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

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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 ($\dot{V}O_{2peak}$) and exercise-limiting factors were evaluated by a treadmill cardiopulmonary exercise test (CPET) 6–60 months after BLTx. 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), $\dot{V}O_{2peak}$ (mL × kg^{-1} × 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 $\dot{V}O_{2peak}$. Deconditioning limited $\dot{V}O_{2peak}$ 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 $\dot{V}O_{2peak}$ 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 $\dot{V}O_{2peak}$. ***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.

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Introduction

Lung transplantation (LTx) is a well-established life-saving 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 ($\dot{V}O_{2peak}$) 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 transplantations 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.

Eligible patients were ≥18 years of age with stable condition 6 months to 5 years after BLTx. The patients were classified as "stable" if their pulmonary function had not changed precipitously (defined as a reduction in forced expiratory volume after 1 second [FEV_1] >10%) over the past 6 months and if they did not have any other acute and/or function-limiting conditions under ongoing treatment in the opinion of the treating pulmonologist. Patients were not eligible if they could not communicate in Norwegian or were unable to walk on a treadmill until exhaustion due to musculoskeletal conditions. All patients received triple-drug immunosuppression (tacrolimus or cyclosporine, mycophenolate mofetil, and corticosteroids) except 1 who did not take mycophenolate mofetil due to leukopenia. All BLTx recipients at our institution start postoperative physical therapy as soon as medically advisable. During the hospital stay – usually lasting 4–6 weeks – they have daily sessions with a physical therapist. After discharge, the patients are referred to local physical therapists. Most patients attend sessions 1–2 times per week for up to 6 months. Patients who need more intensive training are referred to a 4-week inpatient program at a national facility for cardiopulmonary rehabilitation. After 6 months, the patients are encouraged to maintain regular physical activity at their own discretion. Written informed consent was obtained from all patients prior to enrollment. Ethical approval was obtained from the Regional Committee for Medical and Health Research Ethics (REK South-East, No. 2017/399).

Clinical Characteristics
Data on native lung disease, time since BLTx, comorbidities, and medications were obtained from the patients' medical records. Registered comorbidities included anemia, renal dysfunction, arterial hypertension, diabetes, and overweight. Anemia was defined as a hemoglobin concentration (Hb) $<13 \text{ g} \times dL^{-1}$ for men and $<12 \text{ g} \times dL^{-1}$ for women. Moderate anemia was defined as Hb <11 and $<10 \text{ g} \times dL^{-1}$ and severe anemia as Hb <8 and $<7 \text{ g} \times dL^{-1}$ for men and women, respectively [13]. Renal dysfunction was defined as an estimated glomerular filtration rate $<60 \text{ mL} \times min^{-1} \times 1.73 \text{ m}^{-2}$ in accordance with local reference values. Hypertension was defined as the use of antihypertensive drugs, and diabetes was defined as the use of antidiabetic drugs. Overweight was defined as a body mass index (BMI) $\geq 25 \text{ kg} \times m^{-2}$, and obesity was defined as a BMI $\geq 30 \text{ kg} \times m^{-2}$, in line with the World Health Organization (WHO) classification [14]. Chronic lung allograft dysfunction (CLAD) was defined as a persistent decline in FEV_1 of 20% from the mean of the 2 highest posttransplant values in the absence of other explanatory conditions [15].

Pulmonary Function Tests
Pulmonary function was assessed by spirometry and diffusing capacity of the lungs for carbon monoxide (DL_{CO}; Jaeger Master Screen Body, Eric Jaeger, Wurzburg, Germany) in accordance with the recommendations of the ATS/ERS task force [16, 17]. Reference values were calculated using the Global Lung Function Initiative equations [18, 19].

Cardiopulmonary Exercise Test
Under guidance of an exercise physiologist and a physician, all patients performed a maximal symptom-limited cardiopulmonary exercise test (CPET) on a treadmill (TechnoGym Runrace, Forli, Italy) using a modified Balke protocol [20] that was also used for testing the reference population [21]. The speed was set to 1.8, 2.8,

Table 1. Characteristics of the study population

	Male ($n = 27$)	Female ($n = 27$)	All ($n = 54$)
Age, years	53.3±0.6	50.0±14.5	51.6±12.7
BMI, kg×m^{-2}	26.9±4.3	25.4±3.8	26.1±4.1
Hemoglobin, g×dL^{-1}	13.0±1.5	11.8±1.2	12.4±1.5
Time after BLTx, months	30±16	27±16	28±16
History of smoking	11 (41)	17 (63)	28 (52)
CLAD	6 (22)	1 (4)	7 (13)
Use of β-blockers	5 (19)	6 (22)	11 (20)
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			
FVC, L (% of predicted)	3.8±1.0 (79±18)	3.4±0.7 (99±19)	3.6±0.9 (89±21)
FEV$_1$, L×s^{-1} (% of predicted)	2.5±0.8 (67±21)	2.6±0.7 (95±22)	2.6±0.7 (81±25)
MVV, L×min^{-1} (% of predicted)	112.1±34.5 (85±26)	100.2±18.6 (101±18)	106.2±28.1 (93±24)
DL$_{CO}$, mmol×kPa^{-1}×min^{-1}			
(% of predicted)	6.7±1.6 (70±14)	5.9±1.2 (83±18)	6.33±1.5 (77±17)

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; DL$_{CO}$, diffusing capacity for carbon monoxide; FEV$_1$, forced expiratory volume after 1 second; FVC, forced vital capacity; Hb, hemoglobin concentration; MVV, maximum voluntary ventilation.

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 $\dot{V}O_2$ measured over 30 s was defined as $\dot{V}O_{2peak}$. Percutaneous oxygen saturation (SpO$_2$) was measured with finger pulse oximeter (NONIN8600, Medical Inc., Minneapolis, MN, USA), and a 12-lead ECG (Custo cardio 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$_{6-20}$. 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 (VCO$_2$) during CPET below the respiratory compensation point were used to calculate the VE/VCO$_2$ slope. Predicted $\dot{V}O_{2peak}$ and peak heart rate (HR$_{peak}$) 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 $\dot{V}O_{2peak}$ <85% of predicted, ventilatory limitation as breathing reserve <15% or <11 L × min^{-1}, exercise-induced hypoxemia as SpO$_2$ <88%, and signs of ventilation perfusion (VQ) mismatch (gas exchange limitation) were defined as a VE/VCO$_2$ 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

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Table 2. Cardiopulmonary response during cardiopulmonary exercise testing in bilateral lung transplant recipients

	Men ($n = 27$)	Women ($n = 27$)	All ($n = 54$)
$\dot{V}O_{2peak}$, mL×kg^{-1}×min^{-1} (% of predicted)	21.8±7.7 (57±17)	22.4±6.2 (70±12)	22.1±6.9 (64±16)
$\dot{V}O_{2peak}$, L×min^{-1} (% of predicted)	1.78±0.49 (55±13)	1.51±0.24 (69±11)	1.65±0.41 (62±14)
VT, L×min^{-1} (% of predicted)	1.41±0.39 (62±15)	1.18±0.20 (72±12)	1.28±0.32 (67±14)
Peak ventilation, L×min^{-1} (% of predicted)	78.6±22.8 (68±18)	67.48±15.4 (85±17)	73.0±20.1 (77±20)
Respiratory rate, breaths×min^{-1}	38.6±6.9	36.4±8.8	37.5±7.9
Breathing reserve, %	27.9±14.2	31.9±12.7	29.9±13.5
VE/VCO$_2$ slope	35.6±10.5	33.0±4.5	34.3±8.1
HR$_{peak}$, beats×min^{-1} (% of predicted)	145.3±17.1 (84±9)	155.7±19.2 (89±9)	150.5±18.8 (86±9)
O$_2$-pulse, mL×beat^{-1} (% of predicted)	12.2±2.7 (67±14)	9.8±1.5 (80±14)	11.0±2.5 (73±15)
Lowest SpO$_2$ during test, %	94 (87–98)	96 (90–99)	95 (87–99)
Borg scale$_{6-20}$	18.1±1.13	18.3±0.9	18.2±1.0
Blood lactate, mmol×L^{-1}	7.8±2.7	8.7±2.1	8.3±2.4
Respiratory exchange ratio, VCO$_2$/VO$_2$	1.08±0.13	1.15±0.07	1.12±0.11

Data are presented as means ± standard deviations or medians (ranges). HR$_{peak}$, peak heart rate; $\dot{V}O_{2peak}$, peak oxygen consumption; VT, ventilatory threshold; SpO$_2$, peripheral capillary oxygen saturation.

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) as appropriate. 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 $\dot{V}O_{2peak}$, 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 $\dot{V}O_{2peak}$ in % of predicted was set as the dependent variable. To identify the degree of association with $\dot{V}O_{2peak}$, the relevant variables with significant associations in univariate analyses ($p < 0.05$) and other clinical variables known to affect $\dot{V}O_{2peak}$ (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 cardiopulmonary 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

Fig. 1. Objectively measured physical activity expressed as counts per minute (**a**) and steps per day (**b**) (mean ± SD) in 54 bilateral lung transplant recipients. The dotted line represents the Norwegian standard [26].
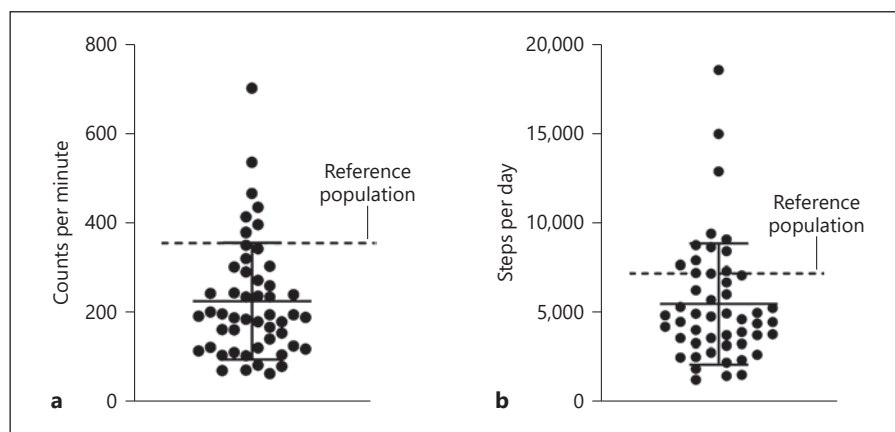

Fig. 2. a Correlation between $\dot{V}O_{2peak}$ (mL × kg^{-1} × min^{-1}) and physical activity (counts per minute). **b** Correlation between peak oxygen uptake ($\dot{V}O_{2peak}$) in percent of predicted and months since bilateral lung transplantation (BLTx). **c**, **d** Correlations between peak oxygen uptake ($\dot{V}O_{2peak}$) in percent of predicted and SF-36 physical component summary score (SF-36 PCS; **c**) and SF-36 mental component summary score (SF-36 MCS; **d**). Higher SF-36 score indicates better health-related quality of life.
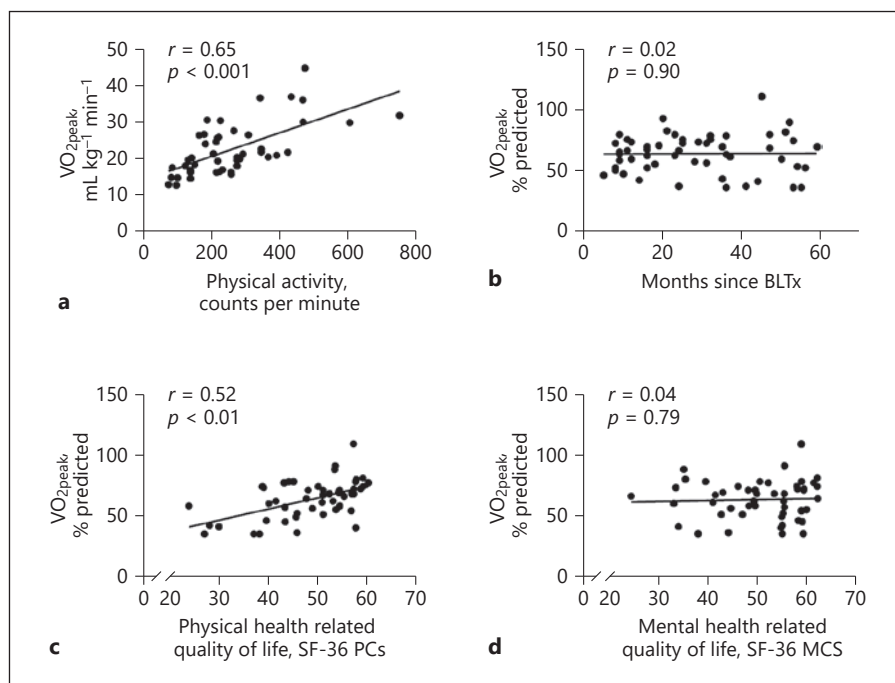
patients (37%) had an elevated VE/VCO$_2$ slope indicating V/Q mismatch. No patient showed signs of myocardial ischemia during CPET. However, 4 patients had poor chronotropic response (3 used β-blockers and 1 had permanent atrial fibrillation). Some patients had more than 1 cardiopulmonary factor limiting 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 $\dot{V}O_{2peak}$ than those who did not (79 ± 7 vs. 62 ± 15% of predicted, $p = 0.001$).

Table 3. Univariate and multiple regression analysis using $\dot{V}O_{2peak}$ % of predicted as dependent variable in BLTx recipients ($n = 54$)

	Univariate regression analysis			Multivariable regression model ($R^2 = 0.726$)
	unstandarized β (95% CI)	R^2	p value	unstandarized β (95% CI)
Gender, female	12.8 (4.9 to 20.7)	0.17	0.002	8.8 (2.6 to 14.9)
Age, years	−0.3 (−0.7 to −0.01)	0.08	0.044	0.1 (−0.2 to 0.3)
BMI, kg×m^{-2}	−2.2 (−3.1 to −1,3)	0.35	<0.001	−2.0 (−2.9 to −1.2)
Physical activity, counts per min	0.08 (0.04 to 0.1)	0.33	<0.001	0.05 (0.03 to 0.07)
Time since BLTx, years	−0.2 (−3.4 to 3.0)	<0.001	0.991	
SF-36 PCS	0.9 (0.5 to 1.4)	0.27	<0.001	
SF-36 MCS	0.1 (−0.4 to 0.6)	0.002	0.788	
FEV$_1$, % of predicted	0.3 (0.1 to 0.4)	0.20	0.001	0.2 (0.1 to 0.3)
DL$_{CO}$, % of predicted	0.4 (0.2 to 0.6)	0.21	0.001	
Hb, g×dL^{-1}	0.1 (−2.8 to 3.0)	<0.001	0.923	2.8 (0.9 to 4.7)
Emphysema prior to BLTx	−0.2 (−8.9 to 8.5)	<0.001	0.960	
Renal insufficiency	−3.8 (−12.4 to 4.7)	0.02	0.371	
Arterial hypertension	−6.1 (−14.7 to 2.6)	0.04	0.165	
Use of β-blockers	−8.9 (−19.4 to 1.5)	0.05	0.093	

BLTx, bilateral lung transplantation; BMI, body mass index; FEV$_1$, forced expiratory volume after 1 second; DL$_{CO}$, diffusing capacity; Hb, hemoglobin concentration; SF-36 MCS, 36-Item Short Form Health Survey Mental Component Summary Score; SF-36 Pcs, Short Form Health Survey Physical Component Summary Score.

Associations with Cardiopulmonary Fitness

Correlations between $\dot{V}O_{2peak}$ and physical activity level, time since transplantation, and HRQoL are presented in Figure 2. There was a moderate correlation between $\dot{V}O_{2peak}$ and physical activity level (measured by counts per minute) and between $\dot{V}O_{2peak}$ and the physical aspect of HRQoL (measured by the SF-36 physical component summary score). There was a negligible correlation between $\dot{V}O_{2peak}$ and time since transplantation, and between $\dot{V}O_{2peak}$ and the mental aspect of HRQoL (measured by the SF-36 mental component summary score). Univariate and multivariable analyses for associations with $\dot{V}O_{2peak}$ 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 $\dot{V}O_{2peak}$. The final multivariable regression model showed that BMI, physical activity, FEV$_1$, sex, and Hb together accounted for 73% of the variability in $\dot{V}O_{2peak}$.

Discussion/Conclusion

We found that only 3 out of 54 BLTx recipients had normal cardiorespiratory fitness ($\dot{V}O_{2peak}$) 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 $\dot{V}O_{2peak}$ is associated with physical activity level after BLTx.

Our results showed that $\dot{V}O_{2peak}$ 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 $\dot{V}O_{2peak}$ 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 HR_{peak} 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 (FEV_1) 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 $\dot{V}O_{2peak}$ because larger muscle groups are involved [24]. Treadmill testing therefore places a higher demand on the cardiopulmonary system. The higher HR_{peak} reported in our study compared to that in previous BLTx studies also supports this possibility [6, 7, 33].

An elevated VE/VCO_2 slope, demonstrating excessive ventilation relative to metabolic demand, is normally caused by increased dead space ventilation (ventilation-perfusion mismatch) [34]. An elevated VE/VCO_2 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 $\dot{V}O_{2peak}$ is moderately associated with physical activity after BLTx. In order to improve $\dot{V}O_{2peak}$ 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 $\dot{V}O_{2peak}$ was associated with higher physical activity level, and patients meeting the WHO recommendations for physical activity had a significantly higher $\dot{V}O_{2peak}$ 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 $\dot{V}O_{2peak}$, we observed a high prevalence of anemia, which is known to affect $\dot{V}O_{2peak}$ negatively [23, 37]. Anemia alone is unlikely to fully explain the low $\dot{V}O_{2peak}$, given that the majority only had mild anemia but still had substantial impairment in $\dot{V}O_{2peak}$ [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 $\dot{V}O_{2peak}$ 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 $\dot{V}O_{2peak}$ 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 $\dot{V}O_{2peak}$ % of predicted than males, which is interesting as female recipients have shown significantly improved survival over 5 years compared to males [39], and higher $\dot{V}O_{2peak}$ is associated with improved survival in the general population [4]. To our knowledge, no study has assessed $\dot{V}O_{2peak}$ 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 $\dot{V}O_{2peak}$ 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 $\dot{V}O_{2peak}$ 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 exercise interventions after BLTx. CPET appears to identify a deconditioned subgroup of BLTx recipients for whom exercise training may be especially beneficial.

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Statement of Ethics

Disclosure Statement

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Author Contributions

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