chair, University Health Network Research Ethics Board
PROTOCOL REFERENCE # 31935

July 23, 2015

DEPT OF PHYSICAL THERAPY
FACULTY OF MEDICINE

DEPT OF PHYSICAL THERAPY
FACULTY OF MEDICINE

Dear [Name]

Re: Administrative Approval of your research protocol entitled, "Relationship of oxygen requirements to exercise capacity and training in interstitial lung disease"

We are writing to advise you that the Office of Research Ethics (ORE) has granted administrative approval to the above-named research protocol. The level of approval is based on the following role(s) of the University of Toronto (University), as you have identified with your submission and administered under the terms and conditions of the affiliation agreement between the University and the associated TAHSN hospital:

- Graduate Student research - hospital-based only
- Storage or analysis of De-identified Personal Information (data)

This approval does not substitute for ethics approval, which has been obtained from your hospital Research Ethics Board (REB). Please note that you do not need to submit Annual Renewals, Study Completion Reports or Amendments to the ORE unless the involvement of the University changes so that ethics review is required. Please contact the ORE to determine whether a particular change to the University’s involvement requires ethics review.

Best wishes for the successful completion of your research.

Yours sincerely,

REB Manager

OFFICE OF RESEARCH ETHICS
McMurrich Building, 12 Queen’s Park Crescent West, 2nd Floor, Toronto, ON M5S 1S8 Canada
Tel: +1 416 946-3273 • Fax: +1 416 946-3763 • ethics.review@utoronto.ca • http://www.research.utoronto.ca/orc/researchers-administrators/ethics
Date: April 11th, 2016
To: Rehabilitation Aimed at Muscle Performance (RAMP) Lab, Toronto Rehabilitation Institute, 55 University Avenue, Toronto, Ontario, Canada, M5G 2A2
Re: 16-5088-DE
Deoxygenation of Limb Muscles During Incremental Exercise in Persons with Interstitial Lung Disease

REB Review Type: Expedited
REB Initial Approval Date: April 11th, 2016
REB Expiry Date: April 11th, 2017
Documents Approved:
- Protocol
- Consent Form
- Data Collection Form
- Telephone Script
- Letter of Appreciation
- Recruitment Poster
- Recruitment E-mail
- Screening Questionnaire

Version date: March 13th, 2016
Version date: April 11th, 2016
Version date: March 23rd, 2016
Version date: March 13th, 2016
Version date: April 7th, 2016
Version date: March 13th, 2016
Version date: January 2nd, 2016

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Gui for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Div of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Device Regulations of Health Canada. The approval and the views of the REB have been documented in writing.

Furthermore, members of the Research Ethics Board who are named as Investigators in research studies participate in discussions related to, nor vote on such studies when they are presented to the REB.

Best wishes on the successful completion of your project.

Sincerely,

Co-Chair, University Health Network Research Ethics Board
September 9, 2016

DEPT OF PHYSICAL THERAPY
FACULTY OF MEDICINE

Dear [Name],

Re: Your research protocol entitled, "Deoxygenation of limb muscles during incremental exercise in persons with interstitial lung disease"

ETHICS APPROVAL

Original Approval Date: September 9, 2016
Expiry Date: September 8, 2017
Continuing Review Level: 1

We are writing to advise you that the Health Sciences Research Ethics Board (REB) has granted approval to the above-named research protocol under the REB's delegated review process. Your protocol has been approved for a period of one year and ongoing research under this protocol must be renewed prior to the expiry date.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events in the research should be reported to the Research Oversight and Compliance Office - Human Research Ethics Program as soon as possible.

Please ensure that you submit an Ethics Renewal Form or a Study Completion/Closure Report 15 to 30 days prior to the expiry date of your current ethics approval. Note that ethics renewals for studies cannot be accepted more than 30 days prior to the date of expiry.

If your research is funded by a third party, please contact the assigned Research Funding Officer in Research Services to ensure that your funds are released.

Please note, all approved research studies are eligible for a routine Post-Approval Review (PAR) site visit. If chosen, you will receive a notification letter from our office. For information on PAR, please see http://www.research.utoronto.ca/wp-content/uploads/documents/2014/09/PAR-Program-Description-R1.pdf

Best wishes for the successful completion of your research.

Yours sincerely,

[Signature]

REB Chair

Research Oversight and Compliance Office - Human Research Ethics Program
McMurrich Building, 12 Queen's Park Crescent West, 2nd Floor, Toronto, ON M5S 1S8 Canada
Tel: +1 416 946-3273 • Fax: +1 416 946-5763 • ethicsreview@utoronto.ca • http://www.research.utoronto.ca/licences/for-researchers-administrative-ethical-research-approval-systems
NOTIFICATION OF REB INITIAL APPROVAL

Date: May 16, 2017
To:  
Toronto General Hospital; 200 Elizabeth St., M5G 2C4; Toronto, Ontario, Canada
Re: 16-6345
High intensity interval versus moderate intensity continuous exercise in individuals with advanced interstitial lung disease.

REB Review Type: Full Board
REB Meeting Date(s): March 27, 2017
REB Initial Approval Date: May 16, 2017
REB Expiry Date: May 16, 2018

Documents Approved:

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<th>Version Date</th>
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<td>consent form</td>
<td>May 15, 2017</td>
<td>15-May2017</td>
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<tr>
<td>Data collection form</td>
<td>May 11, 2017</td>
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<tr>
<td>Protocol</td>
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<tr>
<td>Questionnaire-Dyspnea</td>
<td>February 24,</td>
<td>24-Feb2017</td>
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<td>descriptors</td>
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The University Health Network Research Ethics Board approves the above mentioned study as it has been found to comply with relevant research ethics guidelines, as well as the Ontario Personal Health Informatics Protection Act (PHIPA), 2004.

Best wishes on the successful completion of your project.

Sincerely,

Co-Chair, University Health Network Research Ethics Board

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement: ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada. The approval and the views of the REB have been documented in writing. The REB has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named in the letter. Furthermore, members of the Research Ethics Board who are named as investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.
Documents Currently Approved by the
University Health Network Research Ethics Board as of
May 16, 2017

CAPCR # 16-6345

High intensity interval versus moderate intensity continuous exercise in individuals with advanced interstitial lung disease.

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Dear Dr. Brooks and Ms. Lisa Wickerson,

Re: Administrative Approval of your research protocol entitled, "High intensity interval versus moderate intensity continuous exercise in individuals with advanced interstitial lung disease"

We are writing to advise you that the Office of Research Ethics (ORE) has granted administrative approval to the above-named research protocol. The level of approval is based on the following role(s) of the University of Toronto (University), as you have identified with your submission and administered under the terms and conditions of the affiliation agreement between the University and the associated TAHSN hospital:

- Graduate Student research - hospital-based only
- Storage or analysis of De-identified Personal Information (data)

This approval does not substitute for ethics approval, which has been obtained from your hospital Research Ethics Board (REB). Please note that you do not need to submit Annual Renewals, Study Completion Reports or Amendments to the ORE unless the involvement of the University changes so that ethics review is required. Please contact the ORE to determine whether a particular change to the University's involvement requires ethics review.

Best wishes for the successful completion of your research.

Yours sincerely,

[Signature]

REB Manager
Appendix 2: Informed consent forms for studies 2 and 3

CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

Study Title: High intensity interval versus moderate intensity continuous exercise in individuals with advanced interstitial lung disease

Introduction:

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

Background/Purpose:

People waiting for lung transplantation participate in exercise training to increase or maintain fitness for surgery. The exercise training program typically involves cycling for up to 20 minutes at a moderate intensity. The purpose of this study is to compare response (oxygen saturation levels and symptoms of breathlessness) and preference of two types of cycling exercise: 20 minutes of moderate intensity cycling and 20 minutes of cycling involving short periods of high intensity exercise combined with rest periods. About 18 people with interstitial lung disease waiting for a lung transplant and attending pulmonary rehabilitation at the University Health Network (UHN) will be in this study.
**Study Visits and Procedures:**

You will be required to attend **2 test and 2 exercise sessions** as part of this study. All study procedures will be performed at the University Health Network, Toronto General Site. These include:

1. **Test # 1: Resting electrocardiogram (ECG)** – this test involves measuring the electrical activity of your heart. Patches attached by wires to a machine will be put on your chest while you are lying down and the machine will record the pattern of your heart beats. This test will be performed in the lung transplant physiotherapy rehabilitation room. It should take 20 minutes and will be done up to one week before test # 2 to make sure there are no restrictions for exercise testing.

2. **Test # 2: Maximal cardiopulmonary exercise test (CPET)** – this test will be performed in the Pulmonary Function Lab by a trained technician to determine the highest amount of exercise you can achieve on a bicycle. You will pedal on a stationary bike initially with no wheel tension, followed by increasing tension every minute until you can no longer maintain a specific speed of pedaling, request to stop or are asked to stop. During this test the following measures will be monitored: oxygen saturation using a pulse oximeter, heart rate and rhythm using ECG, blood pressure, and symptoms of breathlessness and leg fatigue using the Borg scale. Blood lactate using finger-prick testing which involves taking a few drops of blood from your fingertip to look at how hard you are exercising will be performed once at the end of the test. A physician will be in the area during the testing for consultation if required, and will interpret the test afterwards. This test should take one hour.

3. **Exercise sessions** – you will perform two exercise sessions on a stationary bike on the same day, separated by at least one hour. These sessions will take place in the lung transplant physiotherapy rehabilitation room. One session (**High intensity interval exercise**) will involve cycling for 30 seconds at 100% of the highest amount of exercise
you reached on test # 2 alternating with 30 seconds of rest for a total of 20 minutes. The other session (Moderate intensity continuous exercise) will involve cycling for 20 minutes at 50% of the highest amount of exercise you reached on the test # 2. During both exercise sessions oxygen saturation and heart rate will be measured using a pulse oximeter. Blood lactate using finger-prick testing will be done twice (at the midpoint and the end) of each cycle exercise. Before and after the test blood pressure, respiratory rate, symptoms of shortness of breath and leg fatigue using the Borg scale will be measures. You will answer a questionnaire to describe the breathlessness you experienced during the exercise. After you have completed both exercise sessions we will ask you to pick your preference of exercise sessions. Each session will take 30 minutes, and the total time will be two hours.

**Risks:**

Taking part in this study has risks. Some of the risks we know about. There is a possibility of risks that we do not know about and have not been seen in people to date. Please call the study investigator if you have any side effects even if you do not think it has anything to do with this study.

The risks we know of are:

- Muscle soreness or fatigue during the exercise or the next two days. These are common and normal response to muscle testing and exercise and should not affect your daily activities. The fatigue will recover after 1 or 2 hours, and any muscle soreness should disappear in 1 or 2 days following the test and/or exercise.
- Risk of cardiac events during the CPET and the exercise sessions. Since you will have a resting ECG prior to the exercise test and sessions, your heart rate will monitored and the sessions will be performed by a trained professionals using standardized guidelines, these risks are low (< 1%).
- Infection, pain, or bruising from blood lactate finger-prick blood testing. As this testing only involves a few drops of blood using a very small needle and will be done by a person trained in finger-prick testing according to UHN infection control guidelines, the risks are low.

**Benefits:**

You will not receive direct benefit from being in this study. Information learned from this study may help other people with interstitial lung disease and people waiting for lung transplantation in the future.

**Reminders and Responsibilities:**

It is required that you refrain from alcohol, caffeine and excessive physical activity 12 hours prior to the CPET and the exercise sessions. Also minimize fluid consumption 4 hours prior to each of the study visits.

**Confidentiality:**

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

- Name
- New or existing medical records that includes types, dates and results of medical tests or procedures
The information that is collected for the study will be kept in a locked and secure area by the study investigator for 10 years. Only the study team will be allowed to look at your records. Your participation in this study also may be recorded in your medical record at UHN. Representatives from the UHN 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, and only group findings will be made public.

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

**Voluntary Participation:**

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study and then change your mind later. You may leave the study at any time without it affecting your care.

**Costs and Reimbursement:**

You may incur costs for participating in this study such as transportation or parking expenses. Although we cannot reimburse these costs, you will receive a $20.00 gift card to Indigo to compensate for your time.
Rights as a Participant:

If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost.

By signing this form you do not give up any of your legal rights against the investigators, sponsor or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.

Conflict of Interest:

The researchers have an interest in completing the study. Their interest should not influence your decision to participate in this study.

Questions about the Study:

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 (UHN REB) or the Research Ethics office number at XXXXXXXX. The REB is a group of people who oversee the ethical conduct of research studies. The UHN REB is not part of the study team. Everything that you discuss will be kept confidential.

You will be given a signed copy of this consent form.

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 the use of my information as described in this form. I agree to take part in this study.
Print Study Participant’s Name  Signature  Date

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
Study Title: Deoxygenation of limb muscles during incremental exercise in persons with interstitial lung disease.

Introduction:

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

Background/Purpose:

People with interstitial lung disease often experience a drop in blood oxygen levels during exercise. The purpose of this study is to determine if and when oxygen levels drop in arm and leg muscles during exercise using near infrared spectroscopy (NIRS), a non-invasive technique. About 40 people with interstitial lung disease attending medical clinics or pulmonary rehabilitation at the University Health Network (UHN) and 20 people without lung disease will be in this study.

Study Visits and Procedures:
You will be required to attend **one 2 hour session** as part of this study. The study procedures will be performed at the Rehabilitation Science Building, University of Toronto located at 500 University Ave, Toronto. These include:

1. **Spirometry** (only for participants without lung disease): This standardized test is widely used to measure lung function. You will be asked to breathe in deeply and then blow into a mouthpiece connected to a tube as hard and as long as you can until your lungs empty completely (approximately 2-6 seconds).

2. **Questionnaire on participation in physical activity** (only for participants without lung disease):

   You will fill out a questionnaire to describe your current health conditions.

3. **Anthropometric measures**: We will assess your height and weight using a doctor’s scale. We will measure skinfold thickness and muscle size using ultrasound over your arm, thigh and palm using a small probe. This involves putting a small amount of water soluble gel on the measurement areas and then gliding a probe over the area.

4. **Arm and leg strength and performance**: We will test your muscle strength and performance during two separate tests using a Biodex dynamometer while seated. This is a sophisticated computerized weight lifting device. Both tests will be done on your dominant side (the arm that you use to write and the leg that you would kick a ball) with a 30 minute rest in-between.

   **Arm test** – You will first be asked to flex your elbow against the Biodex arm cuff as hard as you can for 3 to 5 repetitions. The machine will record your maximum level of strength. Second, you will be asked to perform a repetitive exercise of flexing your elbow...
against gradually increasing resistance. Lastly, you will be asked to pull against the cuff as hard as you can for 10 seconds.

**Leg test** – You will repeat the same procedures as the arm test, however you will be asked to push (straighten) your knee against the Biodex leg cuff.

5. **Measures of muscle oxygenation**: During the strength tests described above, you will have 3 small devices taped to your arm, thigh and palm. These devices shine infrared light through your tissue to measure the oxygen level in your muscle. You will not feel any sensation from these devices and the devices are harmless. Hair will be shaved around the area (if required) and cleaned with an alcohol swab. The 3 devices will be attached with skin sensitive, hypoallergenic tape.

**Risks:**

Taking part in this study has risks. Some of the risks we know about. There is a possibility of risks that we do not know about and have not been seen in people to date. Please call the study
investigator if you have any side effects even if you do not think it has anything to do with this study.

The risks we know of are:

- Muscle soreness or fatigue during the exercise or the next day. These are normal response to muscle testing and should not affect your daily activities. The fatigue will recover after 1 or 2 hours, and any muscle soreness should disappear in 1 or 2 days following the test.
- Lightheadedness after performing several breathing tests. These effects are rare and usually temporary, and tend to disappear without any treatment.
- Allergic reaction to adhesive tape (rare) because we will use a hypoallergenic tape. If you have allergies to adhesive tapes, you should not participate in the study.

**Benefits:**

You will not receive direct benefit from being in this study. Information learned from this study may help other people with interstitial lung disease in the future.

**Reminders and Responsibilities:**

It is your responsibility to bring shorts to wear. It is also required that you refrain from alcohol, caffeine and excessive physical activity 12 hours prior to the visit. Also minimize fluid consumption 4 hours prior to the study visit.

**Confidentiality:**

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

- Name
- Date of birth
- New or existing medical records that includes types, dates and results of medical tests or procedures

The information that is collected for the study will be kept in a locked and secure area by the study investigator for 10 years. Only the study team will be allowed to look at your records. Your participation in this study also may be recorded in your medical record at UHN (for participants with interstitial lung disease). Representatives from the UHN 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, and only group findings will be made public.

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

**Voluntary Participation:**
Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study and then change your mind later. You may leave the study at any time without it affecting your care.

**Costs and Reimbursement:**

You may incur costs for participating in this study such as transportation or parking expenses. Although we cannot reimburse these costs, you will receive a $35.00 gift card to Shoppers Drug Mart or Tim Horton’s to compensate for your time.

**Rights as a Participant:**

If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost.

By signing this form you do not give up any of your legal rights against the investigators, sponsor or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.

**Conflict of Interest:**

The researchers have an interest in completing the study. Their interest should not influence your decision to participate in this study.

**E-mail disclaimer:**
Please note that the security of email is not guaranteed. Messages may be forged, forwarded or kept indefinitely by others using the internet. Do not use the e-mail to discuss information you think is sensitive. Do not use e-mail in an emergency since e-mail may be delayed.

**Questions about the Study:**

If you have any questions, concerns or would like to speak to the study team for any reason, please call: XXXXXX at XXXXXXXXX or email XXXXXXXX.

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 (UHN REB) or the Research Ethics office number at XXXXXXXX. The REB is a group of people who oversee the ethical conduct of research studies. The UHN REB is not part of the study team. Everything that you discuss will be kept confidential.

You will be given a signed copy of this consent form.

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 the use of my information as described in this form. I agree to take part in this study.

_________________________  ___________________  ___________
Print Study Participant’s Name   Signature   Date
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
## Appendix 3: Estimated FiO$_2$ based on oxygen delivery system and flow rate (Study 1)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Estimated FiO$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regular nasal prongs</strong></td>
<td>1lpm</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>2lpm</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>3lpm</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>4lpm</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>5lpm</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>6lpm</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>High-flow nasal prongs</strong></td>
<td>6lpm</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>7lpm</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>8lpm</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>10lpm</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>12lpm</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>15lpm</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>oxymizers</strong></td>
<td>4lpm</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>6lpm</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>8lpm</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>10lpm</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>12lpm</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>15lpm</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Venturi</strong></td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Oxymask</strong></td>
<td>4lpm</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>5lpm</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>6lpm</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>7lpm</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>8lpm</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>10lpm</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>12lpm</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>15lpm</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Non-rebreather mask</strong></td>
<td>10lpm</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>12lpm</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>15lpm</td>
<td>0.75</td>
</tr>
</tbody>
</table>

**Abbreviations:** lpm: litres per minute; FiO$_2$: fraction of inspired oxygen

FiO$_2$ estimates for nasal prongs ≤ 6L/min was done using the following equation: \( \text{FiO}_2 = 0.2 + (\text{litre flow}) \times 0.04. \)\(^80\)

Estimated FiO$_2$ based on oxygen delivery system and flow rate.\(^75-80\) Specifically, regular (> 6L/min) and high-flow nasal prongs FiO$_2$ estimates were based on a study by Wettstein et al 2005\(^75\) where the delivered pharyngeal FiO$_2$
was measured by inserting a nasal catheter behind the uvula and attaching it to an oxygen gas analyzer. Healthy people were told to breathe at their normal rate and at double their normal rate. The latter estimates (for rapid breathing) were used as people with ILD exhibit a rapid shallow breathing pattern during exertion. For the Oxymizer, the same values as the high-flow nasal prongs, as the oxygen savings for the Oxymizer decrease when on higher than 5L per minute flow. The Venturi mask is a fixed performance device so the FiO₂ values were taken from the manufacturer. For the oxymask the lower end of the FiO₂ range provided by the supplier was taken for a conservative estimate. For the non-rebreather mask values were calculated by Garcia et al 2005 76 who used a gas analyzer to measure delivered FiO₂.

High-flow nasal prongs refers to nasal prongs used to deliver up to 15 litres per minute of oxygen flow providing a variable FiO₂ and not the humidified high-flow nasal prongs that utilize an air blender and heated circuit to deliver a fixed FiO₂.
Appendix 4: Measures of central tendency and dispersion of \( \text{FiO}_2 \) (Study 1)

Baseline to 4 weeks \((n=375)\)

Baseline to 6 months \((n=196)\)
## Appendix 5: Resting and exertional oxygen requirements at baseline and four weeks (n=375). *(Study 1)*

### Baseline resting and exertional oxygen requirements (n=375)

<table>
<thead>
<tr>
<th>Resting oxygen requirement *</th>
<th>N (%), median (IQR) or range</th>
<th>Exertional oxygen requirement*</th>
<th>N (%), median (IQR) or range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery system:</td>
<td></td>
<td>Delivery system:</td>
<td></td>
</tr>
<tr>
<td>Room air</td>
<td>114 (30%)</td>
<td>Room air</td>
<td>19 (5%)</td>
</tr>
<tr>
<td>Nasal cannulae</td>
<td>225 (60%)</td>
<td>Nasal cannulae</td>
<td>175 (47%)</td>
</tr>
<tr>
<td>Oxymizer</td>
<td>28 (8%)</td>
<td>Oxymizer</td>
<td>26 (7%)</td>
</tr>
<tr>
<td>Venturi mask</td>
<td>1 (0.2%)</td>
<td>Venturi mask</td>
<td>55 (14.5%)</td>
</tr>
<tr>
<td>Oxymask</td>
<td>5 (1.3%)</td>
<td>Oxymask</td>
<td>23 (6%)</td>
</tr>
<tr>
<td>Non-rebreather mask</td>
<td>2 (0.5%)</td>
<td>Non-rebreather mask</td>
<td>77 (20.5%)</td>
</tr>
<tr>
<td>Flow rate (LPM)</td>
<td>1-12</td>
<td>Flow rate (LPM)</td>
<td>1-15</td>
</tr>
<tr>
<td>Estimated FiO₂</td>
<td>0.32 (0.28-0.40)</td>
<td>Estimated FiO₂</td>
<td>0.5 (0.40-0.60)</td>
</tr>
</tbody>
</table>

### 4 week resting and exertional oxygen requirements (n=375)

<table>
<thead>
<tr>
<th>Resting oxygen requirement *</th>
<th>N (%), median (IQR) or range</th>
<th>Exertional oxygen requirement*</th>
<th>N (%), median (IQR) or range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery system:</td>
<td></td>
<td>Delivery system:</td>
<td></td>
</tr>
<tr>
<td>Room air</td>
<td>109 (29%)</td>
<td>Room air</td>
<td>15 (4%)</td>
</tr>
<tr>
<td>Nasal cannulae</td>
<td>233 (62.3%)</td>
<td>Nasal cannulae</td>
<td>144 (38.5%)</td>
</tr>
<tr>
<td>Oxymizer</td>
<td>23 (6%)</td>
<td>Oxymizer</td>
<td>25 (6.5%)</td>
</tr>
<tr>
<td>Venturi mask</td>
<td>1 (0.2%)</td>
<td>Venturi mask</td>
<td>61 (16.5%)</td>
</tr>
<tr>
<td>Oxymask</td>
<td>7 (2%)</td>
<td>Oxymask</td>
<td>27 (7%)</td>
</tr>
<tr>
<td>Non-rebreather mask</td>
<td>2 (0.5%)</td>
<td>Non-rebreather mask</td>
<td>103 (27.5%)</td>
</tr>
<tr>
<td>Flow rate (LPM)</td>
<td>1-12</td>
<td>Flow rate (LPM)</td>
<td>1-15</td>
</tr>
<tr>
<td>Estimated FiO₂</td>
<td>0.32 (0.28-0.40)</td>
<td>Estimated FiO₂</td>
<td>0.50 (0.4-0.73)</td>
</tr>
</tbody>
</table>
### Appendix 6: Resting and exertional oxygen requirements at baseline and six months (n=196). *(Study 1)*

**Baseline resting and exertional oxygen requirements (n=196)**

<table>
<thead>
<tr>
<th>Delivery system:</th>
<th>Resting oxygen requirement *</th>
<th>N (%), median (IQR) or range</th>
<th>Exertional oxygen requirement*</th>
<th>Delivery system:</th>
<th>N (%), median (IQR) or range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Room air</td>
<td>70 (36%)</td>
<td>Room air</td>
<td>9 (4.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nasal cannulae</td>
<td>116 (59%)</td>
<td>Nasal cannulae</td>
<td>116 (59%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxymizer</td>
<td>9 (4.5%)</td>
<td>Oxymizer</td>
<td>13 (7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Venturi mask</td>
<td>1 (0.05%)</td>
<td>Venturi mask</td>
<td>28 (14.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxymask</td>
<td>0 (0%)</td>
<td>Oxymask</td>
<td>12 (6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-rebreather mask</td>
<td>0 (0%)</td>
<td>Non-rebreather mask</td>
<td>18 (9%)</td>
<td></td>
</tr>
<tr>
<td>Flow rate (LPM)</td>
<td>1-10</td>
<td></td>
<td>Flow rate (LPM)</td>
<td>2-15</td>
<td></td>
</tr>
<tr>
<td>Estimated FiO₂</td>
<td>0.30 (0.21-0.36)</td>
<td></td>
<td>Estimated FiO₂</td>
<td>0.44 (0.36-0.50)</td>
<td></td>
</tr>
</tbody>
</table>

**6 month resting and exercise FiO₂ (n=196)**

<table>
<thead>
<tr>
<th>Delivery system:</th>
<th>Resting oxygen requirement *</th>
<th>N (%), median (IQR) or range</th>
<th>Exertional oxygen requirement*</th>
<th>Delivery system:</th>
<th>N (%), median (IQR) or range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Room air</td>
<td>48 (24.5%)</td>
<td>Room air</td>
<td>8 (4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nasal cannulae</td>
<td>136 (69.5%)</td>
<td>Nasal cannulae</td>
<td>73 (37%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxymizer</td>
<td>8 (4%)</td>
<td>Oxymizer</td>
<td>12 (6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Venturi mask</td>
<td>2 (1%)</td>
<td>Venturi mask</td>
<td>35 (18%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxymask</td>
<td>2 (1%)</td>
<td>Oxymask</td>
<td>16 (8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-rebreather mask</td>
<td>0 (0%)</td>
<td>Non-rebreather mask</td>
<td>54 (27%)</td>
<td></td>
</tr>
<tr>
<td>Flow rate (LPM)</td>
<td>1.5-10</td>
<td></td>
<td>Flow rate (LPM)</td>
<td>2-15</td>
<td></td>
</tr>
<tr>
<td>Estimated FiO₂</td>
<td>0.32 (0.28-0.40)</td>
<td></td>
<td>Estimated FiO₂</td>
<td>0.50 (0.40-0.75)</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 7: Correlation between baseline FiO$_2$, 6-minute walk distance and treadmill training (n=375). (Study 1)

- Baseline 6MWD (m)
  - $r = -0.4$
  - $p < 0.0001$

- Baseline METS
  - $r = -0.24$
  - $p < 0.001$
Appendix 8: Correlation between 4 week FiO₂, 6-minute walk distance and treadmill training (n=375). (Study 1)

4 week 6MWD (m) vs. 4 week FiO₂

$r = -0.42$

$p < 0.0001$

4 week METS vs. 4 week FiO₂

$r = -0.31$

$p < 0.0001$
Appendix 9: Correlation between 6 month FiO$_2$, 6-minute walk distance and treadmill training (n=196). (Study 1)

\[ r = 0.36 \]
\[ p < 0.0001 \]

\[ r = 0.35 \]
\[ p < 0.0001 \]
**Appendix 10:** Correlation between change in FiO₂ and change in 6-minute walk distance and training METS at 4 weeks and 6 months (Study 1)

![Graphs showing correlation between change in FiO₂ and change in 6MWD and METS at 4 weeks and 6 months.](image)

- **4 weeks:**
  - ΔFiO₂ vs. Δ6MWD (m): $r=0.02, p=0.8$
  - ΔFiO₂ vs. ΔMETS: $r=-0.05, p=0.42$

- **6 months:**
  - ΔFiO₂ vs. Δ6MWD (m): $r=-0.26, p=0.0008$
  - ΔFiO₂ vs. ΔMETS: $r=-0.13, p=0.08$
Appendix 11: Change in FiO$_2$ vs. no change at 4 weeks and 6 months. (Study 1)

<table>
<thead>
<tr>
<th></th>
<th>Baseline to 4 weeks</th>
<th>Baseline to 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>375</td>
<td>196</td>
</tr>
<tr>
<td>Baseline FiO$_2$ 0.75*</td>
<td>71 (19%)</td>
<td>16 (8%)</td>
</tr>
<tr>
<td>Change in FiO$_2$ **</td>
<td>109 (36%)</td>
<td>114 (63%)</td>
</tr>
<tr>
<td>No change in FiO$_2$ **</td>
<td>195 (64%)</td>
<td>66 (37%)</td>
</tr>
<tr>
<td></td>
<td>(n=304)</td>
<td>(n=180)</td>
</tr>
</tbody>
</table>

* A FiO$_2$ is the highest level of oxygen requirement delivered in the outpatient rehabilitation setting, therefore no further change (e.g. increase) can occur.

** excluding people with a baseline FiO$_2$ of 0.75.
Appendix 12: Interval and continuous exercise matched for total work (time x workload). (Study 2)

Example: peak work rate 100 W

<table>
<thead>
<tr>
<th>Interval</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm-up:</td>
<td>Warm-up:</td>
</tr>
<tr>
<td>1 min @ 25 W</td>
<td>1 min @ 25 W</td>
</tr>
<tr>
<td>Exercise:</td>
<td>Exercise:</td>
</tr>
<tr>
<td>9.5 mins @ 100 W (950 W)</td>
<td>19 mins @ 50 W (950 W)</td>
</tr>
<tr>
<td>9.5 mins 0 W</td>
<td></td>
</tr>
</tbody>
</table>

Total 975 W      Total 975 W

* Pedaling speed at 50 rpm for both exercise bouts
Appendix 13: Dyspnea descriptors \(^{104}\) (Study 2)

Which phrases best describe the awareness of your breathing:

*My breath does not go in all the way*

*My breathing requires effort*

*I feel that I am suffocating*

*I feel a need for more air*

*My breathing is heavy*

*I cannot take a deep breath in*

*My chest feel tight*

*My breathing requires more work*

*I feel that my breathing is rapid*

*My breathing is shallow*

*I feel that I am breathing more air*

*I cannot get enough air in*

*My breath does not go out all the way*

**The best 3 descriptors (best descriptor first)**

At rest:

___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________

At the end of exercise:

___________________________________________________________________________
___________________________________________________________________________

Dyspnea descriptors were clustered as follows: \(^{104}\)
Cluster name/ descriptor

Increased work/ effort
   My breathing requires more work
   My breathing requires effort

Unrewarded inspiration
   My breath does not go in all the way
   I feel a need for more air
   I cannot get enough air in

Inspiratory difficulty
   My breath does not go in all the way
   I cannot take a deep breath in

Heavy
   My breathing is heavy
   I feel that I am breathing more air

Shallow
   My breathing is shallow

Rapid
   I feel that my breathing is rapid

Tight chest
   My chest feels tight

Expiratory difficulty
   My breath does not go out all the way

Suffocating
   I feel that I am suffocating
**Appendix 14: Effect of the order of testing (Study 2)**

<table>
<thead>
<tr>
<th></th>
<th>Interval</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadir $\text{SpO}_2$</td>
<td>91</td>
<td>87</td>
</tr>
<tr>
<td>Drop $\text{SpO}_2$</td>
<td>8.5</td>
<td>13</td>
</tr>
<tr>
<td>Peak HR</td>
<td>117</td>
<td>130</td>
</tr>
<tr>
<td>End leg fatigue</td>
<td>4.5</td>
<td>5</td>
</tr>
<tr>
<td>Change lactate</td>
<td>3.2</td>
<td>5.3</td>
</tr>
<tr>
<td>More overall effort/ dyspnea</td>
<td>n=1</td>
<td>n=3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Interval</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadir $\text{SpO}_2$</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>Drop $\text{SpO}_2$</td>
<td>8</td>
<td>9.5</td>
</tr>
<tr>
<td>Peak HR</td>
<td>129</td>
<td>135</td>
</tr>
<tr>
<td>End leg fatigue</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Change lactate</td>
<td>1.1</td>
<td>2.8</td>
</tr>
<tr>
<td>More overall effort/ dyspnea</td>
<td>n=1</td>
<td>n=4</td>
</tr>
</tbody>
</table>
Appendix 15: Participant screening questionnaire for healthy controls (Study 3)

The American Heart Association and the American College of Sports Medicine Health/Fitness Facility Pre-participation Screening Questionnaire

Assess your health status by marking all TRUE statements

History

You have had:

- [ ] a heart attack
- [ ] heart surgery
- [ ] cardiac catheterization
- [ ] coronary angioplasty (PTCA)
- [ ] pacemaker/implantable cardiac defibrillator/ rhythm disturbance
- [ ] heart valve disease
- [ ] heart failure
- [ ] heart transplantation
- [ ] congenital heart disease

Symptoms

- [ ] You experience chest discomfort with exertion
- [ ] You experience unreasonable breathlessness
- [ ] You experience dizziness, fainting, or blackouts
- [ ] You take heart medications.

Other health issues

- [ ] You have diabetes
- [ ] You have asthma or other lung disease
<table>
<thead>
<tr>
<th>Physical Signs Suggestive of Cardiovascular, Respiratory or Metabolic Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shortness of breath</strong> at rest, with mild exertion, while lying flat or at night</td>
</tr>
</tbody>
</table>

---

Ankle edema – bilaterally or unilaterally. May be indicative of heart failure, venous insufficiency, lymphatic blockage or thrombosis

Palpitations or tachycardia – see Chapter 12 for details of arrhythmias.

Intermittent claudication – pain that occurs with exertion

Unusual fatigue or shortness of breath – with usual activities

**Interpretation**

- **Low risk (young [men< 45 years; women< 55 years], and no more than 1 cardiovascular risk factor):** can do maximal testing or enter a vigorous exercise program with minimal supervision;

- **Moderate risk (older, or 2 or more cardiovascular risk factors):** can do submaximal testing or enter a moderate exercise program with some monitoring or minimal supervision. If maximal exercise testing is warranted, the presence of a highly trained health professional or physician is recommended. The amount of monitoring and level of supervision might be tempered by other characteristics and lifestyle habits of the patient that is screened.

- **High risk (the presence of a known cardiovascular, pulmonary or metabolic disease or one or more signs/symptoms that is suggestive of these diseases):** requires the presence of a highly trained health professional or physician to monitor and ensure safety during exercise testing and the initial stages of training.

**COMMENTS**
Appendix 16: Participant flow chart for severe ILD recruited from the Toronto Lung Transplant Program, University Health Network (Study 3)

Listed for LTx
n=64

Eligible
n=29

Consent
n=18

Tested
n=13

Transplanted in < 4 weeks n=6
Listed as rapidly deteriorating n=9
Inpatient n=3
Died in first 4 weeks of listing n=1
Listed for re-transplant n=3
Listed for lung/liver transplant n=1
MSK issues n=7
BMI n=5

Travel issues n=8
Taken off transplant list/ on hold n=2
New MSK issue n=1

Called for transplant n=3
Withdrew consent n=1 (too busy)
No show n=1
Appendix 17: Participant flow chart for mild/moderate ILD recruited from the ILD clinic, University Health Network (Study 3)

4 clinics  
$n=110$

Eligible  
$n=28$

Approached  
$n=16$

Consent  
$n=14$

Tested  
$n=10$

Myositis/ RA  $n=23$
BMI  $n=18$
Age  $n=15$
On oxygen  $n=7$
Other medical  $n=3$
New/ Other study recruitment  $n=15$
No ILD  $n=1$

Not interested  $n=2$
MD forgot to ask  $n=4$
Patient left before approached  $n=3$
No show at clinic  $n=3$

Lives too far away  $(n=1)$
Too busy  $(n=1)$

Withdraw consent  $n=1$
No follow-up  $n=1$
Cancelled appointment  $n=2$
Appendix 18: Reasons for task failure (Study 3)

<table>
<thead>
<tr>
<th></th>
<th>Healthy (n=13)</th>
<th>Mild ILD (n=10)</th>
<th>Severe ILD (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KEL</td>
<td>EFL</td>
<td>KEL</td>
</tr>
<tr>
<td>ROM or velocity *</td>
<td>12</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Ask to stop/ symptoms **</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Excessive muscle compensation</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* KEL failure was inability to maintain full ROM  
  EFL failure was inability to maintain contraction velocity

** reasons for requests to stop were leg discomfort or sore arm/wrist