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Cardiopulmonary fitness, its relationship to dyspnea and the effect of high-intensity training among lung transplant recipients

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Abstract

Background: Cardiorespiratory fitness (CRF) remains low after lung transplantation (LTx) despite improvement in pulmonary function. The knowledge about the association to dyspnea is unclear and the effect of high-intensity training (HIT) has so far not been investigated in this group.

Aims: To study the effect of a 20-week HIT program on peak oxygen uptake (VO_{2peak}), as our primary outcome, and pulmonary function. In addition, we want to evaluate VO_{2peak} and pulmonary function at least six months after LTx, and to investigate the association to dyspnea.

Methods: In a randomized controlled trial, bilateral LTx recipients (age 20-67 years) underwent pulmonary function tests, for measurements of forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), diffusing capacity of the lung for carbon monoxide (DL_{CO}), total lung capacity (TLC) and maximum voluntary ventilation (MVV). VO_{2peak} was assessed by a maximal treadmill exercise test, and dyspnea was evaluated with the modified Medical Research Council (mMRC) dyspnea score. The association between FEV_1, DL_{CO}, VO_{2peak} and dyspnea were assessed by Spearman's correlation coefficient. All patients were randomized to either HIT or usual care. The exercise training was individually tailored one to one, and consisted of high intensity endurance- and resistance training, with three sessions per week for 20 weeks.

Results: Forty-eight LTx recipients completed post-transplant measurements 29±16 months after LTx. Pulmonary function were within normal limits for FVC (89±21% pred), FEV_1 (80±24% pred), TLC (90±15% pred) and MVV (93±23% pred), whereas DL_{CO} was impaired (66±15% pred). VO_{2peak}, adjusted for weight ($mL \cdot kg^{-1} \cdot min^{-1}$), was 65±15% of predicted. There was a moderate correlation between VO_{2peak} and FEV_1 ($r=0.555$, $p<0.001$), between VO_{2peak} and dyspnea ($r=-0.437$, $p=0.002$) and between FEV_1 and dyspnea ($r=-0.316$, $p=0.030$). Twenty-one patients completed the exercise training intervention. Intention-to-treat analysis showed that the exercise group had a greater increase in the absolute VO_{2peak} in % of predicted (between-group difference of 5.1 in percent of predicted, $p=0.035$). There were no significant between-group

differences in change in pulmonary function; FVC (p=0.253), FEV_1 (p=0.450), DL_{CO} (p=0.331) and MVV (p=0.844).

Conclusion: The LTx recipients demonstrated a low cardiorespiratory fitness, despite an almost normalized pulmonary function. The associations between pulmonary function, VO_{2peak} and dyspnea were moderate. HIT induced improvements in VO_{2peak}. Further investigations with a sufficient sample size are needed to elucidate the effect of high intensity training in lung transplant recipients.

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Abbreviations

BLT	Bilateral lung transplant
BOS	Bronchiolitis obliterans syndrome
BR	Breathing reserve
CF	Cystic fibrosis
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
CRF	Cardiorespiratory fitness
DL_{CO}	Diffusing capacity of the lung for carbon monoxide ($mmol \cdot kpa^{-1} \cdot min^{-1}$)
ECG	Electrocardiography
FEV_1	Forced expiratory volume after 1 second (L)
FVC	Forced vital capacity (L)
Hb	Hemoglobin
HILT	High-intensity training following lung transplantation
HIT	High-intensity training
HR_{max}	Maximal heart rate ($beat \cdot min^{-1}$)
HTx	Heart transplantation
ISHLT	The international society for heart and lung transplantation
$[La^+]$	Blood lactate concentration
LTx	Lung transplantation
mMRC	modified Medical Research Council
MVV	Maximal voluntary ventilation ($L \cdot min^{-1}$)
OUS	Oslo University Hospital
PFT	Pulmonary function test
Q	Cardiac output
QoL	Quality of life

RAS	Restrictive allograft syndrome
RCT	Randomized controlled trial
RER	Respiratory exchange ratio
RPE	Rated perceived exertion
SD	Standard deviation
SLT	Single lung transplant
TLC	Total lung capacity
VO_2	Oxygen uptake ($mL \cdot kg^{-1} \cdot min^{-1}$ or $L \cdot min^{-1}$)
VO_{2max}	Maximal oxygen uptake
VO_{2peak}	Peak oxygen uptake, used when defined criteria for maximum effort is not fulfilled

1. Introduction

Lung transplantation (LTx) is a potentially life-saving therapy for nearly 5000 patients with end-stage lung disease worldwide each year. There has been an upward trend for overall LTx activity over the last several decades, with stable activity the three last years (1). Surgical and medical advancements have resulted in changes regarding the selection of candidates, where adults of older age, with functional limitations and co-morbidities, now can more frequently be transplanted (2). This may have important implications regarding outcomes and the patients' expectations (1).

After successful transplantation, reduced exercise capacity and quality of life (QoL) often persist for several years despite a normalization of pulmonary function (3, 4). This may be caused by dysfunction in the muscle/skeletal system and impaired cardiorespiratory fitness (CRF) due to prolonged inactivity (5-8). Low CRF in general are associated with ''all-cause'' mortality among individuals with chronic obstructive pulmonary disease (COPD)(9) and in LTx patients (5). This provides a rationale for structured exercise training after LTx. A high CRF can improve QoL (10), prevent mortality (9), and prevent lifestyle diseases (11).

To my knowledge, only two randomized controlled trials (RCT) have evaluated the effect of exercise training on peak oxygen uptake (VO_{2peak}) after LTx (12, 13), and only one study has assessed the change in pulmonary function after such an intervention (12). None were sufficiently powered (10), and the $VO_{2peak}$was only estimated and not directly measured despite the clinical significance of maximum oxygen uptake (VO_{2max})(14, 15). In addition, the exercise training interventions was short, and the training intensity used was moderate (12) or not reported (13). Interestingly, in lung cancer patients and heart transplant recipients, it has been observed that high intensity training (HIT) was well tolerated and increased the patient's VO_{2peak} significantly (16, 17). There is thus a need for a sufficiently powered RCT of HIT to inform evidence-based guidelines for exercise training programs post LTx.

1.1 Aims

The following objectives and aims are addressed in this master thesis:

1. To determine the pulmonary function and cardiorespiratory fitness among stable lung transplant recipients
2. To investigate the association between pulmonary function, peak oxygen uptake and dyspnea among lung transplant recipients
3. To evaluate the effects of a 20-week high-intensity training program on peak oxygen uptake, as primary outcome, and pulmonary function among lung transplant recipients

2. Background information

This chapter will provide an overview of the theory that is relevant to elucidate the aims, as well as the concepts and definitions relevant to this thesis. First, an introduction is given to LTx. Furthermore, relevant lung- anatomy and physiology; pulmonary function, physical fitness, dyspnea and the effect of exercise after LTx are presented.

2.1 Lung transplantation

In 1963, James Hardy performed the first human LTx in Mississippi, USA. However, long-term survival was poor for several decades, due to the lack of effective immunosuppressive therapy, which first was developed in the 1980s. The first bilateral LTx, also called double lung transplant, in Norway was performed at Rikshospitalet in 1991 (18). In recent years, about 30-35 LTx have been performed each year (19), depending on available organs. Survival is increasing, and five-year survival in Norway is today 70% (figure 1) (18).

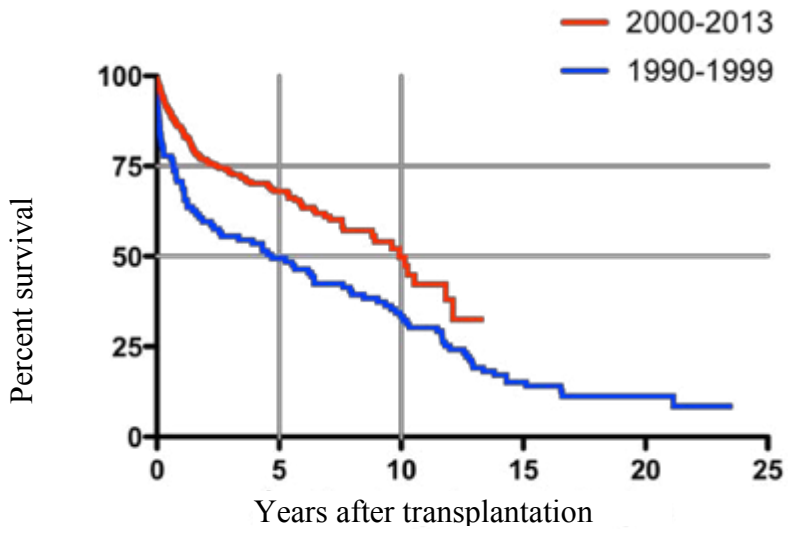

Figure 1: *Survival after LTx in Norway, for patients transplanted in the period 1990-1999 (blue curve) and 2000-2013 (red curve) (18, p23).*

2.1.1 Recipient selection

LTx is considered for patients with chronic, end-stage lung disease with a progressive decline in pulmonary function despite maximal medical treatment (20). Candidates have a high risk of death within the two upcoming years (20), and are symptomatic during activities of daily living (21). Candidates are evaluated through a thorough pre-

transplant screening, with different scoring systems around the world for prioritizing patients with the greatest anticipated benefit on the basis of the native disease and its severity (20).

According to the International Society for Heart and Lung Transplantation (ISHLT) registry (22), the most common primary indication for undergoing LTx is COPD (in practice emphysema) which accounts for more than one third of all transplants (33%)(1). COPD is a progressive condition, where most patients have a long history of cigarette smoking (23). The second most common indication is interstitial lung disease, including idiopathic pulmonary fibrosis (IPF) (30%), followed by bronchiectasis, including cystic fibrosis (CF)(16%), pulmonary arterial hypertension (4.4 %) and others (1). Despite the increase in performed LTx, there is still a gap between the demand and the availability of organs. Because of this, there are strict criteria for selection, and candidates therefore cannot have other diseases that will increase the risk of a transplant, for example severe heart disease or cancer. More contraindications that are unspecific include severe obesity, active substance abuse, and history of non-adherence to medical therapy. In much of the world, an age limit of 65 years has been adopted with a certain room for discretion.

2.1.2 Transplantation and immunosuppression

LTx is a complex surgical procedure, where one or two of the lungs are replaced with healthy ones (figure 2)(24). Several components of respiratory physiology are altered, for example denervation of the lung, reduced mucociliary clearance and interrupted cough reflex (25). Gastroesophageal reflux disease, also known as acid reflux, is common after LTx, and considered a possible risk factor for the development of chronic lung allograft dysfunction (CLAD). Injury of the vagal nerve during surgery, medication-induced gastroparesis due to immunosuppressive therapy in addition to the underlying pathology preceding LTx are considered as potential causes (26).

Pulmonary function tests (PFT) after transplantation typically reflects the native lung disease, type of transplantation procedure and eventual complications. For example, transplantation from COPD gives bigger advantage in PFT compared to especially IPF (27-29). BLT is a more extensive operation compared to SLT and pulmonary function therefore stabilizes later (28). This is among other things due to changes in chest wall

mechanics after surgery and the disparity in volume between the graft and the thoracic capacity (30). Eventual development of complications such as infection of rejection will cause deterioration in the pulmonary function (30, 31).

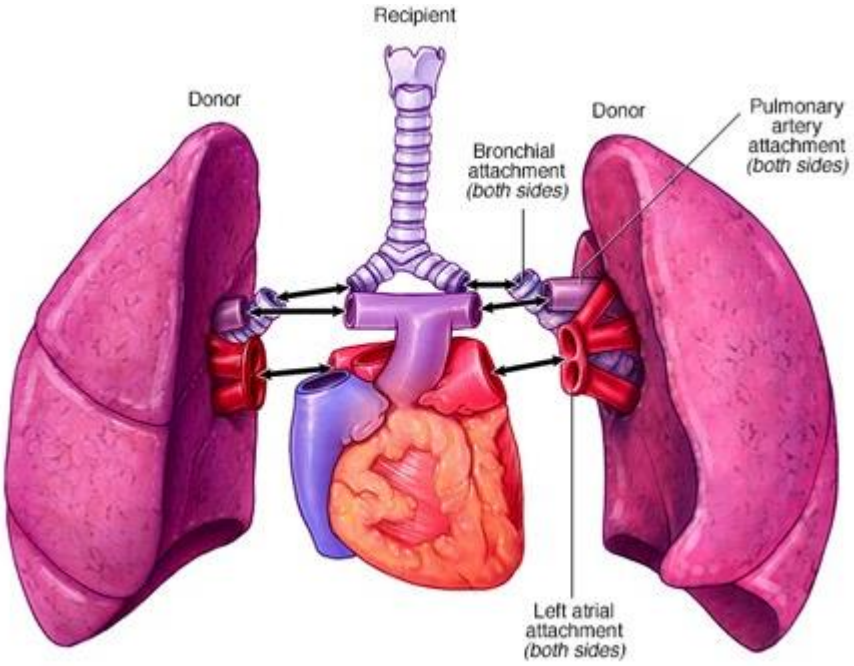

Figure 2: *Bilateral lung transplantation (24). Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved (Appendix 1).*

Immunosuppressive medication is administered to all patients post LTx to reduce the risk of acute and chronic rejection, and will be monitored and adjusted throughout their lives. This results in LTx recipients having a higher risk for infections. The medications may also cause noticeable side effects, including diabetes, weight gain, hyperlipidemia and osteoporosis among others (1). In addition, the majority is diagnosed with hypertension five years after transplantation due to side effects related to treatment (12).

2.1.3 Complications

Factors that may increase the risk, or decrease the expected survival, include older age, ventilator dependence pre-transplant, psychosocial issues, nutritional status, previous cardiothoracic surgery, chronic glucocorticoid use and allosensitization (20), which are considered on a case-by-case basis. Allosensitization is a condition some candidates for LTx have, where antibodies against certain antigens circulate (32). This may decrease the candidate's donor pool, and prolonge the time to transplantation. Some comorbid diseases can increase the risk of complications or affect the benefits from LTx; for

example, coronary heart disease is a risk for many LTx candidates, due to age and long term smoking history (33).

A significant post-transplant complication is acute rejection. One year post LTx, 28% have experienced one or more episodes (1). A major limitation of long-term survival is CLAD, which is a persistent and chronic decline in the function of the transplanted lungs (34). CLAD has two subtypes, bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS). BOS affect about 10% each year, primarily the first four years post-transplant, and re-transplant recipients are at even higher risk. The incidence and prevalence of CLAD may be even greater (1). CLAD, early graft failure and intractable airway complications are the most common indications for re-transplantation (1). According to the ISHLT registry (22), re-transplantation is infrequent and is an indication in only 4% of lung and heart-lung procedures, with second re-transplant being even more infrequent, accounting for 0.1% (2).

2.1.4 Results and prognosis

Survival after LTx is increasing, and is particularly high in Norway with 85-90% alive after one year (35), 70% after five years and 50% after 10 years (figure 1)(18); by comparison, 84% are alive after one year and 57% after five years internationally (1). More male than female are transplanted, but median female survival is better than male. The median recipient age have gradually increased up to 55 years (1), but survival rates are worsened with increasing age at transplantation (36). An important factor in deciding which LTx procedure to perform is the native disease, but BLT is the most common procedure now, due to BLT recipients having better long-term outcomes (1). The native disease also influences the mortality post-transplant. COPD have the lowest one-year mortality, but their ten-year survival is lower compared to CF (1). This might be due to differences in recipients' characteristics, where patients with COPD are older and have more comorbidities due to long term smoking, compared to generally younger patients with CF.

LTx recipients have reported improved QoL and normalized pulmonary function (37, 38) compared to pre-transplant, where exercise tolerance and QoL are impacted by several factors. These include amount of time spent in hospital post LTx, the use of

immunosuppressive medications, post-transplant complications in addition to persisting inactivity (39).

2.2 Lung anatomy and lung physiology

The lungs occupy the thoracic cavity, which is subdivided into the upper and lower respiratory tract, where O_2 and CO_2 are transported (figure 3)(40). The upper respiratory tract consists of the nasal cavity and pharynx, which warm and humidify the incoming air. The lower respiratory tract consists of the larynx, trachea, the bronchi, and the bronchioles terminated by alveoli. The transfer of oxygen to blood vessels, aided by hemoglobin (41), takes place in the alveoli (42).

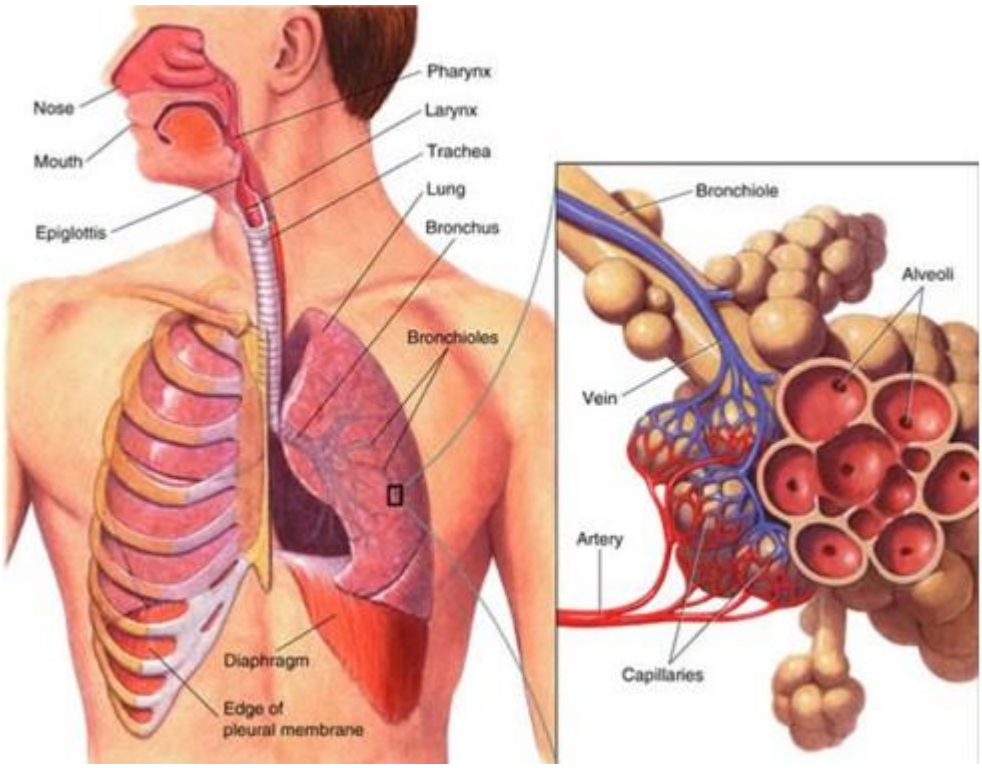

Figure 3: *Lung anatomy. Obtained from http://www.med-health.net/Lungs-Function.html (40).*

The air is also a source for contaminants, microorganisms, low humidity and cold temperatures (42, 43), and much of this material is removed in the nose, and by the cilia and mucus in almost the entire respiratory tract (41, 42). The reminder is either exhaled or ingested and to some extent inactivated by phagocytic cells (42). An important mechanism, ‘’mucociliary escalator’’, removes inhaled particles that come to rest in the airways, but patients who cannot clear their tracheobronchial secretions, for example patients who cannot cough adequately, accumulate secretion nevertheless (43).

2.3 Pulmonary function

There are several different methods for measuring pulmonary function, and predicted reference values are used to decide whether the values are within normal range or not (42). In this study, forced vital capacity (FVC), forced expiratory volume after one second (FEV_1), diffusing capacity of the lung for carbon monoxide (DLco) total lung capacity (TLC) and maximum voluntary ventilation (MVV) are measured.

2.3.1 Spirometry and flow-volume curves

The severity of lung disease may be detected, characterized and quantified by spirometry (44). Spirometry is a widely used measurement in the assessment of dynamic lung volumes, like FVC and FEV_1, where the flow-volume curve is used as a visual assessment during the evaluation. FVC is the total volume of air exhaled with maximal effort after a maximal inhalation, while FEV_1 is the volume of air exhaled during the first second of the FVC maneuver (42). FEV_1 is reproducible and both FEV_1 and FVC are expressed in liters (42). FEV_1 is an important measurement following LTx, and are measured regularly, both with home monitoring with a portable spirometer and at the hospital (30). With a persistent decline in FEV_1, comprehensive evaluation is performed, to rule out infection or rejection (22).

2.3.2 Diffusing capacity of the lung for carbon monoxide

The lungs ability to transfer gas from the air to the red blood cells in the pulmonary capillaries (figure 4)(45) is measured by DL_{CO} through a single breath method, and is recommended as the index for the gas exchange in the lungs (42). DL_{CO} varies with age, gender, height and possibly ehnicity; in addition to physiological variables such as Hb concentration, total lung volumes, carboxyhemoglobin, altitude, exercise and body position (42). The diffusing capacity is determined by several properties, both structural and functional (46). The product of the carbon monoxide-Hb chemical reaction rate (θ) and the volume of alveolar capillary blood (Vc) represents the binding of carbon monoxide and Hb (θVc), and make up the process of carbon monoxide uptake along with membrane conductivity (46). Several physiological changes can influence DL_{CO}, and due to these changes, DL_{CO} tends to increase as the lung inflates. Since exercise can recruit and dilate alveolar capillaries, it also increases the Vc and DL_{CO} (46). During exercise, with more capillaries recruited, the surface available for diffusion will also

increase (43). Hb concentration influences DL_{CO} (43); therefore, specific adjustments for Hb should always be made to ensure appropriate interpretation.

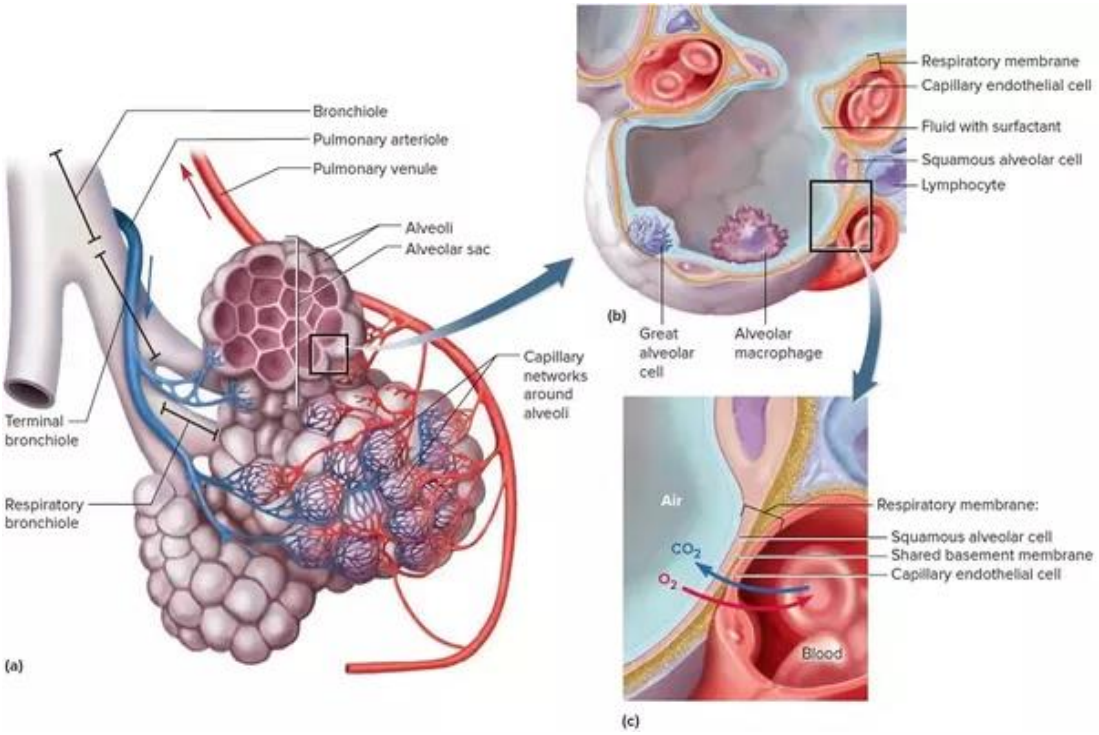

Figure 4: *Alveoli and gas exchange (45).*

2.3.3 Lung volumes

TLC is one of the most important variables for pulmonary function in clinical practice, and is the sum of its four subdivisions (figure 5), which amounts to approximately 5.5-6.6 litres in healthy adults, depending on age, gender, height and ethnicity (42).

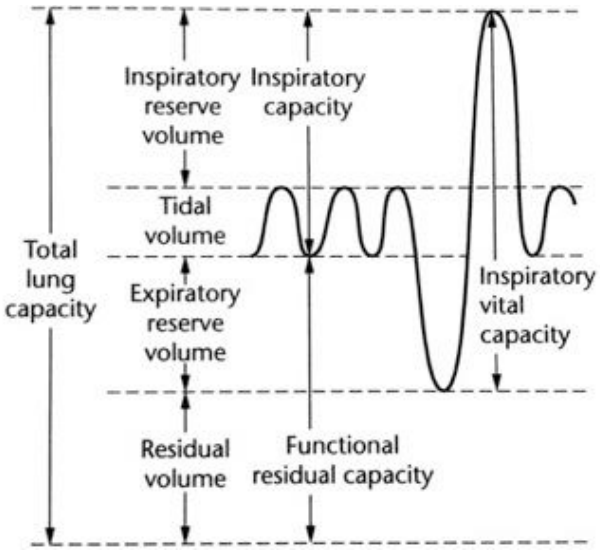

Figure 5: *Subdivisions of total lung capacity (42).*

TLC can be measured by whole body plethysmography, and any changes are normally explained by the lung's ability to expand, which is among others determined by the compliance and the elastic recoil of the lung tissue (42). After adjusting for the decrease in height seen in older people, TLC seems to stay fairly constant with age (43). Perfusion (blood-flow) and ventilation affects the gas exchange in the lungs, and must be matched on the alveolar-capillary level to optimize gas exchange (43).

2.3.4 Maximum voluntary ventilation

MVV is a measure of the ventilatory capacity, and is the *''maximum volume of air a subject can breathe over a specified period of time (e.g. 12s)''* (47), expressed in $L \cdot min^{-1}$. MVV is used to determine the breathing reserve (BR), in order to investigate whether the pulmonary function is the limiting factor under maximal exercise or not. The BR is approximately 20-40% of the MVV at maximal load in healthy individuals (48). Patients with impaired pulmonary function may reach their limits earlier, which might suggest the pulmonary function as the limiting factor in exercise capacity (48). BR is expressed as a percentage of MVV:

$$\frac{(MVV - V_{Emax})\ x\ 100}{MVV} = BR\ \%\ (49).$$

Healthy individuals use 60-80% of their ventilatory capacity during maximal exercise, compared to athletes who may use 100% or more of their ventilatory capacity (50).

2.3.5 Pulmonary function pre- and post lung transplantation

Pulmonary function tests seem to reflect LTx recipients' pre-transplant native disease, whether there is a SLTx or BLTx, in addition to eventual development of infection or rejection(51). A selection of previous studies examining pulmonary function and CRF after LTx in BLTx recipients is summarized in table 1.

Prior to LTx, FVC and FEV_1 are severely reduced, to an average of 59% and 37% of predicted, respectively (52). FVC and FEV_1 usually improve immediately, and through the first months post LTx, reaching a plateau within the first year (53). An average FVC and FEV_1, respectively, in the range of 66-92% and 78-86% of predicted are observed in BLTx recipients six to nine months post LTx (52, 54-57), which indicate that LTx recipients may achieve pulmonary function values within the low normal range. Acute

or chronic rejection, among other complications, can lead to declines in FVC and FEV_1 as well as the ratio of FEV_1/FVC (58).

A significant improvement in ventilatory capacity from pre- to post-LTx, from 44% to 86% of predicted, respectively, is seen in MVV (52).

A decline from 86% of predicted to 81% of predicted are observed in TLC from pre- to post-transplant (52). Following LTx, recipients seem to achieve their pre-transplant TLC within the first year irrespective of the size of the donor lungs, suggesting characteristics of the chest wall rather than donor lung size or compliance as determinants of post-transplant lung volume (59, 60). However, this must be interpreted with caution as TLC pre- and post-transplant depends on the native disease. Patients with COPD have an abnormal high TLC pre-transplant, but are supposed to have a lower TLC post-transplant, unlike patients with IPF, where it is opposite. Additional factors that affect TLC are respiratory muscle weakness, phrenic nerve dysfunction and/or pleural effusion. However, the major determinant of TLC appears to be the recipient's predicted or pre-transplant TLC (59-62).

An improvement in DL_{CO} from 30% of predicted to 57% of predicted has been observed from pre- to post-transplant (52). Others have demonstrated a greater increase (7, 54, 63, 64). Interestingly, Shaver et al (2017) performed a retrospective analysis of 104 BLTx, and found a significantly reduced DL_{CO} (% pred) in the majority of LTx recipients (65). A decline in the first 3 years post-transplant was observed with a median of 74% vs 60% of predicted after one and three years, respectively. The range was 32-109% of predicted the first year, and 29-106% of predicted the third year, indicating major individual differences.

Schultz et al (2016) investigated the impact of native disease on baseline pulmonary function values in 236 BLTx recipients (29). Recipients that had COPD got the biggest advantage in PFT compared to other indications, especially IPF and sarcoidosis. This clearly illustrates the importance of interpreting the values of pulmonary function tests after LTx with caution. Unfortunately, existing studies have reported measurements of pulmonary function in a mix of BLTx and SLTx recipients, various sample of native

diseases, in addition to varying time points after LTx, which makes comparisons difficult, e.g. due to the natural recovery observed in pulmonary function after LTx.

Table 1: *A sample of previous studies on pulmonary function and cardiorespiratory fitness after lung transplantation.*

Author, year	**Time after LTx**	**Number of participants**	**FVC (%pred)**	**FEV_1 (%pred)**	**DL_{CO} (%pred)**	**TLC (%pred)**	**MVV (%pred)**	**VO_{2peak} (%pred)**
Miyoshi et al., 1990 (63)	> 9 months	6	NR	92	90	94	NR	49
Williams et al., 1992 (66)	1-2 years	7	NR	101	76	NR	NR	55
Ross et al., 1993 (64)	1 year	1	93	71	66	NR	122 $L \cdot min^{-1}$	38
Levy et al., 1993 (67)	6 months	6	75	71	NR	NR	NR	59
Orens et al., 1995 (54)	3 months	11	69	86	66	94	127 $L \cdot min^{-1}$	50
Oelberg et al., 1998 (68)	NR	10	NR	NR	NR	NR	NR	31
Pellegrino et al., 1998 (69)	> 6 months	8	77	78	NR	NR	125 $L \cdot min^{-1}$	42
Tirdel et al., 1998 (70)	NR	6	NR	NR	NR	NR	NR	45
Schwaiblmair et al., 1999 (7)	< 3 months	32	63	67	69	NR	NR	14.6 $mL \cdot kg^{-1} \cdot min^{-1}$
Reinsma et al., 2006 (71)	1 year	21	86	83	NR	82	NR	57
Mason et al., 2008 (28)	1 year	194	67	65	NR	NR	NR	NR
Pêgo- Fernandez et al., 2009 (31)	1 year	18	82	85	NR	NR	NR	NR
Habedank et al., 2011 (72)	2 years	20	NR	NR	NR	NR	NR	18.6 $mL \cdot kg^{-1} \cdot min^{-1}$
Bartels et al., 2011 (52)	Average 2,5 years	119	87	90	57	84	88	52
Armstrong et al., 2015 (73)	Average 1 year	54	NR	NR	NR	NR	NR	55

LTx, lung Transplantation; FVC, forced vital capacity; %pred, percent of predicted; NR, not reported; FEV_1, forced expiratory volume after 1 sec; DL_{CO}, diffusing capacity of the lung for carbon monoxide; TLC, total lung capacity; MVV, maximal voluntary ventilation; VO_{2peak}, peak oxygen uptake.
Only results from BLTx recipients in the studies are presented.

2.4 Physical fitness

Physical fitness is defined as *''a set of attributes that people have or achieve that relates to the ability to perform physical activity'',* and there is distinction between physical fitness related to performance or health (74). Performance-related physical fitness comprises the qualities that are necessary to optimize a given work- or sports-related performance, while health-related physical fitness comprises the qualities that may be affected by habitual physical activity, in a favorable or unfavorable way, and is related to people's health-status (75). An important component of health-related physical fitness is cardiorespiratory fitness, which further will be discussed.

2.4.1 Maximum oxygen uptake

$\dot{V}O_{2max}$ is often reported in $L \cdot min^{-1}$ or $mL \cdot kg^{-1} \cdot min^{-1}$ and today there are a number of different gas analyzers for measuring oxygen uptake (76). Nevertheless, the principal calculation of $\dot{V}O_2$ is similar and assumes that all expiratory air is analyzed for volume per unit time, $\%O_2$ and $\%CO_2$.When $\%O_2$ and $\%CO_2$ in the inspiratory air is known; $\dot{V}O_2$ can be calculated (76). $\dot{V}O_{2max}$ depends on gender, age, body size and composition, heredity, state of training and mode of exercise (50, 76). Genetic effects are discussed and researchers estimate that 20-30% of $\dot{V}O_{2max}$, 50% of maximum heart rate and 70% of physical working capacity are explained by genetic factors (76). $\dot{V}O_{2max}$ can be expressed through the Ficks equation, where $\dot{V}O_{2max}$ is the product of the cardiac output (Q) and the arterial-mixed venous oxygen difference (a-vO_2 diff)(77):

$$\dot{V}O_2 = Q(a - \text{v}O_2 \text{ diff})$$

Different end criteria are used to consider achievement of $\dot{V}O_{2max}$, and these include a plateau in $\dot{V}O_2$ despite increased work rate, respiratory exchange ratio (RER), maximal heart rate (HR_{max}) and blood lactate concentration [La^+](78). The term $\dot{V}O_{2peak}$ is used instead of $\dot{V}O_{2max}$ if several of these criteria are not met (79).

Different forms of exercise reflect variations in the quantity of muscle mass activated and variations in $\dot{V}O_{2max}$ are observed. Among diverse exercise models, treadmill exercise usually produces the highest values (76). Outside laboratory setting, cycle ergometer remains a suitable alternative, though 10-20 % lower values are observed (76). Women achieve lower $\dot{V}O_2$ values than men, with a difference in the range 15-30

% (76). The difference may be explained by body composition, hemoglobin concentration and size of the heart. After adjusting for lean body mass the difference becomes smaller (50, 76).

There are several factors that can limit $\dot{V}O_{2max}$, including the cardiac stroke volume and the blood's ability to transport oxygen from the lungs to the working muscles (76). In addition, capillarization and mitochondrial enzyme activity will be peripheral conditions in the muscles that can limit VO_{2peak} (76). A cardiopulmonary exercise test (CPET) is the most common method to measure $\dot{V}O_{2max}$ in a clinical setting (48).

2.4.2 Cardiopulmonary exercise test

CPET provides information about the responses of the cardiovascular and ventilatory systems to a known exercise stress through measurement of gas exchange (48). In addition, there is measurement of electrocardiography (ECG), heart rate, blood pressure and pulse oximeter (48). Several different protocols can be used during CPET, but a RAMP protocol with progressively increasing work-rate until exhaustion during 8-12 minutes is recommended (48). CPET is an inexpensive examination, and can be performed in modern cardiology and cardiopulmonary function laboratories to diagnose, treat and for risk assessment in patients (48).

2.4.3 Physical fitness pre- and post lung transplantation

LTx recipients have an impaired cardiorespiratory fitness (table 1), often with values in the range of 40-60% of predicted (71, 80). Miyoshi et al (1990) evaluated CPET one year after LTx in six patients undergone BLTx, and found VO_{2max} to be markedly reduced with only 49% of predicted (63). This has been confirmed by, among others, Williams et al (1992) who demonstrated unchanged CPET results in a cohort of 13 patients, two years after LTx (57). VO_{2peak} as low as 31% of predicted (68) and as high as 60% of predicted (67) has been reported, but the studies only included ten and six patients, respectively. Although a statistically significant improvement in $\dot{V}O_{2peak}$ following LTx from 43% to 52% of predicted has been observed, the degree of increase does not match the improvement observed in pulmonary function (52), which is also the case in the younger recipients, for example those with CF (52).

Pellegrino et al (1998) reported peak VO_2 at six months post transplant, and further observed decreases between nine and 12 months post LTx (69). This is in contrast to the study by Habedank et al (2011), who suggested the highest VO_{2peak} at 12 or even 24 months (72).

Interestingly, Bartels et al (2011) evaluated VO_{2peak} before and after LTx in 153 participants, and observed different degrees of gains across native disease pathologies (52). E.g. patients with COPD achieved the most benefit, in contrast to patients with interstitial lung disease in which improvement was more modest. Previous studies have not found any cardiac or pulmonary limitations to exercise tolerance, and leg fatigue has overwhelmingly been cited as cause for termination of CPET (52). Summarized, CPET may be useful following LTx in order to identify causes of poor exercise tolerance despite improvement of pulmonary function.

2.5 Dyspnea

Dyspnea is defined as *''a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity''* (81). Dyspnea is a complex symptom, where the assessment is dependent on self-report. It can be a sign of disease, as well as a symptom caused by fear and anxiety among others. Patients with cardiopulmonary diseases has much greater dyspnea compared to healthy individuals, and may therefore lead to avoiding activities that may precipitate breathlessness, causing increased sedentary behavior (81) and reduced exercise tolerance (82). CPET may be a helpful test in the evaluation, due to possibility of multiple problems that can contribute to dyspnea, in example non-respiratory causes as leg discomfort, fatigue or weakness. Today, there are several methods for measuring dyspnea. One of them are the modified Medical Research Council (mMRC) Dyspnea score, which has been used in many years, and is recommended for scoring grade of breathlessness in daily activities (83). mMRC dyspnea score is used in research contexts, but is not routinely used neither pre- or post LTx.

2.5.1 Dyspnea post lung transplantation

Jastrzębski et al. (2014) assessed the long-term results of LTx two years after the procedure on dyspnea, measured by mMRC (84). Before LTx, one patient reported maximum, and 10 patients reported submaximal dyspnea. After LTx, a significant

improvement was observed (3.55±0.69 vs 1.55±1.0, p = 0.001). Out of 20 patients, only four underwent BLTx. COPD received the greatest improvement (2.33 points) compared to idiopathic pulmonary fibrosis (1.78 points), although both groups achieved statistically significant improvement (84).

To my knowledge, no previous studies have investigated the association between mMRC, FEV_1, DL_{CO} and VO_{2peak} in BLTx recipients.

2.6 Exercise training after lung transplantation

The effect of exercise regarding VO_{2max} and pulmonary function in BLTx recipients has to my knowledge been evaluated in eight studies, whereby two randomized controlled trials (12, 13) and six prospective cohort studies (3, 64, 85-88)(table 2).

Langer et al. (2012) investigated the effect of 12 weeks endurance- and resistance training, resulting in no significant between-group difference in VO_{2max} (12). Measurements remained below predicted values for age and gender. No significant between-group difference was observed in percent of predicted FEV_1, and it was within normal values in both groups three months and one year after hospital discharge (12). However, the exercise training was initiated immediately following hospital discharge, which limits the study as a natural improvement is to be expected after returning to daily activities. We speculate that this may be the reason for the lack of a statistical significant improvement as a result of the intervention. Ihle et al. (2011) found significant improved VO_{2peak} in both study groups of four weeks inpatient rehabilitation and outpatient physical therapy, respectively, but no between-group difference were found (table 2)(13). This might be due to the ‘’active’’ control-group or the short intervention period. VO_{2peak} was found to remain limited after the intervention, compared to predicted values (13).

Three cohort studies investigated effect of exercise in the phase from hospital-discharge and up to one year post-transplant (table 2). They had duration of eight to 12 weeks, with endurance (64) and combined endurance and resistance training (3, 87) right after discharge from hospital. Significant improvement was observed in VO_{2peak} (64) and six-minute walk distance (3, 87). Maury et al. (2008) showed significant improvements in FEV_1 (%pred) from pre-LTx to both post-LTx and post-rehabilitation (3). Significant

improvements in FEV_1 and FVC was also observed by Munro et al. (2009), where improvement in FEV_1 was significant from one to two months, but not from two to three months (87). FVC, on the other hand, significant improved between each time point.

Three cohort-studies were assessed more than one year following LTx (table 2)(85, 86, 89). Stiebellehner et al. demonstrated improved VO_{2peak} with 13% in nine LTx recipients after endurance training for six weeks (85). The two other cohort-studies investigated the effects of home-based endurance training, three times a week for three months, resulting in significant improved endurance time and QoL.

Knowledge regarding training regimens after LTx is severely limited, and no evidence-based guidelines has been developed. However, some evidence exists to suggest a potential to reverse the abnormalities observed regarding cardiorespiratory fitness in LTx recipients. 128 transplant recipients, including 6 LTx, competing in the World Transplant Games were tested (90). Cardiorespiratory fitness was found to be 30.2±9.5 $mL \cdot kg^{-1} \cdot min^{-1}$corresponding to 95%±30% age-predicted VO_{2peak}. The intensity of exercise and duration of training was not described, but more than half of the recipients reported four or more days per week of cardiovascular exercise training.

Improved physical fitness may decrease the risk for co-morbidities that LTx recipients are at risk for, but unfortunately, previous studies have been insufficiently powered and with moderate or not reported intensity. The possible advantages of HIT have to my knowledge not been published. On the other hand, a Norwegian study observed that HIT was safe and effective in increasing physical fitness in heart transplant recipients (HTx) (91). The intervention, lasting a year, led to significantly higher VO_{2peak} in the exercise group.

Findings from the cohort-studies must be interpreted with caution due to the absence of a control group. The studies were also performed in small samples. There is a need for future research regarding the association between pulmonary function, peak oxygen uptake and dyspnea. In addition, the need for research regarding the possible effects of HIT on pulmonary function and CRF, to allow patients to realize the full potential of their restored pulmonary function, is eminent.

Table 2: *Studies investigating the effect of exercise after lung transplantation.*

Author, year	Subjects (M/F)	Time since LTx (average)	BLT, SLT or HLT	Study design	Type of exercise	Intensity	Frequency and length of intervention	FVC	FEV_1	DL_{CO}	TLC	MVV	$\dot{V}O_{2peak}$
Ross et al. 1993 (64)	4/4	8 months	1 BLT, 7 SLT	Non randomized controlled trial	Endurance	60-70% pred HR_{max}	3 d/week for 6-8 weeks	NR	NR	NR	NR	NR	+4.2 $ml \cdot kg^{1} \cdot min^{-1}$ **
Stiebellehner et al.1998 (85)	6/3	1 year	7 BLT, 2 SLT	Non randomized controlled trial	Endurance	30-60% of HRR	3-5 d/week for 6 weeks	+0.07L*	+0.08L*	NR	NR	NR	+13%*
Guerrero et al. 2005 (86)	12	35 months	9 BLT, 2 SLT, 1 HLT	Non randomized controlled trial	Endurance	30 - 80%W_{max}	3 months	+4%	+3%	NR	NR	NR	+5%
Maury et al. 2008 (3)	17/19	1 month	21 BLT, 15 SLT	Non randomized controlled trial	Endurance Resistance	3x8 repetitions at 60% of 1RM	3 d/week for 12 weeks	NR	+8%*	NR	NR	NR	NR
Munro et al. 2009 (87)	18/18	1 month	29 BLT, 7 SLT	Non randomized controlled trial	Endurance Resistance	Borg 13-14 3x10-15 repetitions	3 d/week for 8 weeks	+12%**	+10%**	NR	NR	NR	NR
Vivodtzev et al. 2011 (88)	10/2	3 years	9 BLT, 2 SLT, 1 HLT	Non randomized controlled trial	Endurance	Home based, 50-80% of peak work load	3 d/week for 12 weeks	NR	NR	NR	NR	NR	+0.13L
Ihle et al. 2011 (13)	30/30	4.5 years	39 BLT, 21 SLT	Randomized controlled trial	Endurance Resistance	NR	5 d/week for 4 weeks	NR	NR	NR	NR	NR	+15%*
Langer et al. 2012 (12)	16/18	1 month	29 BLT, 5 SLT	Randomized controlled trial	Endurance Resistance	60-75% of peak work load 4-6 on a modified Borg scale 3x12 repetitions at 70% of 1RM	3 d/week for 12 weeks	NR	+10%	NR	NR	NR	+16%

LTx, lung transplantation; BLT, bilateral lung transplant; SLT, single lung transplant; HLT, heart-lung transplant; RM, repetition maximum; HRR, heart rate reserve (HR_{max}-HR_{rest}) · % intensity + rest; FVC, forced vital capacity; NR, not reported; FEV_1, forced expiratory volume after 1 sec; DL_{CO}, diffusing capacity of the lung for carbon monoxide; TLC, total lung capacity; MVV, maximal voluntary ventilation; $\dot{V}O_{2peak}$, peak oxygen uptake; W_{max}, maximum workload. Improvements are within-group.
*Significant difference from baseline ($p<0.05$). ** Significant difference from baseline ($p<0.01$).

3. Methods and materials

3.1 Design and ethics

HILT (High-intensity training following lung transplantation) is a two-armed, randomized controlled trial at the Department of Respiratory medicine at Oslo University Hospital (OUS), Rikshospitalet, in cooperation with the Norwegian University of Sport Sciences. Examinations and tests were conducted at the Pulmonary laboratory at Rikshospitalet.

The HILT study was conducted in accordance with the Helsinki Declaration, approved by the Ethics Committee (nr 2017/399)(Appendix 2) and registered in Clinical Trials.gov (OsloUH record 2017/399). Before signing the informed consents (Appendix 3), all participants were given written and oral information about the project's procedures and intentions, and were informed that they could withdraw without giving reasons and without negative consequences for on-going treatment at the hospital. All data were treated confidentially and only project management was able to identify the individual participant.

Data collection included in this master thesis, involves data from visit 1 and visit 2 in the HILT study, collected between August 2017 and April 2018 (figure 6).

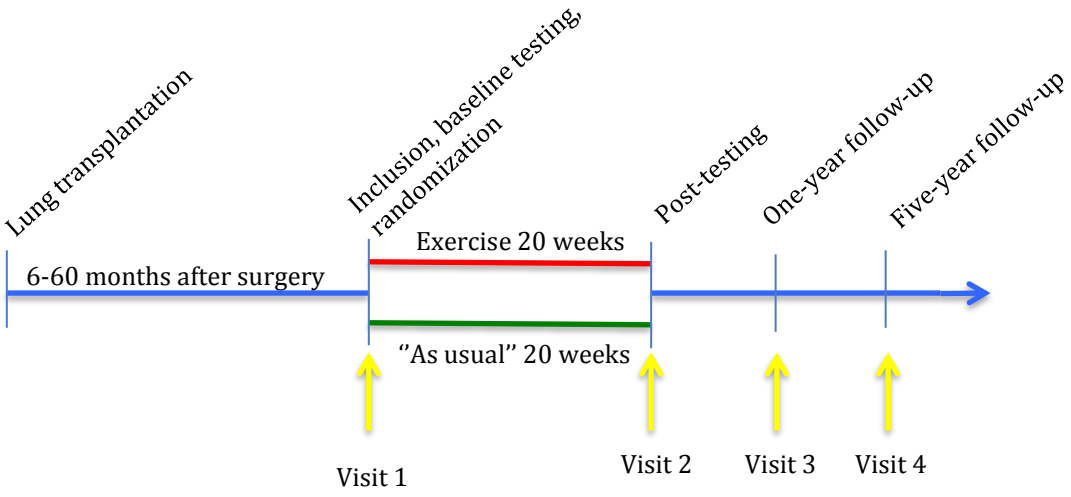

Figure 6: *Timeline for the HILT study from transplant surgery to the end of the study. Visit 1 and 2 are included in this master's thesis.*

3.2 Participants

One-hundred and six patients who undergo LTx at OUS were eligible to participate in the study six-60 months after LTx. The inclusion- and exclusion criteria are listed in Table 3. After baseline testing, all participants were randomized to either an intervention group (exercise) or a control group. The randomization was done in blocks with varying block size and put into sealed envelopes generated by an external statistician.

Table 3: *Inclusion- and exclusion criteria in the study.*

Inclusion criteria	Exclusion criteria
Stable condition 6 months after lung transplantation	Complication with poor prognosis (expected survival <12 months)
≥18 years	Unable to perform a cardiopulmonary exercise test to exhaustion
Signed consent form	Language issues that interfere with data collection
	Participation in another investigational intervention study

3.3 Test procedures

All equipment was calibrated daily for volume and gas concentration. Experienced technicians conducted all procedures during pre- and post-intervention. Participants were asked to bring comfortable clothes and suitable shoes, and all test procedures were explained thoroughly before start of each test. In addition, the participants answered a questionnaire about dyspnea.

3.3.1 Sosiodemographic- and clinical data

Age, gender, education, work status, living situation, exercise- and diet- habits, medicines (coded by ATC) and pre-transplant medical history were retrieved from medical records and updated by self-reporting.

3.3.2 Anthropometric measurements

Height and weight (Seca, Hamburg, Germany) were measured to the nearest 1,0 cm and 0,1 kg respectively, where the patients wearing no shoes and with light clothing.

3.3.3 Pulmonary function

FVC, FEV_1, MVV, TLC and DL_{CO} were conducted using SentrySuite (CareFusion Corporation, Wursburg, Germany) according to guidelines (92). All tests were performed in accordance with the American Thoracic Society/European Respiratory Society guidelines. Percent predicted values for FVC and FEV_1 were calculated, using reference values based on the equations from GLI 2012 (93). Pulmonary function was measured in sitting position wearing a nose clip to avoid leakage.

1.3.3.1 Spirometry and flow-volume curves

Spirometry measurements were conducted by maximum expiratory flow-volume curves. Participants started with tidal breathing followed by a maximum inhalation. Then the participant exhaled as quickly, hard and long as possible to residual volume for a minimum of 6s, before maximal inhalation, all after signal from the technician to terminate the test. Participants had to perform at least two measurements of FEV_1 with a variation within 150ml and 5%, during maximal effort. The highest FEV_1 and FVC were used from all tests.

1.3.3.2 Maximal Voluntary Ventilation

Ventilatory capacity was directly measured by MVV, asking the participant to breathe as rapidly and deeply as possible for 12 seconds in a standing position. A minimum of two maneuvers was performed, and the highest acceptable MVV was reported.

1.3.3.3 Lung volume

TLC was measured using plethysmography (44). Participants were told to put their hands on the cheek and continue with tidal breathing until a stable end-expiratory level was achieved. At or near functional residual capacity, a shutter was closed for ~2-3s and the participant performed gentle pants in a given frequency (0.5 1.0 Hz), where the mouth pressure and box pressure continuously were measured. After three to four panting maneuvers the shutter was opened and the participant instructed to perform a spirometry. The test was conducted once.

1.3.3.4 Diffusing capacity of the lung for carbon monoxide

Measurements of DL_{CO} were performed in a sitting position inhaling carbon monoxide and methane according to guidelines (46). The participant started with tidal breathing followed by unforced exhalation to residual volume. Then the test gasses were inhaled rapidly (<4s) to TLC holding the breath for 10 ± 2s so the CO could diffuse from the alveoli to the blood. Further the participant exhaled completely to residual volume. The test was repeated after 4 minutes, to ensure that the test gas in the lungs was exhaled and to let the CO-pressure in the blood disappear. For measurement of $DL_{CO,}$ each patient had to complete two satisfying measurements with less than 10% deviations between measurements to ensure reproducibility (46).

Figure 7: *Measurement of pulmonary function: spirometry and diffusing capacity of the lung for carbon monoxide, total lung capacity, and maximal voluntary ventilation, respectively. Private photo with permission (Appendix 4).*

3.3.4 Cardiorespiratory fitness

CPET was performed for measurement of VO_{2peak} while the patients walked uphill on a treadmill (Technogym, Gambettola, Italy) using a modified Balke protocol until exhaustion (94). During CPET, gas exchanges and ventilatory variables was measured, breath-by-breath measurement. In addition, measurement of percutaneous oxygen saturation (SPO_2), blood pressure and a 12-wire ECG (Cardiosoft custo med cardio 100 BT) were performed at rest in a sitting position, and throughout the CPET for evaluation of hypoxia, blood pressure response, ischemia and/or arrythmias. The equipment has been found to have a false percentage at ± 3% (95). CPET was

terminated when the participant no longer were able to continue, even after continuous encouragement. The rating of perceived exertion (96) was assessed with BORG 6-20 scale (97), and a capillary blood sample was taken 60s after termination for measure of [La^+] (ABL 800, Radiometer, Copenhagen, Denmark)(78).

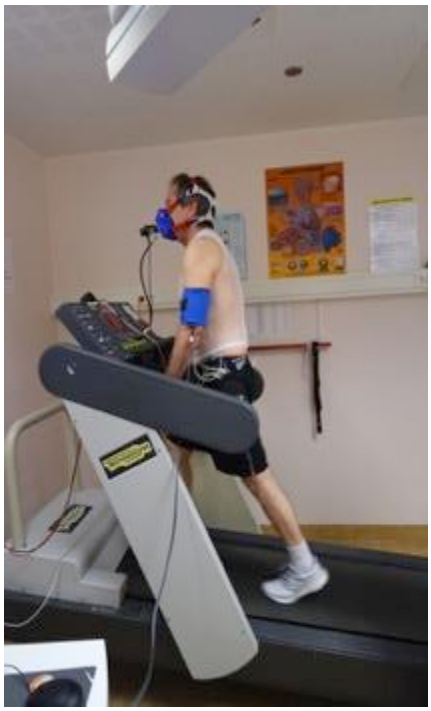

Figure 8: *Cardiopulmonary exercise test by uphill-walking on the treadmill. Private photo with permission.*

3.3.5 Questionnaire

In daily living, dyspnea was evaluated by the mMRC scale that consists of five statements that describe almost the entire range of dyspnea from none (Grade 0) to almost complete incapacity (Grade 4) (Appendix 5) (83).

3.3.6 Intervention

The exercise intervention, was individually tailored, and took place at a fitness center near the participant's home. Each training session lasted 60 minutes, and was conducted three times a week for 20 weeks (Appendix 6). The exercise started one to two weeks after randomization and were conducted by highly qualified personal trainers and physiotherapists. The intervention focused on high intensity interval training, mainly by walking upwards on a treadmill at 80-95% of HF_{peak} and progressive resistance training in three 4-12RM series for leg press, breast press, leg curl, leg extension and pull-down.

During the first four weeks, participants were introduced to the program focusing on safety, technique and familiarization. The intensity of endurance training and load on the resistance exercises then continuously increased based on participant's improvement, dyspnea and feeling of well-being or fatigue on each exercise day. All participants had a training diary in addition to the training instructor taking notes.

Patients in the control group were encouraged to follow the hospital recommendations for physical activity.

3.4 Data processing and statistical analyses

Demographic data are presented as mean ± standard deviation (SD), or counts and percentages. Change in outcome variables and graphic representations are reported as mean ± SD or mean and confidence interval (CI).

Sample size calculations were conducted for the HILT study overall, but not for this substudy. The normal distribution was doubtful in some cases; therefore both parametric and non-parametric tests were conducted. As they led to the same conclusions, parametric tests are presented. Independent samples t-test was used to investigate differences between the groups at baseline. To investigate whether there was a difference in change from baseline to follow-up between the groups, analysis of covariance (ANCOVA) was used. Change score was set as dependent variable, group as factor and baseline as covariate. Mean change within the groups was estimated using paired sample t-test. Correlations between mMRC, FEV1, DL_{CO} and VO_{2peak} were assessed by Spearman's rank correlation coefficient. A low correlation was defined as $r<0.3$, a moderate correlation as $r= 0.3$-0.7 and a high correlation as $r>0.7$ (98). Effects were evaluated on an intention-to-treat basis, using last observation carried forward to impute any missing values. Per-protocol analyses were also evaluated where the analysis included a comparison between exercising and non-exercising patients.

All statistical analyses were performed using IBM Statistical Package for the Social Science (IBM SPSS Statistics) V.25. Graphic representations were performed in GraphPad Prism 7. $P<0.05$ was considered significant.

4. Results

First, demographic characteristics of the study population will be presented. Then, the patients' cardiopulmonary fitness and the correlation between pulmonary function, peak oxygen uptake and dyspnea will be presented. Last, the effect of HIT will be presented regarding pulmonary function and VO_{2peak}.

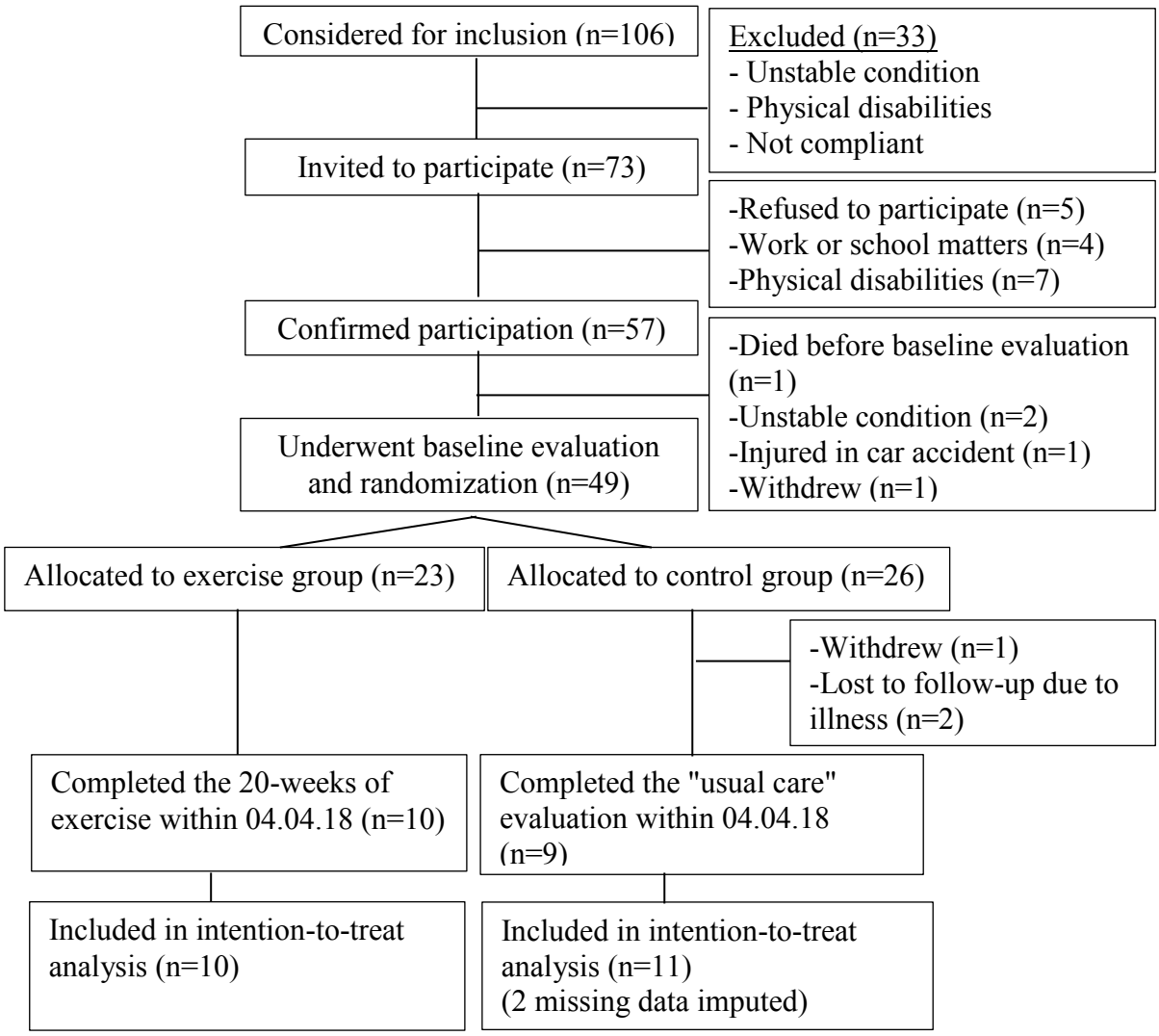

Figure 9: *Eligibility, randomization and follow-up of the study population.*

4.1 Study population and characteristics

Characteristics of the study population are given in Table 4. Age ranged from 20 to 67 years, and time since LTx ranged from six to 59 months. All patients had undergone BLTx, one had undergone combined heart-lung transplantation, and two patients had undergone re-transplantation. Six patients (12%) were diagnosed with CLAD.

Table 4: *Baseline characteristics of the patients.*

	Total n=48	Male n=23	Female n=25
Age (years)	51±13	53±11	49±15
Weight (kg)	76.1±13.7	82.4±13.5	70.2±11.2
Height (cm)	171±9	176±6	165±7
BMI (kg/m^2)	25.9±4.1	26.5±4.5	25.4±3.7
Time since LTx (months)	29±16	30±17	28±16
Native lung disease			
Emphysema	21 (44)	10 (44)	11 (44)
Pulmonary fibrosis	13 (27)	7 (30)	6 (24)
Cystic fibrosis	2 (4)	0	2 (8)
Other	12 (2)	6 (26)	6 (24)
BOS status			
None	35 (73)	16 (70)	19 (76)
Potentially BOS	8 (17)	3 (13)	5 (20)
Stage 1	2 (4)	1 (4)	1 (4)
Stage 2	3 (6)	3 (13)	0

Data are presented as mean±SD, or n (%).
BMI, body mass index; LTx, lung transplantation; BOS, bronchiolitis obliterans syndrome.
Potentially BOS, FEV_1 81-90% of baseline; Stage 1, 66-80% of baseline; Stage 2, 51-65% of baseline. Baseline is defined as the average of the two best FEV_1 values >3 weeks apart (22).
Other native lung disease included pulmonary hypertension (n=5), acute respiratory distress syndrome, (n=1), sarcoidosis (n=1), mycoplasma (n=1), graft-vs-host disease (n=2), scleroderma (n=1) and lymphangioleiomyomatosis (n=1).

4.2 Pulmonary function at baseline

Percent of predicted FVC and FEV_1 ranged from 48-152% and 36-131%, respectively. DL_{CO}, TLC and MVV ranged from 33-101%, 54-115% and 41-132% of predicted, respectively. Twenty-three patients (48 %) had an impaired FEV_1 defined as FEV_1 <80% of predicted (93). FEV_1 was higher in the patients between six months to two years after transplantation (n=31) with a mean of 84% of predicted, compared to 74 % of predicted in those greater than two years since LTx (p=0.190).

Table 5: *Pulmonary function and dyspnea score at baseline.*

	Total n=48	Male n=23	Female n=25
FVC $L \cdot min^{-1}$	3.6±0.9	3.4±0.9	3.8±0.9
% of predicted	89±21	89±21	90±21
FEV_1 L	2.6±0.8	2.3±0.7	2.8±0.7
% of predicted	80±24	77±24	85±23
DL_{CO} $mmol \cdot min^{-1} \cdot kPa^{-1}$	6.0±1.5	6.1±1.5	6.0±1.5
% of predicted	66±15	69±15	64±14
TLC $L \cdot min^{-1}$ [a]	5.3±1.2	5.3±1.3	5.4±1.0
% of predicted	90±15	91±16	89±13
MVV $L \cdot min^{-1}$	105.6±28.1	101.7±30.9	110.3±25.2
% of predicted	93±23	92±25	95±22
mMRC	0.4±0.7	0.6±0.9	0.2±0.4

Data are presented as mean±SD.
FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s; DL_{CO}, diffusing capacity of the lung for carbon monoxide; TLC, total lung capacity; MVV, maximal voluntary ventilation, mMRC, modified Medical Research Council dyspnea score.
[a] Based on 39 patients who had a TLC test.

4.3 Cardiorespiratory fitness at baseline

After CPET, 21 (45%) patients reported leg fatigue, 14 (30%) dyspnea and 12 (26%) general fatigue as the reason for termination.

VO_{2peak} varied between 12.9 $mL \cdot kg^{-1} \cdot min^{-1}$ and 45.04 $mL \cdot kg^{-1} \cdot min^{-1}$, which was 36% and 110% of predicted. The absolute values of VO_{2peak} were in the range 1.03-2.92 $L \cdot min^{-1}$, which was 33-91% of predicted. Forty-three (90%) patients had an impaired $VO_{2peak,}$ defined as a VO_{2peak} < 85% of predicted (99). Percent of predicted HR_{max} ranged from 67-105%.

Table 6: *Cardiorespiratory fitness at baseline.*

	Total n=48	Male n=23	Female n=25
VO_{2peak} $mL \cdot kg^{-1} \cdot min^{-1}$	22.6±7.1	22.3±7.7	23.0±6.8
% of predicted	65±15	66±17	64±15
VO_{2peak} $L \cdot min^{-1}$	1.66±0.42	1.62±0.42	1.71±0.44
% of predicted	63±14	64±14	63±14
Maximum heart rate, beats/min	151±19	147±18	155±18
Maximum heart rate, % of predicted	87±8	85±8	89±9
Respiratory exchange ratio	1.12±0.11	1.10±0.09	1.15±0.11
6-20 BORG scale, rating number	18.3±1.0	18.3±0.9	18.3±1.1
Blood lactate concentration†, mmol/L [B]	8.4±2.4	8.5±2.8	8.4±2.2

Data are presented as mean±SD.
VO_{2peak}, peak oxygen uptake.
Blood lactate concentration was taken 60 sec after termination as an indicator of high effort (78).
[B] Based on 37 patients who had measures of lactate concentration.

4.4 Association between pulmonary function, peak oxygen uptake and dyspnea

There was a moderate correlation between pulmonary function, VO_{2peak} and dyspnea (figure 10).

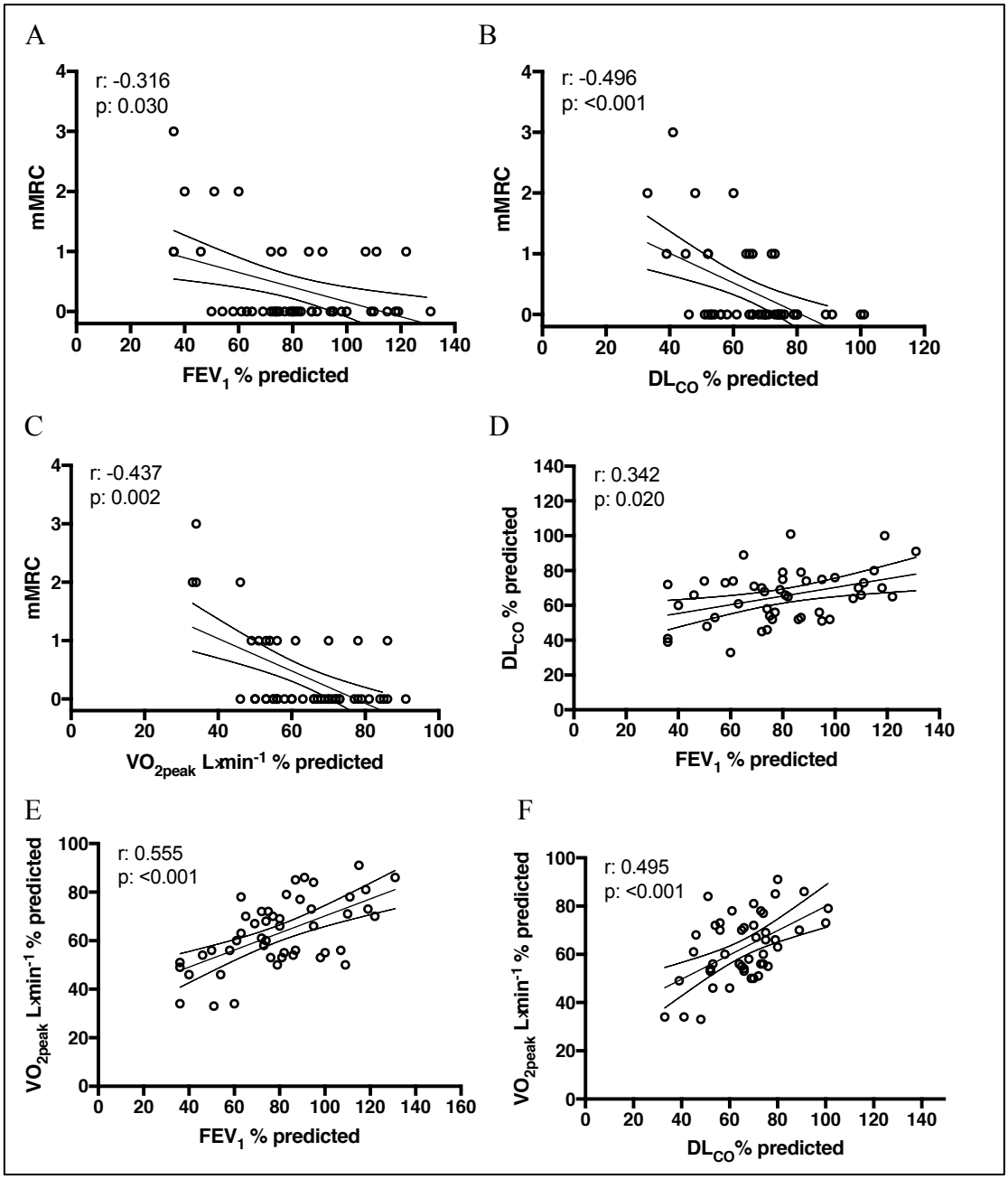

Figure 10: *Correlation between mMRC dyspnea score and FEV_1 (A), mMRC dyspnea score and DL_{CO} (B), mMRC dyspnea score and VO_{2peak} (C), DL_{CO} and FEV_1 (D), VO_{2peak} and FEV_1 (E), VO_{2peak} and DL_{CO} (F). Each solid circle represents results from one patient.*

4.5 Characteristics of the patients at post-intervention evaluation

Of the 49 patients who underwent baseline evaluation and randomization, 22 completed the intervention by 04.04.18 (figure 9). One of the 22 initially included patients withdrew due to dissatisfaction with the randomization. Two from the control group lacked post-intervention measurements due to illness, but were included in intention-to-treat analyses where the last observation was used in the respective analyses. Statistical analyses comprised 10 and 11 recipients in the exercise group and control group, respectively. There were no between-group differences at baseline.

Table 7: *Patient characteristics at baseline for the patients who underwent the exercise training intervention.*

	Total n=21	Exercise n=10	Control n= 11
Age (years)	52±13	54±12	49±14
Gender ♂/♀	9/12	4/6	5/6
Weight (kg)	77.3±12.0	74.1±12.1	80.1±11.8
Height (cm)	170±9	170±11	169±7
BMI (kg/m^2)	27.1±4.1	25.6±3.2	28.2±4.3
Time since LTx (months)	26±15	23±13	28±16
BOS status			
None	16 (75)	8 (80)	8 (73)
Potentially BOS	2 (10)	1 (10)	1 (9)
Stage 1	2 (10)	1 (10)	1 (9)
Stage 2	1 (5)		1 (9)

Data are presented as mean±SD, or n (%).
BMI, body mass index; LTx, lung transplantation; BOS, bronchiolitis obliterans syndrome.
Potentially BOS, FEV_1 81-90% of baseline; Stage 1, 66-80% of baseline; Stage 2, 51-65% of baseline. Baseline is defined as the average of the two best FEV_1 values >3 weeks apart (22).

4.6 Effect of high-intensity training on pulmonary function

Of the 60 planned HIT training sessions, the adherence rate during the 20 weeks of exercise was 48±12.1 (71±12.8%), ranging from 18-59 sessions.

Following the intervention there were no significant between-group differences in change in FVC, FEV_1, DL_{CO} or MVV (table 8). There was a decrease of 5.5% in the exercise group in FEV_1 L (p=0.007), which was 4.2% of predicted (p=0.030), and an increase in the control group of 4% in MVV $L \cdot min^{-1}$ (p=0.033), which was 5.6% of predicted (p=0.032) (Figure 11). Correspondingly, per protocol analysis showed no significant between-group differences in FVC, FEV_1, DL_{CO} or MVV (data not shown).

Two patients in the exercise group had a reduction in % predicted FEV_1 of 11% and 18%, respectively, due to BOS. When these two were excluded from the analysis, the decrease was 3.2% (p=0.141).

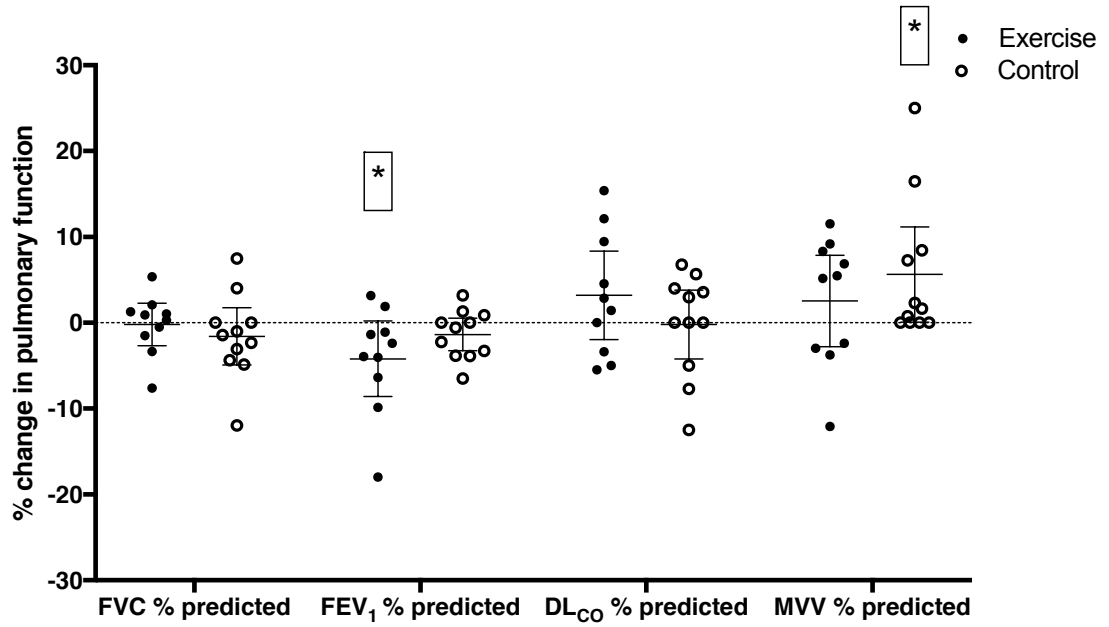

Figure 11: *Percent change in pulmonary function in percent of predicted from baseline to after the intervention according to intervention group. Error bars indicate 95% CI of the mean. The dots represent the individual change.*
**= significant mean difference from baseline to follow-up within the group (p<0.05).*

Table 8: *Between-group differences between baseline and after intervention for pulmonary function and peak oxygen uptake.*

	Baseline		After intervention		Between-group difference	
Outcome variable	**Exercise**	**Control**	**Exercise**	**Control**	**Difference (95% CI)**	**p value**
FVC L	3.6±0.8	3.4±1.1	3.6±0.7	3.3±1.1	0.02 (-0.1 – 0,1)	0.641
% of predicted	93±19	85±23	93±19	84±22.	1.5 (-1.5 – 4.4)	0.253
FEV_1 L	2.6±0.7	2.2±0.7	2.4±0.7	2.1±0.6	-0.1 (-0.2 – 0.01)	0.118
% of predicted	85±28	70±22	82±29	68±20	-1.2 (-3.8 – 1.4)	0.450
DL_{CO} $mmoL \cdot min^{-1} \cdot kPa^{-1}$	6.2±1.6	5.9±1.8	6.3±1.4	5.9±1.8	0.2 (-0.1 – 0.6)	0.202
% of predicted	70±17	65±17	71±15	65±18	1,6 (-2.4 – 5.6)	0.331
MVV $L \cdot min^{-1}$	108.7±25.1	97.6±36.1	111.8±28.6	101.0±35.8	-0.3 (-6.1 – 5.4)	0.826
% of predicted	100±21	86±28	104±27	90±26	-0.03 (-5.5 – 2.6)	0.844
VO_{2peak} $mL \cdot kg^{-1} \cdot min^{-1}$	22.9±8.4	21.1±6.5	25.2±8.4	22.1±6.5	1.1 (-0.3 – 2.5)	0.115
% of predicted	67±16	59±15	74±16	62±15	3.8 (-0.3 – 7.9)	0.059
VO_{2peak} $L \cdot min^{-1}$	1.6±0.4	1.6±0.4	1.8±0.4	1.7±0.4	0.1 (-0.01 – 0.2)	0.086
% of predicted	66±12	63±17	74±13	66±16	5.1 (0.4 – 9.8)	0.035

Data are presented as mean±SD.
FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s; DL_{CO}, diffusing capacity of the lung for carbon monoxide; MVV, maximal voluntary ventilation, VO_{2peak}, peak oxygen uptake.

4.7 *Effect of high-intensity training on cardiorespiratory fitness*

Intention-to-treat analysis showed that the % of predicted VO_{2peak} ($L \cdot min^{-1}$) in the exercise group increased by 13% (p=0.001), and the control group by 7% (p=0.030), giving a between-group difference of 5.1 in % of predicted (p=0.035) (table 8). Percent of predicted VO_{2peak}, adjusted for weight, was borderline significant (p=0.059). Five patients in the exercise group increased by greater than 15% , and one patient in the control group decreased -9.75%. There were no significant between-group differences in VO_{2peak} regarding $mL \cdot kg^{-1} \cdot min^{-1}$, and in $L \cdot min^{-1}$. Per-protocol analysis did not lead to other conclusions (data not shown).

One patient in the control group increased 27% in VO_{2peak} $ml \cdot kg^{-1} \cdot min^{-1}$. The patient had not exercised, but had begun with continuous positive airway pressure (CPAP) during the nights after the randomization.

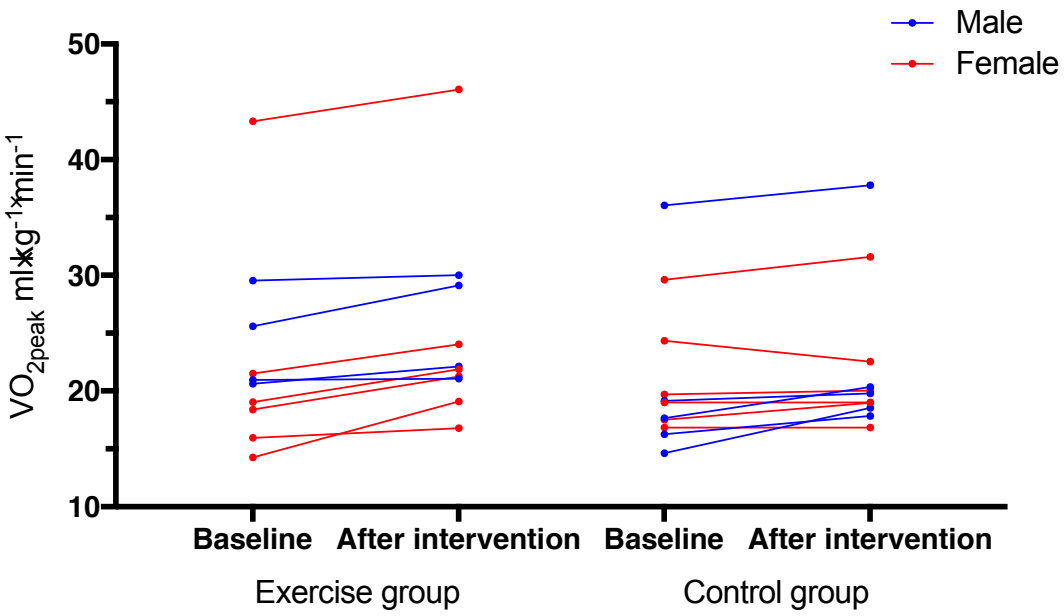

Figure 12: *Peak oxygen uptake (VO_{2peak}) from baseline to after the intervention according to intervention group and gender.*

There were no significant between-group differences in respiratory exchange ratio, blood lactate concentration or Borg RPE before and after the intervention (table 9).

Table 9: *Typical end criteria for maximum effort and reason for termination during the cardiopulmonary exercise test at baseline and after the intervention for the exercise- and the control group.*

Variables	Exercise	Control	p Value
Mean baseline			
Respiratory exchange ratio	1.08±0.09	1.10±0.11	0.592
Blood lactate concentration, mmol/L[a]	8.8±3.1	8.6±2.7	0.771
6-20 Borg scale, rating number	18.4±1.1	18.3±1.1	0.783
Hemoglobin $g \cdot dL^{-1}$	12.4±1.7	13.0±1.8	0.430
Reason for test termination			
Leg fatigue, n (%)	3 (30)	5 (46)	
Dyspnea, n (%)	3 (30)	5 (46)	
General fatigue, n (%)	4 (40)	1 (9)	
After intervention			
Respiratory exchange ratio	1.11±0.09	1.05±0.11	0.502
Blood lactate concentration, mmol/L[B]	10.6±3.3	9±2.9	0.217
6-20 Borg scale, rating number	18.6±0.8	18.3±1.1	0.458
Hemoglobin $g \cdot dL^{-1}$	12.6±1.6	13.1±1.8	0.527
Reason for test termination			
Leg fatigue, n (%)	2 (20)	1 (11)	
Dyspnea, n (%)	5 (50)	3 (33)	
General fatigue, n (%)	3 (30)	5 (50)	

Data are presented as mean±SD or n (%).
Blood lactate concentration was taken 60 sec after termination as an indicator of high effort (78).
[a] Based on 15 patients who had measures of lactate concentration.
[B] Based on 19 patients who had measures of lactate concentration.

5. Discussion

5.1 Main findings

Our study demonstrated that LTx recipients have a low cardiorespiratory fitness, even among those with normalized pulmonary function. Our analysis revealed moderate correlations between pulmonary function, VO_{2peak} and dyspnea. More importantly, the HIT-program significantly improved VO_{2peak} % of predicted, as compared to the control group. HIT did not result in any significant between-group differences for change in pulmonary function.

5.2 Methodological considerations

The HILT study is a randomized controlled trial, which are considered the preferred study design when the purpose is to investigate whether an intervention has a causal effect on differences in outcomes between an intervention- and a control group (41). Block randomization was conducted by an external statistician and therefore proceeded without subjective influence. This avoids systematic differences between the groups and reduces the risk of selection bias (41). It was not possible to implement a double-blinded RCT due to the intervention involving exercise. During follow-up, study technicians were also often un-blinded, due to the patients revealing which group they were randomized to. This increase the risk of performance bias (41), and may have resulted in different degrees of encouragement during the follow-up test procedures. However, end criteria for maximal effort did not differ between the groups, neither before randomization nor after, suggesting no difference in effort between the groups.

Participants

The study sample in this thesis is small compared to the sample size calculation for the HILT-study (data not shown). Therefore, the results may not be generalizable. However, participants were representative of LTx recipients generally, including patients with a broad age range, some with chronic rejection and some re-transplanted patients. Participation was voluntary and thorough information about the purpose of the study was given before participation; therefore some of the patients who were already physically active may have been more likely to participate. The patients who were

randomized to the control group, but desired to be in the intervention group, may have been motivated to exercise on their own.

Test procedures

All technicians followed the same test procedures according to current guidelines (46, 93, 94), to ensure as reliable and accurate measurements as possible. The same equipment was used for all measurements, calibrated daily and with the same protocol. Most pulmonary function procedures were well known to all the patients. Unfortunately, DL_{CO} was not adjusted for Hb, which was not available in all patients. This may have underestimated the results in those with a low Hb.

Cardiopulmonary exercise test

CPET was performed by uphill walking on a treadmill, where VO_{2peak} has been shown to be 10-20% higher compared to bicycle due to weight bearing activity involving large muscle groups (48). This is an important factor when comparing our results to the studies that have performed CPET using bicycle. Furthermore, there may have been a learning effect after the first CPET. However, there were no between-group differences in end criteria for maximum effort during CPET.

Intervention

The exercise was performed with one-on-one supervision individually tailored, which made it possible to ensure individual exercise progressions from week to week. Different trainers and physical therapists exercised the patients regarding follow-up and exercise intensity. This was addressed by clear guidelines and regular follow-up, as well as only including trainers having relevant education. In addition, choosing different trainers throughout the country reflects the real-world clinical situation.

Statistics

Considering the sample size calculations conducted for the HILT study (data not shown), the sample size in this thesis is not adequate size to achieve sufficient power. In other words, there may not be a sufficient number of patients to have a high probability of detecting a clinically important difference between the groups if a difference truly exists. All patients were included in the intention-to-treat analysis, and the patients with 70% compliance to the intervention were included in the per-protocol analysis.

5.3 Discussion of the results

5.3.1 Pulmonary function

The patients in the present study had pulmonary function values (FVC, FEV_1, TLC and MVV) in the lower range of predicted. Among the 48 patients who were tested, 48% had an impaired FEV_1 (<80% of predicted). Among the patients with impaired FEV_1, there were more males (65%) than females and two patients had been re-transplanted. Forty-four percent had pulmonary fibrosis as native disease, and 40% were former smokers. Interestingly, the patients with impaired FEV_1 were transplanted an average of 32 months prior to enrollment in the study, in contrast to 26 months in those with normal values. Mean age was comparable. Among the patients with impaired FEV_1, three patients had BOS stage 1, two patients had BOS stage 2 and three patients had BOS stage 3. BOS results in a reduction in FEV_1, and therefore the prevalence affects the mean value for the total population.

The majority of the patients (87%) had an impaired DL_{CO} (<80% of predicted). Mean time after LTx was 29 months, in contrast to 25 months among those with normal values. Mean age was lower among the patients with impaired DL_{CO}, compared with those within normal values (50 vs 58 years).

5.3.1.1 Comparison with other studies

Pulmonary function following LTx has not been well described in a large cohort of bilateral LTx recipients, especially for DL_{CO}, TLC and MVV. Most studies have investigated pulmonary function during the first six months following LTx (7, 54, 67), and the majority of the studies investigating pulmonary function greater than six months after LTx have very small sample sizes (31, 63, 64, 66, 69, 71, 72). Therefore, this study gives added insight into the post-BLTx pulmonary function of a substantial amount of patients with varied native diseases.

Two studies have examined pulmonary function greater than six months after BLTx in a large cohort (28, 52). Mason et al (2008) investigated pulmonary function in 194 patients one year after BLTx, where mean values of FEV_1 and FVC was 65% and 67% of predicted, respectively (28). Bartels et al (2011) found a mean FEV_1 and FVC of 90% and 87% of predicted, respectively, in 119 BLTx recipients within 30 months post-transplant (52). Furthermore, TLC, DL_{CO} and MVV were 85%, 57% and 99% of

predicted, respectively. Results from our study are comparable to the results from Bartels et al (2011), and the mean time after BLTx (30 vs 29 months) was approximately the same. The study by Mason et al (2008) included ten patients who had undergone single lung transplantation (28), and this will explain the lower values compared to our study. In addition, reference values have not been specified or it has been used different reference values compared to our study, which makes comparisons difficult.

FEV_1 and FVC have been found to peak between six months and one year after LTx, and further persisted with a minimal, continuous decline to five years post-transplant (28). This corresponds to some extent with our results where FEV_1 was higher in the patients transplanted within two years prior to study inclusion, compared to the patients transplanted greater than two years prior to study inclusion.

Interestingly, a retrospective analysis of 104 BLTx recipients observed a decline in DL_{CO} following the first three years post-transplant, with a median of 60% of predicted after three years (65). This is in accordance with our findings, with a mean of 66% of predicted. However, our population was assessed in the range of six to 59 months post-transplant in contrast to at three years post-transplant in the mentioned study. Anyway, our findings gives new information about DL_{CO} following LTx, as this previously has not been well described in large cohorts following LTx.

The explanation for the unexpectedly lower pulmonary function is somewhat unclear and warrants further investigation. However, among different native diseases for BLTx, patients with COPD have been found to have higher values of FEV_1, perhaps related to chest size (28). On the other hand, patients with previous emphysema have been found to have higher TLC values than predicted. Differences in recipient and donor age have been found to impact the outcomes, where smaller differences are associated with higher FEV_1, and to some extent also FVC (28). This might be due to the physiological changes occurring with increasing age, for example changes in lung elastic recoil strength (100). However, it is not given that a minor difference between donor and recipient age means that the lungs are younger and more elastic.

5.3.2 Cardiorespiratory fitness

Adjusted for weight, VO_{2peak} was only 65% of predicted in our study. Forty-three patients had an impaired VO_{2peak}, despite an overall near normal pulmonary function, except for DL_{CO}. Among the patients with impaired DL_{CO}, two patients had a fall in SPO_2 of 10% during CPET, and one of these was re-transplanted. Three patients with impaired DL_{CO} had a fall of 5% in SPO_2, probably due to an impaired diffusing capacity in the lung. Peak heart rates reflected good effort, and the high RER and $[La^+]$ levels during CPET indicated anaerobic metabolism. Leg fatigue was the most common reason for termination of the CPET.

5.3.2.1 Comparison with other studies

Our results for VO_{2peak} are somewhat higher compared to Bartels et al (2011) and Armstrong et al (2015) with 52% and 55% of predicted, respectively (52, 73). These results are perhaps not surprising, as 10 patients in the study by Armstrong et al (2015) had undergone single lung transplantation (73), which affects the results. In addition, both studies used cycle ergometry for the measurement of VO_{2peak}, which have been found to produce lower values compared to treadmill (76), which was used in our study. Mean age was comparable between the studies, although our study had a much greater age range, where the youngest patient was 20 years. However, comparisons of the studies becomes difficult as it either has not been specified or it has been used differenct reference values in comparison to our study.

Only a few patients had a reduction in SPO_2 during CPET, which may indicate that the limitations in VO_{2peak} are due to cardiovascular factors or deconditioning. In accordance with the findings from the present study, Bartels et al (2011) also reported leg fatigue as the main reason for termination of CPET (52). The same study failed to find a primary pulmonary or cardiac limit to the reduced VO_{2peak}.

Peripheral factors such as skeletal muscle oxygen delivery, uptake, and utilization seem to be the most important factors for the limitation in cardiorespiratory fitness (80). The use of immunosuppressant medication, including glucocorticoids that induce muscle atrophy (101), and deconditioning seem to play a role regarding this reduced oxidative capacity. However, this has not yet been fully explored. The physiologic data supporting the presence of muscular and peripheral limitations to exercise in LTx

recipients have been documented in several studies, where the reduced capacity in m. Quadriceps seems to play a key role (102, 103). Evans et al (1997) found reduced m. Quadriceps pH and phosphorylation, suggesting this abnormal skeletal muscle oxidative capacity as a role in the limitation of VO_{2peak} (102). This was confirmed by Reinsma et al (2006) who found a correlation between m. Quadriceps force and exercise capacity (71). Morton et al (1999) performed muscle biopsies of m. Quadriceps and found a reduction in proportion of type 1 muscle fibers and oxidative enzymes, both before and after LTx (104), suggesting that these changes occur in the pre-transplant condition (104). The muscle dysfunction may be caused by several factors, including proximal myopathy due to high doses of corticosteroids (105).

Pre-transplant levels of functioning, rather than the native disease, have been found to be a decisive factor regarding VO_{2peak} post-transplant (52). Age does not seem to play a role in VO_{2peak} following LTx (52), therefore skeletal abnormalities inherent to the patients of younger age, typically those with previous cystic fibrosis, are suggested as cause for the reduced VO_{2peak}.

5.3.3 Association between pulmonary function, peak oxygen uptake and dyspnea

In the present study we aimed to investigate the association between mMRC, pulmonary function and VO_{2peak} in lung transplant recipients, and all the correlations were moderate. The patients reported a very low degree of subjectively measured dyspnea, which may not be surprising given their near normalized pulmonary function. However, we speculate that transplanted patients experience dyspnea differently than other patient groups, perhaps reporting less dyspnea at a given degree of objective respiratory limitation. This could be related to their experience of large, natural improvements following LTx compared to their pre-transplant status. Dyspnea correlated better with DL_{CO} than FEV_1, which may indicate that diffusion capacity is of greater importance than ventilation with regard to dyspnea.

There was a negative, moderate correlation between dyspnea and VO_{2peak}. It may therefore appear that dyspnea to some extent can predict lower VO_{2peak}. Exercise can increase VO_{2peak}, and therefore perhaps reduce the degree of dyspnea via increasing in VO_{2peak}.

There was a positive, moderate correlation between VO_{2peak} and, respectively, FEV_1 and DL_{CO}. It seems that a higher pulmonary function to some extent can predict better VO_{2peak}. VO_{2peak} was significantly impaired in our study, as opposed to pulmonary function. To my knowledge, no studies have previously evaluated this association in the LTx population. However, there are some studies from other patient populations. One study found a high correlation between VO_{2peak} and FEV_1 (r: 0.71) in 102 patients with cystic fibrosis (106). This latter is in accordance with the findings from Chaurasia et al (2014) where VO_{2peak} correlated with FEV_1 (r:0.79) in 50 stable patients with COPD (107). Furthermore, a systematic review reported a moderate to strong correlation in all seven studies regarding VO_{2peak} and FEV_1 (r:0.42-0.83) in patients with COPD (108). The above discrepancies among previous studies may be related to a more impaired pulmonary function in the patients investigated, where they could have been more ventilation limited, which may influence the results. Therefore, findings from the mentioned studies must be interpreted with caution, due to the use of other patient populations.

According to our results, all of the key variables we investigated were moderately correlated. No previous studies have investigated these associations in the LTx population. Therefore, further investigation is needed to determine the association between dyspnea, pulmonary function and peak oxygen uptake.

5.3.4 Effect of exercise on pulmonary function

Neither intention-to-treat analysis nor per-protocol analysis showed significant between-group differences in pulmonary function, following HIT. These findings were expected, as exercise is not known to improve pulmonary function in other settings.

5.3.3.1 Forced vital capacity and forced expiratory volume in one second

HIT resulted in a non-significant increase of 1.5 % and a decrease of 1.2% of predicted value in FVC and FEV_1, respectively, between the groups. These changes are not considered clinically important.

None of the previous RCT studies have reported the effect of exercise training on FVC, and only one on FEV_1. Langer et al (2010) found an insignificant between-group difference in FEV_1 after 12 weeks of moderate exercise (12). Importantly, they used

differenct reference values compared to our study, which makes comparisons difficult. In addition, small sample size, a mix of single and bilateral LTx recipients in addition to measurements within the three first months following hospital discharge, makes it impossible to separate the effects of exercise training with the natural recovery process that could occur with the gradual return to normal activities after LTx.

5.3.3.2 Diffusing capacity of the lung for carbon monoxide

There was no significant between-group difference in the change in DL_{CO} between exercise training and control. However, previous studies are strikingly inconsistent with respect to the effect of exercise on DL_{CO} in adults in general. Some have found improvements (109, 110), while others have not (96, 111, 112). Within-day variations in DL_{CO} have been found, in addition to a variability as much as 9% in repeated measurements (46). The natural variation may possibly be leveled out in a big population; however, the present study included a small sample. Therefore, results must be interpreted with caution, as bigger improvements in DL_{CO} are needed to state a true effect of exercise and a physiological change, rather than natural biological variation or technical variation of the equipment. No previous studies have investigated the effect of exercise on DL_{CO} in LTx recipients.

5.3.3.3 Ventilatory capacity

The ventilatory capacity measured as MVV was within normal limits in both groups, and no significant between-group difference in the change in MVV was observed following HIT. Two patients in the control group had an increase in % of predicted MVV of 16% and 25%, respectively. However, MVV is effort-dependent, and an optimal respiratory rate might be difficult to achieve. A learning effect can therefore not been ruled out. No previous studies have investigated the effect of exercise on MVV in BLTx recipients.

5.3.5 Effect of exercise on peak oxygen uptake

HIT resulted in a significant improvement in % of predicted absolute VO_{2peak} compared to the control group. At follow-up, the mean change in VO_{2peak} between the groups was 1.1 $ml \cdot kg^{-1} \cdot min^{-1}$, which was borderline significant when investigating percent of predicted. This is far less than expected, as HIT has shown far greater effects in other patient groups (16, 113-115) including heart transplant patients (91). There may be

several explanations for this. First, genetic factors have been found to contribute to approximately 50% of an individual's VO_{2max} trainability (116), while the remaining 50% depends on the environment, such as exercise and diet (117). Second, we have not investigated details of the actual training intensity or of progression achieved by each patient in the exercise group; therefore it is difficult to determine whether the training stimulus was adequate to induce improvements in VO_{2peak}. However, one patient in the control group increased by as much as 27% in VO_{2peak} $mL \cdot kg^{-1} \cdot min^{-1}$. When this patient was excluded from the intention-to-treat analyses, HIT resulted in significant between-group differences in VO_{2peak}. The patient had not exercised, but had started with CPAP at night after the randomization. The use of CPAP over several months have been found to significantly increase VO_{2peak} (118), therefore, we speculate that this could be a factor contributing to the patient's improvement. Peak RER levels achieved indicated good exercise effort in both groups. Furthermore, the patient-stated cause for termination of exercise was leg fatigue and dyspnea at baseline, in contrast to dyspnea in the exercise group and general fatigue in the control group at follow-up.

5.3.4.1 Comparison with other studies

To my knowledge, no previous studies have investigated the effect of HIT on VO_{2peak} in LTx recipients. However, as previously mentioned, two studies have examined the effect of exercise in LTx recipients using a randomized controlled design (12, 13). Langer et al (2012) assessed the effects of a 12-week endurance- and resistance training program focusing on functional recovery and cardiovascular morbidity upon hospital discharge. Adherence was not reported, and the study showed a non-significant between-group difference in VO_{2max}. The patients were older and had better pulmonary function and higher VO_{2peak} compared with the patients in the present study. Importantly, Langer et al (2012) excluded more than 70% of the LTx recipients at their center, 85% had a pre-transplant diagnosis of COPD and all experienced an uncomplicated post-operative course. Therefore, the participants in the latter study are not representative for the LTx population as a whole. The HIT in the present study had an eight-week longer intervention performed. In addition, the mode of endurance training differed between the studies, where Langer et al (2012) used a combination of cycle ergometry and treadmill walking with moderate intensity, in contrast to treadmill uphill walking with high intensity in our study. We included heavy, progressive resistance training, in contrast to Langer et al (2012) who only included one resistance

exercise with a load set at 70% of 1RM. This may have contributed to a greater increase in VO_{2peak} in our study. It is known that resistance training can increase VO_{2peak}, especially in severely deconditioned adults (119, 120). Importantly, Langer et al (2012) used different referance values for VO_{2peak} compared to our study, which makes comparisons even more difficult.

Five other studies have been published about the effect of exercise on VO_{2peak} in LTx recipients (13, 64, 85, 86, 89). All the studies could document positive training effects, but none had a non-exercising control group with LTx recipients. Therefore, they must be interpreted with caution. In addition, the interventions has been short, with low exercise intensity, home-based programs and used a lower quality of methodology for the measurements.

5.3.4.2 Effect of exercise on peak oxygen uptake in other populations

In general, VO_{2peak} is a strong and independent predictor of survival, including in LTx recipients (5). The net increase of VO_{2peak} of 1.1 $ml \cdot kg^{-1} \cdot min^{-1}$ in the present thesis using intention-to-treat analysis is low compared with results seen in heart transplant (HTx) recipients from Norway (91). HTx recipients were randomized one to eight years after transplantation to either HIT or a control group, exercising three times per week for eight weeks at 85-95% of peak heart rate three times during one year. HIT resulted in a significant between-group difference in VO_{2peak} of 3.2 $ml \cdot kg^{-1} \cdot min^{-1}$ (13%) (91). However, HTx recipients demonstrate other responses to exercise compared to LTx recipients, although they also go through a deconditioning pre-transplant in addition to taking similar immunosuppressive medications post-transplant. Importantly, they often do not go through a deconditioning to the same degree as the LTx recipients, which may explain some of the differences in results. In addition, the majority of the LTx patients have used heavy doses of corticosteroids pre LTx, which we know have a severe impact on the muscle function (101), in contrast to the HTx patients.

Percent of predicted VO_{2peak} in the present study ranged from 42% to 97% at follow-up, and are on average below predicted values compared to a Norwegian study with a broad age-range (121). An increase in VO_{2peak} following exercise between 2.6 and 5.5 $ml \cdot kg^{-1} \cdot min^{-1}$ are observed in patients with coronary heart disease (113), following lung cancer surgery (16), in older healthy adults (114, 115). However, one may not take for granted

that there isn't a difference, as there are completely different populations than LTx recipients.

The potential reasons for reduced cardiorespiratory fitness after LTx are only partially understood, but have been found to include immunosuppressive medications, deconditioning, muscular and peripheral limitations, which are discussed in chapter *5.3.2.1.* Unfortunately, muscle biopsy was not performed in the present study, and details about mitochondrial dysfunction, as observed in other studies (70, 103), are thus not available. The significant increase in VO_{2peak} indicates that the adverse effects of immunosuppressives could be partially reversed by exercise. This finding may foster future exercise interventions in the time after LTx, in effort to further enhance cardiorespiratory fitness up to levels within normal values.

6. Future research

Few studies have examined pulmonary function and peak oxygen uptake in a large group of exclusively BLTx recipients, with a range of age and native diseases. Additional studies are needed to investigate this and also to better understand the association between dyspnea, pulmonary function and maximum oxygen uptake in BLTx recipients. Few randomized controlled studies have investigated the effect of exercise training on pulmonary function and VO_{2peak} among LTx recipients, and thus no evidence-based guidelines for exercise training for this patient group exist. Lung transplantation is very expensive; most costs occur after transplantation and the patients need follow-up throughout their lives. Since a high CRF can improve QoL (10), prevent mortality (9), and prevent lifestyle diseases (11), the need for further research about the effect of exercise in this group is eminent.

7. Conclusion

The LTx recipients demonstrated a low cardiorespiratory fitness, despite near normalized pulmonary function. The correlation between pulmonary function, cardiorespiratory fitness and dyspnea was moderate. High-intensity endurance and resistance training induced improvements in peak oxygen uptake. Investigations with a sufficient sample size are needed to further elucidate the effect of high intensity training in lung transplant recipients.

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Appendix 4: Picture permission of private photo (Norwegian)

Appendix 5: modified Medical Research Council Dyspnea Scale

Appendix 6: Training-program used in HILT (Norwegian)

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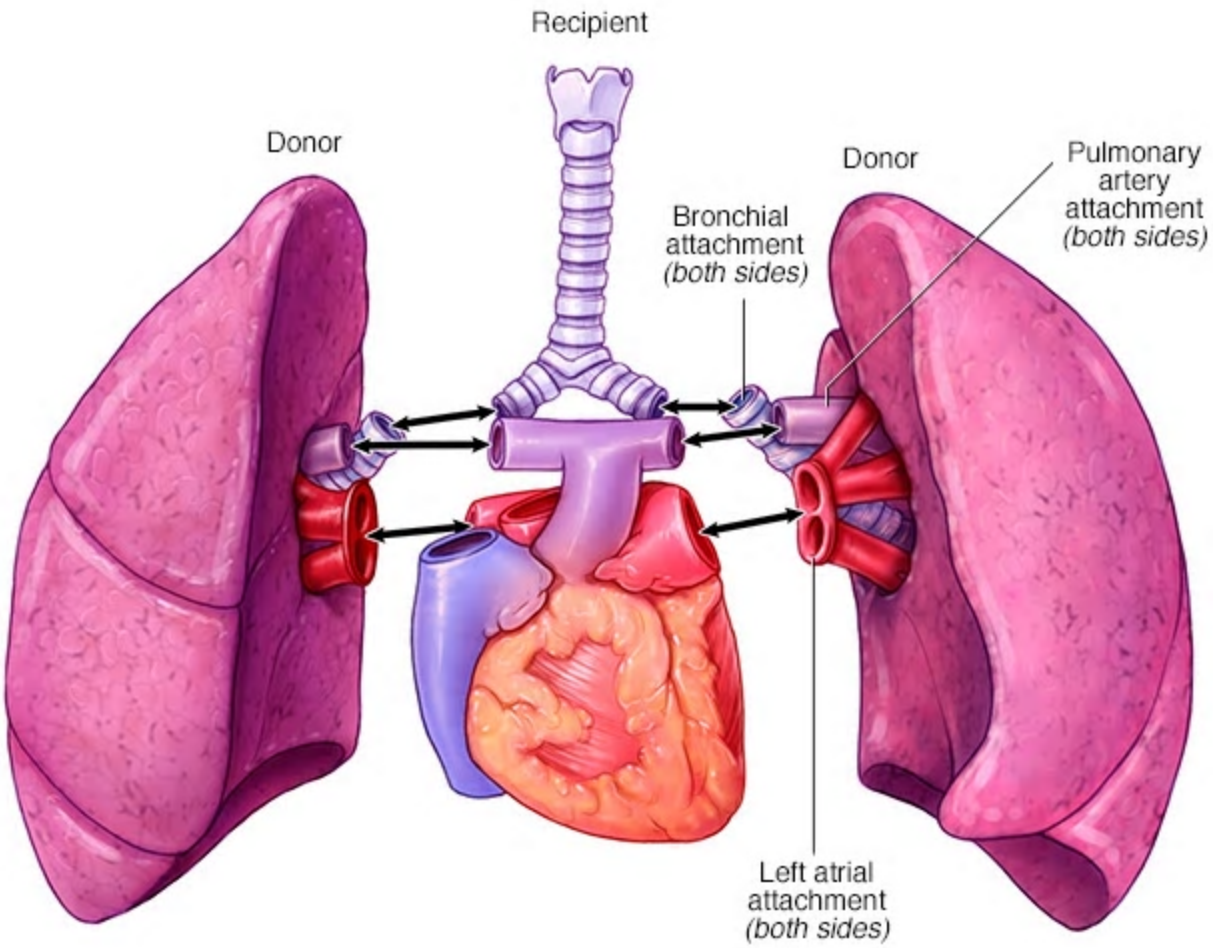

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			Deres dato:	**Deres referanse:**
			14.02.2017	

Vår referanse må oppgis ved alle henvendelser

Elisabeth Edvardsen
Oslo universitetssykehus HF

2017/399 Effekt av høyintensiv trening etter lungetransplantasjon

Forskningsansvarlig: Oslo universitetssykehus HF
Prosjektleder: Elisabeth Edvardsen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 23.03.2017. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektomtale
Pasienter som har gjennomgått lungetransplantasjon (LTx) har betydelig redusert fysisk form pga langvarig inaktivitet før LTx. Funksjonsnedsettelsen vedvarer lenge etter LTx til tross for normalisering av lungefunksjon, og er relatert til nedsatt skjelettmuskelfunksjon og dårlig fysisk form. Ca 30-50% utvikler livsstilssykdommer, og de fleste får med hyperkolesterolemi, hypertensjon, overvekt og osteoporose. Formål med prosjektet er å undersøke effekt av et høyintensivt 20 ukers treningsprogram gjennom en randomisert kontrollert studie hvor primærutfallsmål er endring i maksimalt oksygenopptak. Videre vil vi 1) kartlegge fysisk form, fysisk aktivitet og livskvalitet, 2)identifisere eventuelle fysiologiske begrensninger, 3) vurdere langtidseffekter av trening på komorbiditet og overlevelse. Studien kan ha betydning for "Standard of Care", dvs gi kunnskapsbaserte retningslinjer for rehabilitering etter LTx. Gunstig effekt på komorbiditet og overlevelse gir også helseøkonomisk gevinst.

Vurdering
I denne studien vil pasienter som har gjennomgått lungetransplantasjon ved Oslo universitetssykehus de siste tre årene, rekrutteres til et opplegg som medfører høyintensiv trening. Programmet beskrives av søker som både tidkrevende og slitsomt, og mange pasienter er engstelige for å drive med fysisk aktivitet i etterkant av operasjonen. De står dermed også i fare for å utvikle komorbiditet i form av livsstilssykdommer. Studien har som formål å finne ut om veiledet trening kan bidra til å redusere denne faren.

Medisinsk og helsefaglig forskning skal organiseres og utøves forsvarlig, jf. helseforskningslovens § 5. Før forskning på mennesker gjennomføres skal det gjøres en grundig vurdering av risiko og belastning for deltakerne. Disse må stå i forhold til påregnelige fordeler for forskningsdeltakeren selv eller for andre mennesker, jf. § 22.

Prosjektleder gir i søknaden en utførlig redegjørelse for fordeler, ulemper og forsvarlighet knyttet til prosjektet. Deltakerne vil få individuelt tilpassede treningsprogrammer, undersøkelser gjøres i sykehusmiljø og man følger opp tett underveis i prosjektperioden. Tidligere erfaring med samme intervensjon i en gruppe hjertetransplanterte, viser at studien er gjennomførbar og trygg.

Komiteen konkluderer med at prosjektet fremstår som forsvarlig.

Angående biologisk materiale i studien
Det angis i søknaden at humant biologisk materiale vil oppbevares i den godkjente generelle forskningsbiobanken *Biologiske prøver fra pasienter på Lungeavdelingen* (REK-ref. 2013/1001). Johnny Kongerud er ansvarshavende for forskningsbiobanken, som i følge søknad vil inneholde fullblod, serum, plasma og biopsimateriale.

Komiteen kan ikke gjenfinne opplysninger om en såpass omfattende prøvetaking i søknad, protokoll eller informasjonsskriv til deltakerne. I informasjonsskrivet angis det at det kun vil tas en enkelt blodprøve fra fingertupp, og skrivet inneholder ingen opplysninger om biobank.

Komiteen har dermed kun realitetsbehandlet den angitte blodprøven fra fingertupp. Øvrige prøver må søkes som en eventuell prosjektendring, etter helseforskningslovens § 11, og er således ikke dekket av denne godkjenningen.

Oppbevaring av data etter prosjektslutt
Det er i søknaden angitt en oppbevaringstid for opplysninger etter prosjektslutt på 15 år. Vanlig tid før sletting eller anonymisering etter avslutningen av et forskningsprosjekt er 5 år, jf. helseforskningslovens § 38. Komiteen kan ikke se at det er angitt noen særskilte grunner til forlenget oppbevaring av studiedata, og setter derfor en tidsavgrensning for oppbevaring av data i tråd med dagens praksis.

Ut fra dette setter komiteen følgende vilkår for prosjektet:

1. Prøvetaking utover blodprøve fra fingertupp må søkes som prosjektendring, jf. helseforskningslovens § 11.
2. Prosjektdata skal kun oppbevares i fem år etter prosjektslutt.

Vedtak
Prosjektet godkjennes under forutsetning av at ovennevnte vilkår oppfylles, jf. helseforskningslovens §§ 9 og 33.

Tillatelsen gjelder til 31.12.2032. Av dokumentasjonshensyn skal prosjektopplysningene likevel bevares inntil 31.12.2037. Opplysningene skal lagres atskilt i en nøkkel- og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Komiteens avgjørelse var enstemmig.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. Forvaltningslovens § 28 flg. Eventuell klage sendes til REK Sør-Øst. Klagefristen er tre uker fra mottak av dette brevet.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK sør-øst på eget skjema senest 15.10.2032, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK sør-øst dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Med vennlig hilsen

Britt-Ingjerd Nesheim
Professor dr.med
leder REK sør-øst C

Forespørsel om deltakelse i forskningsprosjektet

Fysisk form og effekt av høyintensiv kondisjon- og styrketrening etter lungetransplantasjon

Bakgrunn og hensikt

Dette er et spørsmål til deg om å delta i en forskningsstudie som har til hensikt å undersøke fysisk aktivitet og fysisk form etter lungetransplantasjon, samt studere effekt av et høyintensivt kondisjon- og styrketreningprogram.

Du har nå gjennomført en lungetransplantasjon for minst seks måneder siden. Transplantasjonen har bedre lungefunksjonen din betraktelig, noe som bør øke din fysiske form og bedre livskvaliteten. Man har imidlertid sett at transplanterte pasienter bruker overraskende lang tid på å hente seg inn igjen etter langvarig sykdom, og funksjonsnivået og helsestatusen bedres i mindre grad enn først forventet. Kunnskap om helse koblet opp mot funksjonsnivå og aktivitetsnivå etter transplantasjon er således mangelfull. Samtidig vet vi at systematisk trening har vist god effekt på overlevelse og økt livskvalitet hos andre pasientgrupper, men det er ikke undersøkt tidligere hos pasienter etter lungetransplantasjon. Vi ønsker derfor å invitere deg til deltakelse i et forskningsprosjekt som går ut på å kartlegge fysisk form, aktivitetsnivå og helsestatus etter transplantasjon, samt finne ut om trening kan ha positiv effekt på arbeidskapasitet, muskelfunksjon, helse, livskvalitet og overlevelse. En tilsvarende studie er gjort blant hjertetransplanterte pasienter ved Rikshospitalet, men resultatene lar seg ikke direkte overføre til lungetransplanterte. Det er Oslo Universitetssykehus som er ansvarlig for studien. Den gjennomføres i samarbeid med Norges idrettshøgskole.

Hva innebærer studien?

Studien innebærer at du må møte til en utvidet undersøkelse fire ganger i løpet av de neste to årene. Undersøkelsene vil bli samkjørt med de faste kontrollene etter transplantasjon. Den første undersøkelsen vil bli foretatt minst 6 mnd etter transplantasjon, den andre ca 6 mnd etter inklusjon, og den tredje og fjerde etter henholdsvis ett og to år etter inklusjon. Undersøkelsen omfatter grundig måling av lungefunksjonen samt gange på tredemølle fra lett til tung belastning for bestemmelse av arbeidskapasitet. Under belastningen måles også pusteevne og oksygenopptak i lungene. Det vil bli tatt en enkel blodprøve fra fingertuppen for måling av melkesyrenivå. I forbindelse med undersøkelsen vil vi også måle muskelstyrke, fysisk funksjon og kroppssammensetning. Sistnevnte for vurdering av bentetthet og størrelsen på muskelmassen. Hensikten er å se hvordan muskelmassen endrer seg i tiden etterpå. Det vil bli tatt blodprøve fra armen på vanlig måte til rutineanalyser (standardprøver etter transplantasjon). I tillegg vil det bli tatt ekstra blodprøverør til forskningsprosjektet. Disse prøvene skal langtidslagres i en egen generell biobank ved Lungeavdelingen (Navn på biobanken er Biologiske prøver fra pasienter på Lungeavdelingen (REK-ref. 2013/1001) og ansvarshavende er avdelingsleder Johnny Kongerud. Varighet 2043).

Etter den første undersøkelsen vil du bli tilfeldig trukket ut til deltakelse i enten en treningsgruppe eller en kontrollgruppe. Treningsgruppen skal trene tre ganger pr uke i ca 20 uker hvor hovedmålet er å øke kondisjon og muskelstyrke. Treningen vil foregå individuelt med personlig trener og fysioterapeut på hjemstedet ditt. Du vil starte forsiktig og intensiteten vil være tilpasset ditt eget funksjonsnivå basert på den første undersøkelsen. Deretter vil intensiteten øke både med tanke på kondisjon og muskelstyrke. Etter ca to år gjennomføres den siste undersøkelsen. Kontrollgruppen vil følge sykehusets vanlige rutine etter lungetransplantasjon, hvor vi oppfordrer til å gjennomføre rehabilitering i tråd med sykehusets anbefalinger. Kontrollgruppen deltar for øvrig i alle undersøkelsene.

Etter hver undersøkelse vil vi registrere ditt dagligdagse aktivitetsnivå over en uke. Dette skjer ved at du bærer en aktivitetsmåler (skritteller festet til livet) som registrerer bevegelse. Du må også fylle ut et spørreskjema vedrørende fysisk aktivitet, kosthold og røykevaner, symptomer og plager i forbindelse med sykdomsforløpet, samt hvordan du har det i tiden etter lungetransplantasjonen (livskvalitet).

Relevante opplysninger fra din pasientjournal vil også bli innhentet i studien. Opplysninger som registreres om deg vil være din diagnose, transplantasjonsforløp, lungefunksjonsstatus og data vedrørende fysisk form. I tillegg vil vi registrere eventuelle komplikasjoner og dødsårsak koblet opp mot funksjonell status. Opplysninger om deg kan senere bli koblet med Dødsårsaksregisteret.

Hvis vi i løpet av studien skulle avdekke uforutsette medisinske funn, vil disse blir fulgt opp umiddelbart, og adekvat utredning og behandling vil straks bli iverksatt.

Mulige fordeler og ulemper
Fordelen ved deltakelse i studien er at helsetilstanden din vil bli grundig fulgt opp, og du vil få god innsikt i egen helsesituasjon uansett hvilken gruppe du trekker. Trekkes du til deltakelse i treningsgruppen, vil du gjennom et strukturert treningsprogram og få mulighet til å bedre din fysiske form, med de gunstige innvirkninger dette kan ha på mange kroppslige funksjoner. Du vil også få tildelt en personlig treningsveileder og fysioterapeut som vil følge deg tett gjennom hele treningsperioden. Trekker du tilhørighet i kontrollgruppen vil du ikke få tilbud om ukentlige treningsøkter, men vil bli oppfordret til å delta i rehabiliteringstilbud som gis fra sykehuset og på hjemstedet. Uansett gruppetilhørighet vil du ha mulighet for å treffe likesinnede pasienter i samme situasjon som deg. Erfaringer fra studien vil senere kunne hjelpe andre i samme situasjon.

Hva skjer med informasjonen om deg
Alle målinger og registreringer tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres. Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien uansett tidspunkt, kan du kreve å få slettet innsamlede opplysninger. Opplysningene blir slettet senest i 2032.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke tilbake ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på neste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling.

Prosjektgruppe
Studien ledes av overlege Michael Durheim ved Lungeavd., Rikshospitalet, i samarbeid med fysiolog og forsker Elisabeth Edvardsen ved Lungemed. avd., Ullevål og Norges idrettshøgskole. Fra Lungeavd. Rikshospitalet og Universitetet i Oslo deltar også overlege, førsteamanuensis May Brit Lund og avdelingsleder, professor Johny Kongerud. Sistnevnte er prosjektansvarlig. Overlege, professor Lars Gullestad ved Kardiologisk avd. Rikshospitalet og Universitetet i Oslo er medarbeider i prosjektet. Professor Ingar M Holme og professor Truls Raastad er samarbeidspartnere fra Norges idrettshøgskole.
Dersom du har spørsmål til studien eller senere ønsker å trekke deg, kan du kontakte prosjektleder, overlege Michael Durheim, på tlf 23 07 25 15.

Samtykke for deltakelse i studien

Jeg er villig til å delta i studien

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Signert av prosjektdeltaker Dato

Bekreftelse på at informasjon er gitt deltakeren i studien

Jeg bekrefter å ha gitt informasjon om studien

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Prosjektleder Dato

Samtykkeskjema

Jeg gir med dette tillatelse til at bilder og film tatt av meg under trening ved Norges Idrettshøyskole og testing ved Rikshospitalet i forbindelse med HILT-studien, februar 2018, kan benyttes i arbeid relatert til masteroppgavene til henholdsvis Vibeke Klungerbo, Hanne Flatsetøy og Inger Lise Pladsen Altern. Bilder og film kan også benyttes i forbindelse med presentasjon av resultater.

Bjørn Skansen

Bjørn M. Skansen

Modified Medical Research Council (mMRC) Dyspnea Scale

Grade		Description of breathlessness
☐	0	*Breathless only with strenous exercise* Jeg blir tungpustet bare når jeg trener hardt
☐	1	*Short of breath when hurrying on the level or up a slight hill* Jeg får åndenød når jeg skynder meg på flat mark eller i slakk motbakke
☐	2	*Slower than most people of the same age on a level surface, or have to stop when walking at my own pace on the level* Jeg er tregere enn de fleste på min alder på flat mark, eller jeg må stoppe på grunn av tungpust når jeg går i mitt eget tempo på flat mark
☐	3	*Stop for breathing walking 100 meters, or after walking a few minutes at my own pace on the level* Jeg må stoppe for å få igjen pusten etter 100 meters gange, eller etter noen få minutter i mitt eget tempo på flat mark
☐	4	*Too breathless to leave the house, or breathless when dressing or undressing* Jeg er så tungpustet at jeg ikke kommer meg ut av huset, eller blir tungpusten ved på- og avkledning

HILT
High Intensity training after Lung Transplantation

Treningsprogram i HILT-studien

Informasjon til fysioterapeut/personlig trener
De første fire uker er introduksjonsuker med fokus på innkjøring av belastning på intervalldragene samt innlæring av riktig teknikk i styrkeøvelsene. I tillegg skal dere bli kjent med hverandre og pasienten skal oppleve mestring. Fra uke **fem** starter høyintensiv trening. Kjenner du pasienten fra før, kan du fint korte ned på introduksjonsperioden og øke intensiteten noe raskere.

Utholdenhet:
Hovedmål med utholdenhetstreningen er å øke pasientens maksimale oksygenopptak med minst 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ i løpet av treningsperioden. Det er godt dokumentert at intervalltrening med høy intensitet gir best treningseffekt både hos friske så vel som hos ulike pasientgrupper. Derfor er hovedfokus i HILT studien intervalltrening.

- ✓ Etter gradvis økende oppvarming starter intervalldragene bestående av motbakkegange på tredemølle (lav hastighet, bratt motbakke). Intensiteten skal ligge mellom 85 til 95% av HFmax og/eller Borg skala 15-18. For variasjonens skyld kan man gjennomføre enkelte intervalløkter på ellipse maskin, i trapp eller i motbakke utendørs. Sikre aktive pauser mellom hvert intervalldrag.
- ✓ Enkelte pasienter står på medisiner (betablokker) som bremser hjertefrekvensen, slik at pulsen ikke kan brukes ved styring av treningsintensiteten. Sikre da Borg skala mellom 15 – 18 i siste minutt i hvert intervalldrag.
- ✓ For de pasienter som har redusert lungefunksjon, er det gunstig med kortere intervalldrag for å hente inn pusten mellom hvert drag. Prøv deg frem her.

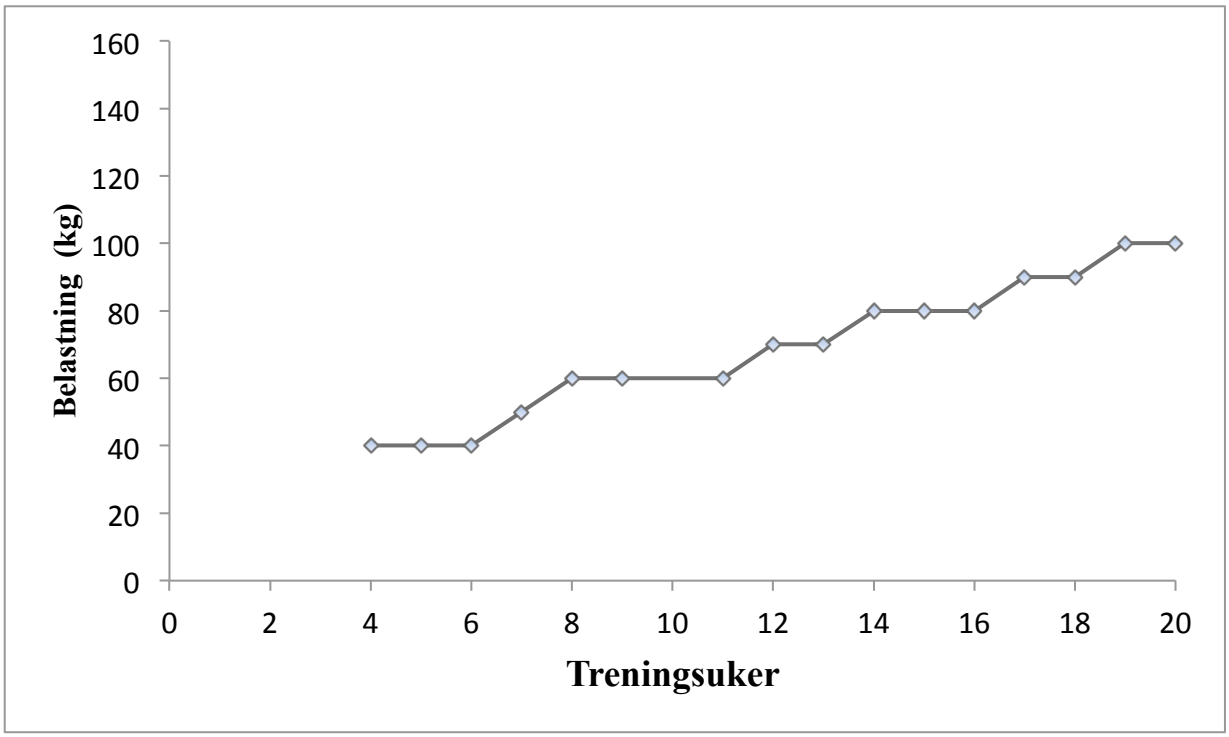
Styrketrening:
Hovedmål med styrketreningen er å øke pasientens maksimale styrke i underkroppen og overkroppen. De viktigste muskelgruppene som skal trenes er følgelig strekkapparatet i beina, brystpress og nedtrekk. Hos friske utrente individer kan man forvente en økning på opptil 1% for hver styrkeøkt hvis belastningen er stor nok (tung belastning, få repetisjoner).

- ✓ Belastningen styres etter RM-prinsippet (xRM=repetisjon maximum), hvor x angir antall ganger man klarer å løfte en angitt belastning. Eksempelvis betyr 8RM at pasienten maksimalt orker 8 repetisjoner på samme belastning. Klarer vedkommende 9 repetisjoner, har belastningen i antall kg vært for lav. Ved 8 av 10RM, skal pasienten ta 8 repetisjoner på en belastning vedkommende maksimalt vil klare 10 repetisjoner. RM-trening skal være tungt. Følelsesmessig oppleves det mer belastende med 15RM istedenfor 6 RM selv om antall kg man kan løfte er lavere ved 15RM.
- ✓ Ved behov for variasjon, bytt ut med øvelser som belaster samme muskelgruppe. Har du ikke brystpressapparat, drill inn teknikk i benkpress og evt varier med push-ups.
- ✓ Sikre god teknikk i alle styrkeøvelser, og gi positiv feedback underveis og i etterkant. Noter ned i øktplan antall serier og kg i hoved-øvelsene

Generelt

- ✓ Sikre god progresjon underveis i treningsprogrammet og tilpass hver økt basert på pasientens dagsform.
- ✓ Pasientene oppfordres til hverdagsaktivitet og turgåing de dager det ikke gjennomføres trening.
- ✓ Pass på at pasienten medbringer treningsdagboken sin til hver trening.
- ✓ Noter ned 10RM i beinpress og brystpress hver 2. uke i treningsdagboken (se figur nederst).
- ✓ Hvis pasienten ikke kan møte til planlagt tidspunkt, avtal nytt tidspunkt samme dag, eller neste dag hvis mulig.
- ✓ Spør alltid hvordan det går.

Ta gjerne kontakt om noe skulle være uklart eller du har andre spørsmål ☺



Figuren viser treningsprogresjon i 10RM i beinpress fra uke til uke hos en 70 år gammel kvinne som nylig var operert for lungekreft. De fire første uker er introduksjonsuker, og således ikke registrert i figuren. Gjennom treningsperioden økte hun fra 40kg i 10RM til 100kg i 10RM. Muskelmassen økte med nesten 3 kg målt med DXA scan. I RM økte med 50 kg.

Utholdenhet: Oppvarming: 5-8 min, 60-75% av HFmax tilsvarende Borg 6-12, med lett gange på tredemølle eller tilsvarende. Deretter påfølgende intervalldrag. Pause mellom dragene: 1-2 min avhengig av lengden på intervallet (2-4 min). Fredager noe kortere intervall pga noe større belastning på styrke
Styrke: Pause mellom hvert sett: 40-60 sekunder. 60-90 sekunder under økt 3 hvis tid.

Periode	Økt 1	Økt 2	Økt 3
Uke 1-3 (intro) **Utholdenhet:**	3x4 min P: 2 min 80-85% HFmax	3x4 min P: 2 min 80-85% HFmax	3x4 min P: 2 min 85% HFmax
Styrke:	2x12 av 15RM	3x8 av 10RM	4x5 av 7RM
Uke 4 **Utholdenhet:**	3x4 min P: 2 min 85-90% HFmax	3x4 min P: 2 min 85-90% HFmax	6 x 2 min P: 1 min 85-95% HFmax
Styrke:	3x10RM	3x8RM	1x5 av 7RM 3x5RM
Uke 5 -7 **Utholdenhet:**	4x4 min P: 2 min 85-95% HFmax	4x4 min P: 2 min 85-95% HFmax	6 x 2 min P: 1 min 85-95% HFmax
Styrke:	3x10RM	3x8RM	4x5RM
Uke 8 (LETT) **Utholdenhet:**	4x4 min P: 2 min 80-85% HFmax	4x4 min P: 2 min 80-85% HFmax	6 x 2 min P: 1 min 85-90% HFmax
Styrke:	3x10 av 15RM	3x8 av 10RM	4x5 av 8RM
Uke 9-12 **Utholdenhet:**	4x4 min P:2 min 85-95% HFmax	4x4 min P: 2 min 85-95% HFmax	8 x 2 min P: 1 min 85-95% HFmax
Styrke:	3x10RM	3x8RM	5x4RM
Uke 13 (LETT) **Utholdenhet:**	4x4 min P: 2 min 80-85% HFmax	4x4 min P: 2 min 80-85% HFmax	8 x 2 min P: 1 min 85-90% HFmax
Styrke:	3x10 av 12RM	3x8 av 10RM	5x4 av 6RM
Uke 14-16 **Utholdenhet:**	4x4 min P: 2 min 90-95 % av HFmax	4x4 min P: 2 min 90- 95% HFmax	8 x 2 min P: 1 min 85-95% HFmax
Styrke:	3x10RM	3x8RM	5x4RM
Uke 17-20 **Utholdenhet:**	5x4 min P: 2 min 90-95% HFmax	5x4 min P: 2 min 90- 95% HFmax	8 x 2 min P: 1 min 85-95% HFmax
Styrke:	3x10RM	3x8RM	5x4RM

Prioriterte øvelser styrketrening

Oppvarming: Utfør ett lett sett med beinpress og brystpress før disse to øvelsene gjennomføres.

Uke 1-4	A Beinpress B Brystpress C Legcurl D Nedtrekk
Uke 5-8	A1 Beinpress A2 Leg extension B1 Brystpress B2 Pushups C Nedtrekk
Uke 9-12	A1 Beinpress A2 Bulgarsk utfall B1 Brystpress B2 Pushups C Sittende roing D Leg curl (hvis tid)
Uke 13-20	A1 Beinpress A2 Bulgarsk utfall B1 Brystpress B2 Pushups C1 Nedtrekk C2 Sittende roing D Leg curl (hvis tid)

A1 og A2 = supersett. To øvelser gjennomføres etter hverandre før det blir pause
B1 og B2 = supersett. To øvelser gjennomføres etter hverandre før det blir pause

Eksempel på loggføring av økt:

Intervalltrening

Drag (min)	Hastighet (km/t)	Motbakke (%)	PULS (s/min)	BORG (6-20)
1 (4)	3, 3, 3, 3	15 – 15 – 15 - 15	120 – 130 – 136 – 139	8 – 11 – 12 – 14
2 (4)	3, 3, 3,5 3,5	15 – 15 – 15 – 15	133 – 139 – 145 – 147	11 – 12 – 13 – 14
3 (4)	3,5 3,5 3,5 4	15 – 15 – 15 - 15	135 – 143 – 148 – 153	12 – 13 – 14 – 14

Styrke

Øvelse	**1.sett**		**2. sett**	
	Reps	Kg	Reps	Kg
A: Beinpress	8	70	8	72,5
B: Brystpress	8	20	7	20
C: Legcurl	8	25	8	27,5
D: Nedtrekk	8	30	7	35