Cardiorespiratory Fitness and Physical Activity following Lung Transplantation: A National Cohort Study

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Keywords
Lung transplantation · Cardiopulmonary exercise testing · Physical activity · Respiratory physiology · Exercise physiology

Abstract

Background: Low cardiorespiratory fitness and inactivity are common after lung transplantation (LTx). The causes of exercise intolerance are incompletely understood. Objectives: The aim of this study was to objectively assess cardiorespiratory fitness and physical activity, evaluate causes of exercise intolerance, and explore clinical factors associated with cardiorespiratory fitness after bilateral LTx (BLTx). Materials and Methods: Peak oxygen uptake (VO₂peak) and exercise-limiting factors were evaluated by a treadmill cardiopulmonary exercise test (CPET) 6–60 months after LTx. Physical activity was measured with accelerometers, and results were compared with Norwegian normative data and the World Health Organization’s (WHO) recommendations for physical activity. Results: In 54 included BLTx recipients (mean age 50 ± 15 years, 50% females), VO₂peak (mL x kg⁻¹ x min⁻¹) was 21.8 ± 7.7 for men and 22.4 ± 6.2 for women, corresponding to 57 ± 17 and 70 ± 12% of predicted, respectively. Three patients (6%) met criteria for normal VO₂peak. Deconditioning limited VO₂peak in 22 patients (41%), while ventilatory limitation and abnormal gas exchange were observed in 14 (26%) and 20 (37%) patients, respectively (some had more than 1 finding). Forty-three patients (86%) did not meet the WHO physical activity recommendations. There was a moderate correlation between VO₂peak and physical activity (r = 0.642, p < 0.01). Body mass index, physical activity, forced expiratory volume after 1 second, sex, and hemoglobin together accounted for 73% of the variability in VO₂peak. Conclusions: Low cardiorespiratory fitness was observed in the majority of BLTx recipients. Both deconditioning and cardiopulmonary limitations were common findings. Nearly 90% were classified as being inactive according to physical activity recommendations. CPET appears to identify a deconditioned subgroup of BLTx recipients for whom exercise training may be especially beneficial.
Introduction

Lung transplantation (LTx) is a well-established lifesaving treatment for patients with end-stage lung disease, with nearly 5,000 transplants performed each year worldwide [1]. Exercise intolerance often persists for several years following LTx, despite success of the surgical procedure and improved lung function [2]. The causes of exercise intolerance in this population are incompletely understood.

In the general population, cardiorespiratory fitness is reported to be a stronger predictor of mortality than well-acknowledged risk factors, such as hypertension, smoking, obesity, hyperlipidemia, and diabetes [3, 4], and is also associated with cardiovascular morbidity and health-related quality of life (HRQoL) [5]. As many as 30–50% of LTx recipients develop comorbid conditions, such as diabetes and hyperlipidemia, in the years after transplantation, and the majority are diagnosed with hypertension by 5 years after transplant [1]. Thus, cardiorespiratory fitness in this vulnerable LTx population is potentially an important factor related to overall health and delaying lifestyle diseases and mortality. While a number of studies have measured cardiorespiratory fitness in LTx recipients, the majority were performed in an earlier era of LTx (in the 1990s) [6–10] or are limited by small sample sizes (n < 25) [6–12]. While physical activity is known to be reduced among LTx recipients both before and after transplant [2], the relationship between physical activity and cardiorespiratory fitness in this population is not well established. Finally, it is unclear which demographic and clinical factors influence cardiorespiratory fitness after LTx.

In this cross-sectional study, we aimed to determine cardiorespiratory fitness and level of physical activity in a nationwide cohort of bilateral LTx (BLTx) recipients. Further, we aimed to identify causes of exercise intolerance, study the relationship between cardiorespiratory fitness and physical activity, and explore clinical factors that may be associated with peak oxygen uptake (VO_{peak}) after LTx.

Materials and Methods

Study Population

In this national cohort study, BLTx recipients were recruited at Oslo University Hospital between August 2017 and June 2018. In Norway, all organ transplantsations are performed in 1 center, which serves the entire Norwegian population of approximately 5.3 million. Since 2012, only BLTx, and no single LTx, has been performed.
3.8, or 4.8 km × h⁻¹, depending on the patient’s self-reported level of fitness and performance during familiarization with the treadmill prior to CPET. The inclination was set to 4% and increased by 2% every minute. If the patient reached the maximum inclination of 20%, the speed was increased by 0.5 km × h⁻¹ every minute until exhaustion. Gas exchange and exhaled volumes were directly measured breath-by-breath (Vyntus CPX Metabolic Cart, CareFusion Corporation, Höchberg, Germany). Prior to each test, the metabolic cart was calibrated for volume and gas according to the standards given by the manufacturer. The highest V˙O₂ measured over 30 s was defined as V˙O₂peak. Percutaneous oxygen saturation (SpO₂) was measured with finger pulse oximeter (NONIN8600, Medical Inc., Minneapolis, MN, USA), and a 12-lead ECG (CustoCardio 100, CustoMed, Ottobrunn, Germany) was conducted for evaluation of ischemia and/or arrhythmias. After test termination, the rating of perceived exertion was assessed by the Borg scale [23]. Postexercise blood lactate concentration was measured within 60 s of stopping to objectively assess the patient’s effort [22].

Ventilatory threshold was determined by the ventilatory equivalent method [23]. Minute ventilation (VE) and carbon dioxide output (VCO₂) during CPET below the respiratory compensation point were used to calculate the VE/VCO₂ slope. Predicted V˙O₂peak and peak heart rate (HRpeak) were calculated based on equations from Edvardsen et al. [21].

The definition of maximal effort was a high respiratory exchange ratio (1.0–1.10) and lactate concentration (≥3.5–9 mmol × L⁻¹) relative to age and gender in accordance with the recommendations by Edvardsen et al. [22]. Low cardiorespiratory fitness was defined as V˙O₂peak <85% of predicted, ventilatory limitation as breathing reserve <15% or <11 L × min⁻¹, exercise-induced hypoxemia as SpO₂ <88%, and signs of ventilation perfusion (VQ) mismatch (gas exchange limitation) were defined as a VE/VCO₂ slope ≥34 [24]. Poor chronotropic response was defined as a HR <80% of predicted in the absence of pulmonary limitations [25]. Deconditioning was defined as low cardiorespiratory fitness in the absence of cardiopulmonary limitations.

**Accelerometer**

For objective assessment of physical activity, all patients were asked to carry an accelerometer (ActiGraph GT1M, LLC, Pensacola, FL, USA) for 7 consecutive days during waking hours, except during water-based activities. The accelerometer registered vertical accelerations in counts per minute and number of steps per day. Moderate-to-vigorous physical activity was defined as all activity ≥2,020 counts per minute (equivalent to 3 metabolic equivalents of task) occurring in bouts lasting for at least 10 min [26, 27]. Adherence to physical activity recommendations was defined as accumulating a daily average of moderate-to-vigorous physical activity accrued in bouts >21.4 min/day in accordance with WHO.

### Table 1. Characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Male (n = 27)</th>
<th>Female (n = 27)</th>
<th>All (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>53.3±0.6</td>
<td>50.0±14.5</td>
<td>51.6±12.7</td>
</tr>
<tr>
<td>BMI, kg×m⁻²</td>
<td>26.9±4.3</td>
<td>25.4±3.8</td>
<td>26.1±4.1</td>
</tr>
<tr>
<td>Hemoglobin, g×dL⁻¹</td>
<td>13.0±1.5</td>
<td>11.8±1.2</td>
<td>12.4±1.5</td>
</tr>
<tr>
<td>Time after BLTx, months</td>
<td>30±16</td>
<td>27±16</td>
<td>28±16</td>
</tr>
<tr>
<td>History of smoking</td>
<td>11 (41)</td>
<td>17 (63)</td>
<td>28 (52)</td>
</tr>
<tr>
<td>CLAD</td>
<td>6 (22)</td>
<td>1 (4)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Use of β-blockers</td>
<td>5 (19)</td>
<td>6 (22)</td>
<td>11 (20)</td>
</tr>
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</table>

**Comorbidities**

- Anemia: 14 (52), 13 (48), 27 (50)
- Arterial hypertension: 13 (48), 9 (33), 22 (41)
- Diabetes: 1 (4), 1 (4), 2 (4)
- Renal dysfunction: 12 (44), 14 (52), 26 (48)

**Native lung disease**

- COPD: 11 (41), 13 (48), 24 (44)
- Interstitial lung disease: 10 (37), 5 (19), 15 (28)
- Cystic fibrosis: 0, 2 (7), 2 (4)
- Other: 6 (22), 7 (26), 13 (24)

**Pulmonary function**

<table>
<thead>
<tr>
<th></th>
<th>Male (n = 27)</th>
<th>Female (n = 27)</th>
<th>All (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, L (% of predicted)</td>
<td>3.8±1.0 (79±18)</td>
<td>3.4±0.7 (99±19)</td>
<td>3.6±0.9 (89±21)</td>
</tr>
<tr>
<td>FEV₁, L×s⁻¹ (% of predicted)</td>
<td>2.5±0.8 (67±21)</td>
<td>2.6±0.7 (95±22)</td>
<td>2.6±0.7 (81±25)</td>
</tr>
<tr>
<td>MVV, L×min⁻¹ (% of predicted)</td>
<td>112.1±34.5 (85±26)</td>
<td>100.2±18.6 (101±18)</td>
<td>106.2±28.1 (93±24)</td>
</tr>
<tr>
<td>DLCO, mmol×kPa⁻¹×min⁻¹ (% of predicted)</td>
<td>6.7±1.6 (70±14)</td>
<td>5.9±1.2 (83±18)</td>
<td>6.3±1.5 (77±17)</td>
</tr>
</tbody>
</table>

Values are means ± standard deviations or n (%). BLTx, bilateral lung transplantation; BMI, body mass index; CLAD, chronic lung allograft dysfunction; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity for carbon monoxide; FEV₁, forced expiratory volume after 1 second; FVC, forced vital capacity; Hb, hemoglobin concentration; MVV, maximum voluntary ventilation.
recommendations [28]. Data was included if the patients had accumulated at least 10 h of activity recordings per day for a minimum of 2 days. The objectively measured physical activity was compared to normative values [26].

Health-Related Quality of Life
The 36-Item Short Form Health Survey (SF-36) was used to evaluate HRQoL. The SF-36 consists of 8 scales, which can be aggregated into 2 summary measures: the Physical and Mental Component Summary scores. The summary scores (scaled from 0 to 100) are based on data for the US general population standardized to a mean of 50 and SD of 10, where higher scores indicate better functioning [29].

Statistics
Descriptive data are presented as means ± standard deviations or medians (ranges). Means for physical activity were compared to Norwegian standard values using a one-sample t test, assuming the difference between BLTx recipients and the Norwegian standard would be equal to zero. A p value of < 0.05 was regarded as statistically significant. Pearson correlation coefficients were calculated between VO\(_2\)peak, physical activity level (counts per minute), time since transplantation, and SF-36 scores. A negligible correlation was defined as < 0.30, a low correlation as 0.30–0.49, a moderate correlation as 0.50–0.69, a high correlation as 0.70–0.89, and a very high correlation as ≥ 0.90 [30].

To explore potential factors associated with cardiorespiratory fitness, univariate regression analyses were used, where VO\(_2\)peak in % of predicted was set as the dependent variable. To identify the degree of association with VO\(_2\)peak, the relevant variables with significant associations in univariate analyses (p < 0.05) and other clinical variables known to affect VO\(_2\)peak (age, sex, BMI, and Hb) were selected for multiple regression analyses. The final model was built using a series of multiple regression analyses with the enter method. All analyses were performed using SPSS version 25.0 (IBM Statistics, Chicago, IL, USA).

Results
Of 73 patients assessed for eligibility, 16 declined participation and 3 could not be tested due to unstable health conditions. In total, 27 men and 27 women (mean age 50 ± 15, range 20–67 years) were included in the study 6–59 months after BLTx. Clinical characteristics and pulmonary function are presented in Table 1. Twenty-two patients (41%) had mild anemia and 5 patients (9%) had moderate anemia. Twenty-seven patients (50%) were overweight (BMI 25–29) and 9 (17%) were obese (BMI > 30). Seven patients, of whom 6 were men, had been diagnosed with CLAD prior to study enrollment (Table 1).

Cardiorespiratory Fitness
No adverse events were recorded during or after the CPET. Table 2 shows cardiorespiratory response during CPET. All but 2 patients reported exertion ≥17 on the Borg scale at peak exercise. Fourteen patients did not reach the recommended age- and gender-adjusted end-criteria for lactate concentration and respiratory exchange ratio. Leg fatigue was the most frequent reason for stopping the CPET (46%) followed by dyspnea (31%) and general exhaustion (22%).

Three patients (6%) had normal cardiorespiratory fitness. Among the 51 patients (95%) with low cardiorespiratory fitness, 14 patients (26%) were ventilatory limited, 1 patient (2%) had exercise-induced hypoxemia, and 20...
patients (37%) had an elevated VE/VCO₂ slope indicating V/Q mismatch. No patient showed signs of myocardial ischemia during CPET. However, 4 patients had poor chronotropic response (3 used β-blockers and 1 had permanent atrial fibrillation). Some patients had more than 1 cardiopulmonary factor limiting exercise and have been counted more than once. Twenty-two patients (41%) were classified as deconditioned without cardiopulmonary limiting factors of whom 13 (59%) had mild anemia. Nine of the patients with ventilatory limitations had known respiratory pathology (CLAD, n = 6; sequela of pulmonary infection, n = 1; dynamic airway collapse, n = 1; airway stenosis, n = 1).

**Physical Activity**

Fifty recipients (93%) accumulated at least 10 h of valid activity recordings per day for at least 2 days. The mean accelerometer wear time was 15 ± 2 h per day for 5.9 ± 1.9 days. Compared to the Norwegian national standard, BLTx recipients walked significantly fewer steps per day (5,451 ± 3,398 vs. 8,241, \( p < 0.001 \)), had significantly fewer counts per minute (226 ± 131 vs. 366, \( p < 0.001 \); Fig. 1), and had 30% higher sedentary time (\( p < 0.001 \)). Forty-three patients (86%) were classified as physically inactive [28]. The 7 patients (14%) meeting the WHO’s physical activity recommendations had significantly higher \( \dot{V}O_2 \text{peak} \) than those who did not (79 ± 7 vs. 62 ± 15% of predicted, \( p = 0.001 \)).
Associations with Cardiopulmonary Fitness

Correlations between VO_{2peak} and physical activity level, time since transplantation, and HRQoL are presented in Figure 2. There was a moderate correlation between VO_{2peak} and physical activity level (measured by counts per minute) and between VO_{2peak} and the physical aspect of HRQoL (measured by the SF-36 physical component summary score). There was a negligible correlation between VO_{2peak} and time since transplantation, and between VO_{2peak} and the mental aspect of HRQoL (measured by the SF-36 mental component summary score). Univariate and multivariable analyses for associations with VO_{2peak} are presented in Table 3. Univariate regression analysis indicated that sex, age, BMI, physical activity, the physical aspect of HRQoL, FEV_{1}, and DL_{CO} were significantly associated with VO_{2peak}. The final multivariable regression model showed that BMI, physical activity, FEV_{1}, sex, and Hb together accounted for 73% of the variability in VO_{2peak}.

Discussion/Conclusion

We found that only 3 out of 54 BLTx recipients had normal cardiorespiratory fitness (VO_{2peak}) and that physical activity level was low. CPET results revealed that both deconditioning and cardiopulmonary factors caused exercise intolerance. Forty-three patients (86%) did not meet the WHO’s physical activity recommendations, and daily sedentary time was 30% greater than in a healthy Norwegian population. We further demonstrated that VO_{2peak} is associated with physical activity level after BLTx. Our results showed that VO_{2peak} is low among BLTx recipients and that considerable exercise intolerance persists after BLTx. This is in line with findings from previous studies showing minimal increase in VO_{2peak} after BLTx and does not match the large improvement in pulmonary function [31, 32]. However, in our population, low cardiorespiratory fitness was caused by both deconditioning and cardiopulmonary limitations. The high number (n = 29) of patients with cardiopulmonary limitations to exercise was somewhat surprising, as chronic muscle deconditioning and skeletal muscle abnormalities have been proposed as the main exercise-limiting factors in previous studies [32].
Patients who were deconditioned had low oxygen pulse, indicating poor stroke volume, but normal gas exchange and adequate breathing reserve. A similar combination has been observed in deconditioned individuals in other clinical settings [24]. For such patients, exercise therapy may be especially beneficial.

A low breathing reserve raises the possibility of ventilatory limitation to exercise [23]. One-fourth of the patients were ventilatory limited. As expected, patients with ventilatory limitations also had low HRpeak and did not reach the end-criteria for maximal effort (high respiratory exchange ratio and blood lactate concentration). Ventilatory limitation to exercise could in most cases be explained by respiratory pathology. Some of the patients had experienced severe loss of pulmonary function (FEV1) due to CLAD or other postoperative complications. Ventilatory limitation has not been reported in earlier studies [8, 31, 33], possibly due to missing data on patients with postoperative lung complications, early CPET termination, or the use of a different exercise mode. The exercise mode may have played an important role in detecting ventilatory limitations in the present study. Our patients were tested by uphill walking on a treadmill, which is a more functional way of moving than cycle ergometer and is known to elicit 10–20% higher VO2peak because larger muscle groups are involved [24]. Treadmill testing therefore places a higher demand on the cardiopulmonary system. The higher HRpeak reported in our study compared to that in previous BLTx studies also supports this possibility [6, 7, 33].

An elevated VE/VCO2 slope, demonstrating excessive ventilation relative to metabolic demand, is normally caused by increased dead space ventilation (ventilation-perfusion mismatch) [34]. An elevated VE/VCO2 slope was seen in many of our patients. This finding was observed in patients with and without known postoperative lung complications and independent of elapsed time since transplantation. Our findings are in line with those reported by Schwaiblmair et al. [33], who described ventilation-perfusion mismatch in patients 3 months after BLTx. However, in contrast to a study by Habedank et al. [12] suggesting that ventilatory inefficiency improves rapidly after BLTx and meets normal values within 24 months, we observed that ventilatory inefficiency persists up to 5 years after BLTx.

Previous studies have shown reduced levels of physical activity after LTx [2, 35, 36]. Our study confirms this finding and further demonstrates that VO2peak is moderately associated with physical activity after BLTx. In order to improve VO2peak and reduce the risk of certain noncommunicable diseases (cardiovascular disease, diabetes, osteoporosis, various cancers, and depression), the WHO recommends at least 150 min of moderate-to-vigorous physical activity, performed in bouts lasting at least 10 min per week [28]. The vast majority of BLTx recipients in our study did not meet this criterion. Importantly, we found that higher VO2peak was associated with higher physical activity level, and patients meeting the WHO recommendations for physical activity had a significantly higher VO2peak than those who did not. In future studies, reporting comparison between national standards and the WHO recommendations may be useful since it will enable comparisons across different centers.

With respect to possible predictors of VO2peak, we observed a high prevalence of anemia, which is known to affect VO2peak negatively [23, 37]. Anemia alone is unlikely to fully explain the low VO2peak given that the majority only had mild anemia but still had substantial impairment in VO2peak [37]; however, multivariable analysis suggests that it may be an important contributor. The causes of anemia in our study population are likely multiple and may include adverse effects of immunosuppressive medications; nonetheless, it is reasonable to speculate that some patients may have modifiable causes of anemia, such as iron deficiency, for which treatment may help improve cardiorespiratory fitness and physical activity.

Another contributor to lower VO2peak was higher BMI. Weight gain after LTx is common, and median weight gain of 10% in the first year after LTx has been observed [38]. The high number of overweight or obese patients in our study is a matter of concern, as it may have an impact on VO2peak and morbidity. This finding, together with the low levels of physical activity, highlights the need to develop targeted exercise interventions after BLTx and assess their effect on patient-centered outcomes in clinical trials. Females in the present study had significantly higher VO2peak % of predicted than males, which is interesting as female recipients have shown significantly improved survival over 5 years compared to males [39], and higher VO2peak is associated with improved survival in the general population [4]. To our knowledge, no study has assessed VO2peak as a predictor of mortality after LTx, and its relevance should be investigated in future prospective studies. We recognize that the impact of gender on VO2peak might be biased by the higher prevalence of CLAD among males in this study (6 of 7 patients with CLAD were males). However, exclusion of the 7 patients diagnosed with CLAD in the analyses did not eliminate the significant gender difference.
Limitations of our study include the cross-sectional design, which does not permit us to define causal relationships. However, our large sample size relative to prior studies and the complexity of our physiological assessments nonetheless allow for a thorough analysis of the factors associated with $\text{VO}_{2\text{peak}}$ and physical activity in BLTx recipients. The causes of exercise intolerance after BLTx are incompletely understood, but impaired oxidative function of skeletal muscle has previously been recognized as a potentially important factor [10, 40]. We did not have the opportunity to formally assess the oxidative function of skeletal muscle, for example with muscle biopsies.

In conclusion, low cardiorespiratory fitness was observed in nearly all BLTx recipients. Deconditioning and cardiopulmonary factors limiting exercise were equally common. Only a small minority met standard recommendations for physical activity. Lower physical activity levels were associated with lower cardiorespiratory fitness. Our findings highlight the need to develop targeted recommendations for physical activity. Lower physical activity could potentially create a conflict of interest.

Acknowledgement

The authors would like to thank physiologist Stan Roterd for technical assistance during the cardiopulmonary exercise testing and Liv Ingunn Bjoner Sikkeland for editing tables and figures.

References


Statement of Ethics

Ethical approval was obtained from the Regional Committee for Medical and Health Research Ethics (REK South-East, No. 2017/399). The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

The study was funded by research grants from the Division of Cardiovascular and Pulmonary Diseases at Oslo University Hospital. The project has not received financial support from any commercial source, and the authors have no financial interests which could potentially create a conflict of interest.

Author Contributions

E.E., M.T.D., M.B.L., and J.S.K. designed the study. M.U. was responsible for data collection, statistical analyses, and drafting the manuscript. B.H.H. contributed to the analyses of the accelerometer data. The manuscript was critically reviewed and approved by all authors.


