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Original article

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Near-normal aerobic capacity in long-term survivors after lung transplantation

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TAKE HOME MESSAGE: This is a multicentre study reporting for the first time near-normal VO2 peak values during cardiopulmonary exercise testing and normal exercise capacity in long-term lung transplant recipients without CLAD.

ABSTRACT

The clinical course of lung transplantation (LT) is diverse: some patients present chronic lung allograft dysfunction (CLAD) and progressive decline in pulmonary function but others, maintain normal spirometric values and active live.

OBJECTIVES: to elucidate whether long-term LT survivors with normal spirometry achieve normal exercise capacity, and to identify predictive factors of exercise capacity.

METHODS: cross-sectional multicentre study where bilateral LT recipients who survived at least 10 years after LT, with normal spirometry, no diagnosis of CLAD and mMRCs dyspnoea degree ≤2 underwent cardiopulmonary exercise testing (CPET).

RESULTS: 28 LT recipients were included with a mean (SD) age of 48.7 (13.6) years. VO_2 had a mean value of 21.49 (6.68) ml/kg/min (75.24 (15.6) %) and the anaerobic threshold was reached at 48.6 (10.1) % of the VO2 max predicted. The mean (SD) HRR at peak exercise was 17.56 (13.6) %. The O_2 pulse increased during exercise and was within normal values at 90.5 (19.4) %. The respiratory exchange ratio exceeded 1.19 at maximum exercise. The median (p25-75) EuroQol- 5D score was 1 (0.95-1), indicating a good quality of life. The median (p25-75) IPAQ score was 5497 (4007-9832) MET-min/week with 89% of patients reporting more than 1500 MET-min/week. In the multivariate regression models, age, sex and DLCO remained significantly associated with VO_2 max (ml/kg/min); Hb and FEV_1 were significantly associated with WR max (watts), after adjusting for confounders.

CONCLUSION: We report for the first time near-normal VO2 peak values during CPET and normal exercise capacity in long-term LT recipients without CLAD.

INTRODUCTION

Lung transplantation (LT) is an established treatment for end-stage respiratory diseases which improves patient's health-related quality of life, especially in the physical functioning domains [1]. Despite improvements in respiratory symptoms and pulmonary function, reports from the early 1990s showed a reduction in peak oxygen consumption (VO_2) ranging between 44 and 59% in single-LT, and between 40 and 50% in bilateral-LT [2–6] with little or no improvement after two years of follow-up.

Transferring the results of these studies to the clinical field is difficult because of their small sample sizes, evaluation of specific LT type, and the different timing of exercise testing and lung function. All the authors that have previously addressed this topic share the statement that LT recipients, either for intrinsic or extrinsic reasons, do not reach normal oxygen consumption values. However, in our clinical experience, while some patients develop chronic lung graft dysfunction and a progressive decline in lung function, others attain normal spirometric values and are able to carry out considerable activities despite presenting good exercise capacity [2–6]. The most common causes invoked to explain low exercise capacity, in spite of the striking recovery of lung function after LT, are anaemia, cardiac and peripheral vascular factors, impaired oxidative capacity of peripheral skeletal muscle, lower limb skeletal muscle dysfunction, muscle weakness and sarcopenia [2, 7, 8]. The literature supporting these mechanisms is scarce and severe muscle deconditioning (which could be reverted with time) is a very plausible additional explanation. To explore this possibility, studies analysing exercise capacity and other exercise variables in long term are needed. As far as we know, such studies are lacking and as a result, obtaining definite conclusions regarding the causes of exercise limitation in LT recipients remains a challenging task. Nevertheless, we hypothesize that LT recipients with normal lung function and generally good health status could preserve near-normal VO_2 values.

We therefore analysed exercise capacity in long-term survivors after bilateral LT with normal lung function tests. Our aims were 1) to establish whether these patients could achieve normal exercise capacity, and 2) to identify predictive factors of exercise capacity in this LT population.

METHODS

Study design

A prospective cross sectional study was performed in LT recipients recruited from six different LT referral centres from all over Spain, between 2015 and 2016. The study was approved by the Institutional Ethics Board (ID of approval: PR(AG)64/2015), and all the participants provided signed informed consent.

Subjects

Inclusion criteria were: 1) bilateral LT conducted at least 10 years prior to the inclusion date; 2) normal spirometry (forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) greater than 80% and FEV_1/FVC greater than 0.7); 3) no diagnosis of chronic lung allograft dysfunction; 4) ability to complete cardiopulmonary exercise testing (CPET); 5) dyspnoea degree 2 or lower on the modified Medical Research Council score (mMRC).

Demographic and clinical data such as sex, age, smoking history, date of LT and current treatment were recorded or obtained from medical records. Physical activity was measured with the long form of the "International Physical Activity Questionnaire" (IPAQ) which calculates the total energy expenditure per week (METs-min/week) from the time (in minutes) spent walking and performing moderate-intensity and vigorous-intensity physical activity in four different domains (leisure time, domestic, work-related and transport-related physical activity) [9]. Health-related quality of life was assessed through the "EuroQol-5D" test [10] which comprises five questions on mobility, self-care, pain, usual activities, and psychological state.

All the tests were performed in the same centre (Hospital Universitari Vall d'Hebron), so the patients were required to travel, if necessary.

Pulmonary function testing

All patients underwent forced spirometry, static lung volume study by plethysmography, and single-breath lung diffusing capacity for carbon monoxide (DLCO) using the single breath-hold method (MasterLab, Vyasisr, Hochburg Germany). These studies were performed following the recommendations of the European [11] and Spanish Respiratory Societies [12].

Cardiopulmonary exercise testing

CPET was performed on a cycle ergometer using a breath-by breath system (MEDGRAPHICS CPX St Paul, MN). The speed of the ramp protocol was determined according to the maximum voluntary ventilation (MVV): for MVV < 40 L/min 10W $\cdot min^{-1}$ and for a > 40 L/min 15W $\cdot min^{-1}$[13], with this adjustments in our experience the test usually lasted between 10 and 15 min. After three minutes resting and three minutes of unloaded pedalling, the work load was progressively increased in order to obtain a test lasting 8 to 12 minutes long. Oxygen saturation and pulse rate was continuously monitored along the test. Breath-by-breath the following features were recorded: O_2 uptake (VO_2, CO_2 output (VCO_2), minute ventilation (V_E), pulse rate (PR), arterial blood pressure (AP), dyspnoea, and leg fatigue (Borg). Subjects were asked to maintain a pedalling cadence between 50 and 60 revolutions per minute (min) for the duration of the test. If cadence declined and fell below 40 revolutions per min for longer than 5 seconds, the test was terminated [13].

Free-Fat body mass measurement

Tissue composition analysis was performed by Electrical bioimpedance equipment 50Hz (BIA 101, Akern Srl; Florence, Italy). Single-frequency BIA was carried out with an impedance plethysmograph which emitted 400 μA and 50 kHz alternating sinusoidal current and was connected to surface electrodes (standard, tetrapolar placement on the right hand and foot) following the method reported elsewhere [14].

Statistics

The results are expressed as absolute frequencies and percentages for qualitative variables, as mean and standard deviation for quantitative variables with a normal distribution, and as the median and interquartile range for quantitative variables with a non-normal distribution. The relationship between socio-demographic, clinical and functional variables and exercise capacity were tested by means of chi-square test, Fisher exact test, T-test, Mann-Whitney U-rank test and Spearman's correlation coefficients as appropriate. For variables significantly related to exercise performance, a stepwise multiple linear regression with a backward elimination (entry threshold, $p<0.05$; removal threshold, $p>0.10$) was performed using VO_2 peak and Work rate peak as dependent variables. To avoid collinearity, we used the variable with the highest correlation (r) with exercise capacity in bivariate regression analyses. Analyses were adjusted for age and sex and goodness of fit was assessed by means of normality of residuals, heteroscedasticity, linearity, collinearity and identification of influential data. Limits of significance were set at $p<0.05$. Data analysis was conducted using Stata 12.1 (StataCorp, College Station, TX, USA).

RESULTS

Subjects' characteristics

Twenty-eight consecutive patients met the inclusion criteria and agreed to participate in this study. Six patients declined to take part in the study due to travelling or competing commitments. Subject demographics are shown in table 1. Mean age was 48.7 (13.6) years, and there was an equal distribution between men and women. The majority of patients (48.3%) had cystic fibrosis as the underlying disease requiring LT, normal body mass index, and normal lean mass. Cardiovascular risk factors were seen in 51.7% of patients.

Regarding immunosuppressive treatment, 79% of patients were receiving tacrolimus (mean blood level 8.6 ng/mL), 20% cyclosporine (mean blood level 181.2 ng/mL), 66% mycophenolate (mean dosage 1087 mg/day) and 28% azathioprine (mean dosage 62.5 mg/day). Twenty-eight patients out of 29 were on oral steroids at a mean dose of 3.89 (1.57) mg.

Metabolic Response to Exercise

VO_2 peak, work rate (WR), heart rate (HR), heart rate reserve (HRR), O_2 pulse, and respiratory exchange ratio (RER) during exercise are shown in table 2. VO_2 had a mean value of 21.49 (6.68) ml/kg/min (75.24 (15.6) % of predicted value) and the anaerobic threshold was reached at 48.6 (10.1) % of predicted value. There were no differences between males and females or CF and non-CF patients (data not shown).

Circulatory Response to Exercise

The mean (SD) HRR at peak exercise was 17.56 (13.6) %. The O_2 pulse increased during exercise in all patients and was within normal values, at 90.5 (19.4) %. The RER exceeded 1.19 in all patients at maximum exercise. The mean (SD) peak venous blood lactate level was 7.35 (1.89) mmol/L (table 2).

Ventilatory and Gas Exchange Response to Exercise

Table 2 shows the ventilatory and gas exchange variables during exercise. The mean peak V_E was 54 (48-67.1) L/min. Maximum V_E averaged 52 (48-57) % of the calculated MVV. The median (IQR) value for V_E/V_{CO2} at ventilatory threshold was 32 (31-35). The oxygen saturation was normal at peak exercise in all individuals.

Health-related quality of life and physical activity

The median (p25-75) EuroQol- 5D score was 1 (0.95-1), showing a good quality of life in all subjects. The median (p25-75) IPAQ score was 5497 (4007-9832) MET-min/week, with the majority of patients (89%) reporting more than 1500 MET-min/week.

Correlations and adjusted analysis to predict VO_2 peak and work rate peak

There was a positive correlation between peak VO_2 peak (ml/kg/min) and haemoglobin (Hb) values (r =0.555; p=0.002), basal FVC (L) (r=0.571; p=0.001), FEV_1 (L) (r=0.675; p<0.001), DLCO (%pred) (r=0.656; p<0.001) and a negative correlation between VO_2 (ml/kg/min) and age (years) (r = -0.491; p=0.007). There was a positive correlation between VO_2 (%pred) and FVC (%pred) (r=0.421; p=0.023), FEV_1 (%pred) (r=0.414; p=0.026), total lung capacity (%pred) (r = 0.427; p= 0.021) and DLCO (%pred) (r=0.569; p=0.002). WR peak correlated positively with Hb (gr/dl) and FEV_1 (L) (r=0.525; p=0.004 and r=0.616; p<0.001 respectively) and negatively with age (years) (r=-0.469; p=0.010) (Figures 1 and 2).

In the multivariate regression models (Table 3), only age, sex and DLCO remained significantly associated with VO_2 peak (ml/kg/min); and Hb and FEV_1 with WR peak (watts), after adjusting for confounders. Linear regression goodness of fit tests did not reveal any abnormality.

The adjusted predicted VO_2peak value (and 95% confidence interval) was plotted against DLCO (Figure 3) and shows that the higher the DLCO value, the greater the exercise capacity, in a linear dose–response manner. Likewise, Figure 4 depicts the adjusted linear dose–response WR peak (watts) predicted values (and 95% confidence intervals) according to Hb (g/dL).

DISCUSSION

In this study long-term LT survivors with preserved lung function presented a mean VO_2 peak value of 75.24% of their maximum predicted value, that is, near-normal exercise capacity. The multivariate regression model revealed significant associations between age, sex and DLCO and VO_2 peak (ml/kg/min), and between Hb and FEV_1 and work rate peak (watts), after adjusting for confounders. The median (p25-75) EuroQol- 5D score was 1 (0.95-1), indicating a good quality of life in all subjects.

During the 1990s, several authors reported small samples of LT patients with VO_2 peak values ranging between 38% and 60% of the maximum predicted value [2–4, 6, 15, 16]. Later, *Bartels et al*. [7] described a sample of 78 bilateral-LT recipients recruited between 2001 and 2009 who presented a mean VO_2 peak value of 52% of the maximum predicted value 30 months after LT. Recently, Ulvestad et al. (17)reported a VO2 peak of 57% and 70% for men and women respectively, in a sample of 54 patients in a period ranging from 6 to 60 months after BLTx. In the present study the mean VO_2 peak value was 75.24% of the maximum predicted value, indicating a much higher exercise capacity than in previous studies. These findings need to be framed in the context of a highly active subpopulation, although it should not be undermined that this study proves that even in a selected LT recipients, near-normal VO_2 peak values are achievable after undergoing lung transplantation.

Like *Bartels et al*. [7], we observed no cardiac or ventilatory limitations. Although in both studies all patients presented normal FEV_1, *Bartels et al*'s mean DLCO value was 57% while ours was 77.5%. Similarly, *Miyoshi et al*. [3] described a mean VO_2 peak value of 48.5% in six double LT patients undergoing CPET in a range between 6 and 48.5 months after surgery. While the six patients presented normal FEV_1 and DLCO values after LT, they had a mean Hb value of 10.8 mg/dl; therefore, the authors suggested anaemia as the main cause for exercise limitation. *Schwaiblmair et al*. [4] also reported peripheral deficiencies in oxygen transport as the major cause of exercise limitation in 32 bilateral LT recipients undergoing CPET within three months of LT. These patients presented a mean

VO_2 peak of 40.2% of the predicted value along with mean FEV_1 and DLCO values of 66.6% and 69.4% respectively, and also a mean Hb of 10.9 g/dl. The positive correlation between the VO_2 peak value (ml/kg/min) and Hb and the inverse correlation between VO_2 peak and age found in the present study suggests that these factors are crucial and determine exercise capacity in LT recipients. Indeed, in our study the stepwise multiple regression analysis for work load peak revealed anaemia as an independent predictor. Medication effects, immune-mediated factors, and various forms of haemolysis may all contribute to developing anaemia, which can affect oxygen transport and tissue extraction even in mild cases [17].

In agreement with previous findings, we recorded a positive correlation between VO_2 peak (mg/kg/min and% respectively) and pulmonary function values. The stepwise multiple regression analysis for VO_2peak (ml/kg/min) showed DLCO (% predicted) as an independent predictor. In a process such as bilateral-LT in which histological alterations reduce the area of gas exchange, it is plausible to think that the determination most able to predict VO_2 max is DLCO. In fact, in other processes such as idiopathic pulmonary fibrosis [18] or COPD [19], which like bilateral-LT show falls in these parameters and hypoxemia and respiratory insufficiency in advanced stages, there is a growing consensus that DLCO should be added not only for patient diagnosis and management but also for the evaluation of the response to new drugs in clinical trials. In this regard, and also in relation to DLCO, the stepwise multiple regression analysis for WR peak (watts) identified Hb (mg/ml) as an independent predictor of VO_2 peak. Although these results suggest that small changes in DLCO might significally impact %VO2 max values, they should be cautiously interpreted and confirmation in other studies is needed.

There is no standard inventory for formally evaluating health-related quality of life in transplant medicine. However, several authors have reported significant improvement in almost all health-related quality of life (HRQoL) domains in the first three years post-transplant [20–22]. *Vermeulen et al.* [23] described HRQoL comparable to that in the general population after lung transplantation

although they observed a fall over time in relation to the rising incidence of bronchiolitis obliterans syndrome and co-morbid conditions. However, there are few studies analysing HRQoL in long-term LT survivors. Other authors [24–26] reported significantly reduced HRQoL in the main domains in LT recipients surviving periods ranging from 5 to 10 years. The median (p25-75) EuroQol-5D score in the present study was 1 (0.95-1), indicating a good quality of life in all subjects. These findings contrast with those described by previous authors, although the differences are most likely to be related to the study entry criteria.

Regarding physical activity, notable improvements with regard to pre-transplant symptoms have been reported by several studies [27–29]. Over time, however, many LT recipients reported new symptoms related to limb muscle dysfunction (muscle atrophy, muscle weakness and changes in muscle composition and metabolism) and other comorbidities. The LT recipients in our study presented a median (p25-75) IPAQ score of 5497 (4007-9832) MET-min/week, and most (89%) reporting more than 1500 MET-min/week. All reported a high amount of activity in the five domains analysed. Again, these findings may well be related to the particular characteristics of our study popu

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REFERENCES

1. Singer JP, Singer LG. Quality of life in lung transplantation. *Semin Respir Crit Care Med* 2013;34:421–30.
2. Levy RD, Ernst P, Levine SM, Shennib H, Anzueto A, Bryan CL, Calhoon JH, Trinkle JK, Jenkinson SG, Gibbons WJ. Exercise performance after lung transplantation. *J Heart Lung Transplant* 12:27–33.
3. Miyoshi S, Trulock EP, Schaefers HJ, Hsieh CM, Patterson GA, Cooper JD. Cardiopulmonary exercise testing after single and double lung transplantation. *Chest* 1990;97:1130–6.
4. Schwaiblmair M, von Scheidt W, Uberfuhr P, Reichart B, Vogelmeier C. Lung function and cardiopulmonary exercise performance after heart transplantation: influence of cardiac allograft vasculopathy. *Chest* 1999;116:332–9.
5. Pellegrino R, Rodarte JR, Frost AE, Reid MB. Breathing by double-lung recipients during exercise: response to expiratory threshold loading. *Am J Respir Crit Care Med* 1998;157:106–10.
6. Williams TJ, Patterson GA, McClean PA, Zamel N, Maurer JR. Maximal Exercise Testing in Single and Double Lung Transplant Recipients. *Am Rev Respir Dis* 1992;145:101–105.
7. Bartels MN, Armstrong HF, Gerardo RE, Layton AM, Emmert-Aronson BO, Sonett JR, Arcasoy SM. Evaluation of Pulmonary Function and Exercise Performance by Cardiopulmonary Exercise Testing Before and After Lung Transplantation. *Chest* 2011;140:1604–1611.
8. Woodson RD, Wills RE, Lenfant C. Effect of acute and established anemia on O2 transport at rest, submaximal and maximal work. *J Appl Physiol* 1978;44:36–43.
9. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, Oja P. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003;35:1381–95.
10. Devlin NJ, Brooks R. EQ-5D and the EuroQol Group: Past, Present and Future. *Appl Health Econ Health Policy* 2017;15:127–137.
11. Miller MR. General considerations for lung function testing. *Eur Respir J* 2005;26:153–161.
12. García-Río F, Calle M, Burgos F, Casan P, Del Campo F, Galdiz JB, Giner J, González-Mangado N, Ortega F, Puente Maestu L, Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). Spirometry. Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). *Arch Bronconeumol* 2013;49:388–401.
13. Weisman IM, Weisman IM, Marciniuk D, Martinez FJ, Sciurba F, Sue D, Myers J, Casaburi R, Marciniuk D, Beck K, Zeballos J, Swanson G, Myers J, Sciurba F, Johnson B, Whipp B, Zeballos J, Weisman IM, Beck K, Mahler D, Cotes J, Sietsema K. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167:211–277.

14. Earthman CP. Body Composition Tools for Assessment of Adult Malnutrition at the Bedside: A Tutorial on Research Considerations and Clinical Applications. *JPEN J Parenter Enteral Nutr* 2015;39:787–822.

15. Pellegrino R, Rodarte JR, Frost AE, Reid MB. Breathing by double-lung recipients during exercise: Response to expiratory threshold loading. *Am J Respir Crit Care Med* 1998;157:106–110.

16. Lands LC, Smountas AA, Mesiano G, Brosseau L, Shennib H, Charbonneau M, Gauthier R. Maximal exercise capacity and peripheral skeletal muscle function following lung transplantation. *J Heart Lung Transplant* 1999;18:113–20.

17. Ulvestad M, Durheim MT, Kongerud JS, Hansen BH, Lund MB, Edvardsen E. Cardiorespiratory Fitness and Physical Activity following Lung Transplantation: A National Cohort Study. *Respiration* 2020;99:316–324.

18. Dudley KA, El-Chemaly S. Cardiopulmonary exercise testing in lung transplantation: a review. *Pulm Med* 2012;2012:237852.

19. Cortes-Telles A, Forkert L, O'Donnell DE, Moran-Mendoza O. Idiopathic pulmonary fibrosis: new insights on functional characteristics at diagnosis. *Can Respir J* 2014;21:e55-60.

20. Balasubramanian A, MacIntyre NR, Henderson RJ, Jensen RL, Kinney G, Stringer WW, Hersh CP, Bowler RP, Casaburi R, Han MK, Porszasz J, Barr RG, Make BJ, Wise RA, McCormack MC. Diffusing Capacity of Carbon Monoxide in Assessment of COPD. *Chest* 2019;doi:10.1016/j.chest.2019.06.035.

21. Gerbase MW, Spiliopoulos A, Rochat T, Archinard M, Nicod LP. Health-related quality of life following single or bilateral lung transplantation: a 7-year comparison to functional outcome. *Chest* 2005;128:1371–8.

22. Künsebeck HW, Kugler C, Fischer S, Simon AR, Gottlieb J, Welte T, Haverich A, Strueber M. Quality of life and bronchiolitis obliterans syndrome in patients after lung transplantation. *Prog Transplant* 2007;17:136–41.

23. Finlen Copeland CA, Vock DM, Pieper K, Mark DB, Palmer SM. Impact of lung transplantation on recipient quality of life: a serial, prospective, multicenter analysis through the first posttransplant year. *Chest* 2013;143:744–750.

24. Vermuelen KM, van der Bij W, Erasmus ME, TenVergert EM. Long-term health-related quality of life after lung transplantation: different predictors for different dimensions. *J Heart Lung Transplant* 2007;26:188–93.

25. Kugler C, Fischer S, Gottlieb J, Welte T, Simon A, Haverich A, Strueber M. Health-related quality of life in two hundred-eighty lung transplant recipients. *J Heart Lung Transplant* 2005;24:2262–8.

26. Rutherford RM, Fisher AJ, Hilton C, Forty J, Hasan A, Gould FK, Dark JH, Corris PA. Functional Status and Quality of Life in Patients Surviving 10 years After Lung Transplantation. *Am J Transplant* 2005;5:1099–1104.

27. Cebrià I Iranzo MÀ, Vos R, Verleden GM, Gosselink R, Langer D. Evolution of Functional Exercise Capacity in Lung Transplant Patients With and Without Bronchiolitis Obliterans Syndrome: A Longitudinal Case-Control Study. *Arch Bronconeumol* 2019;55:239–245.

28. Lanuza DM, Lefaiver CA, Brown R, Muehrer R, Murray M, Yelle M, Bhorade S. A longitudinal study of patients' symptoms before and during the first year after lung transplantation. *Clin Transplant* 2012;26:E576–E589.

29. Langer D, Burtin C, Schepers L, Ivanova A, Verleden G, Decramer M, Troosters T, Gosselink R. Exercise training after lung transplantation improves participation in daily activity: a randomized controlled trial. *Am J Transplant* 2012;12:1584–92.

30. Osho A, Mulvihill M, Lamba N, Hirji S, Yerokun B, Bishawi M, Spencer P, Panda N, Villavicencio M, Hartwig M. Is Functional Independence Associated With Improved Long-Term Survival After Lung Transplantation? *Ann Thorac Surg* 2018;106:79–84.

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FIGURE LEGENDS

FIGURE 1. Correlations between VO2 peak (% predicted) and FEV1 (% predicted), FVC (% predicted), TLC (% predicted) and DLCO (% predicted).

Footnote: FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; TLC: total lung capacity; DLCO: carbon monoxide transfer test.

FIGURE 2. Correlations between Work load max (watts) and age, haemoglobin and FEV_1 (L).

Footnote: Hb: haemoglobin; FEV_1: forced expiratory volume in the first second.

FIGURE 3. Adjusted predicted VO_2max values (and 95% confidence interval) against DLCO.

Footnote: VO_2: oxygen consumption; DLCO: carbon monoxide transfer test.

FIGURE 4. Adjusted predicted Work load max values (and 95% confidence interval) against haemoglobin.

TABLE 1 Clinical characteristics of LT recipients

	All (n=29)
Age (years)	48.7 (13.6)
Sex (males), n (%)	14 (48)
Age at the time of LT (years)	34.7 (14.0)
Years since LT	14.0 (3.1)
Diagnosis	
COPD	3 (10.3)
ILD	4 (13.7)
CF	14 (48.3)
Bronchiectasis	1 (3.5)
PH	1 (3.5)
Other	6 (20.7)
BMI (kg/m^2)	21.6 (5.6)
FFMI (kg/m^2)	16.6 (4.1)
Haemoglobin (g/dL)	13.3 (1.5)
Arterial hypertension, n (%)	15 (51.7)
Diabetes mellitus, n (%)	6 (20.7)
Dyslipidaemia, n (%)	11 (37.9)
Smoking history, n (%)	
Never smoked	21 (72.4)
Former smoker	8 (27.6)
Packs/year	29.7 (23.4)
Lung function	
FVC (L)	3.9 (0.92)
FVC (% predicted)	92.6 (15.7)
FEV_1 (L)	3.1 (0.7)
FEV_1 (% predicted)	97.9(14.5)
DLCO (mL/mmHg/min) median (p25-75)	77.1 (70-83.3)
TLC (% predicted)	96.1 (18.3)
RV (% predicted)	81.0 (8.5)
Oral corticosteroids, n (%)	28 (96.6)
Oral corticosteroids (dosage, mg)	3.9 (1.6)

Data are presented as mean (SD) unless otherwise specified; Some variables have missing values: 8 in FFMI, 1 in packs/year, 1 in corticosteroid dosage; LT: lung transplantation; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; CF: cystic fibrosis; PH: pulmonary hypertension; BMI: body mass index; FFMI: fat free mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; DLCO: diffusing capacity; TLC: total lung capacity; RV: residual volume.

Table 2: Exercise capacity, physical activity and quality of life of LT recipients.

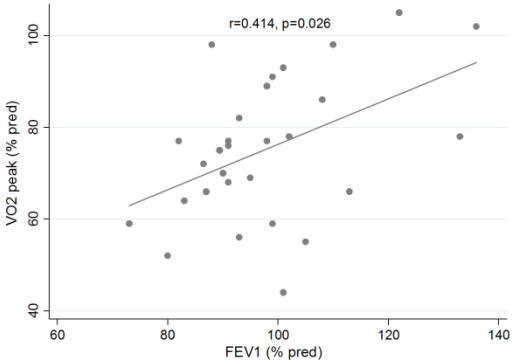
	All (n= 29)
VO_2 peak (ml/kg/min)	21.49 (6.68)
VO_2 peak (% pred)	75.24 (15.6)
VO_2 AT (%)	48.6 (10.1)
VCO_2 peak (L/min) median (p25-75)	1.68 (1.43-2.06)
Work peak (watts)	111.14 (37.13)
V_E/VCO_2 AT	32 (31-35)
V_E Peak (L/min) median (p25-75)	54 (48-67.1)
RER Peak median (p25-75)	1.35 (1.25-1.4)
HR peak (beats/min)	141.5 (21.4)
HRR peak	17.5 (13.6)
VO_2/HR	90.5 (19.4)
VR Peak median (p25-75)	52 (48-57)
Oximetry at V_{O2} max (%)	97.6 (0.8)
Lactic acid peak (mmol/L)	7.35 (1.89)
IPAQ (METs-min/week) median (p25-75)	5497 (4007-9832)
Euroqol 5-D	1 (0.95-1)
Euroqol >0.8	29 (100)

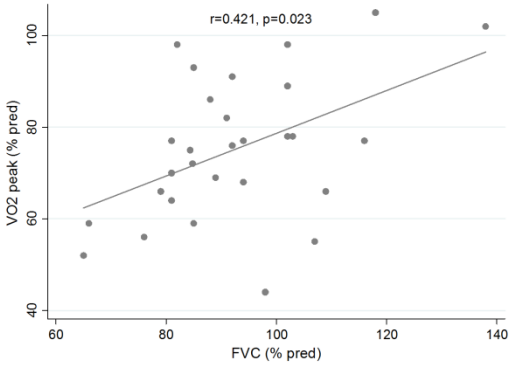
Footnote: Data are presented as mean (SD) unless otherwise specified. VO_2: oxygen uptake; VCO_2: carbon dioxide output; VE: minute ventilation; RER: respiratory exchange ratio; HR: heart rate; HRR: heart rate reserve; VR: ventilator reserve; IPAQ: International Physical Activity Questionnaire.

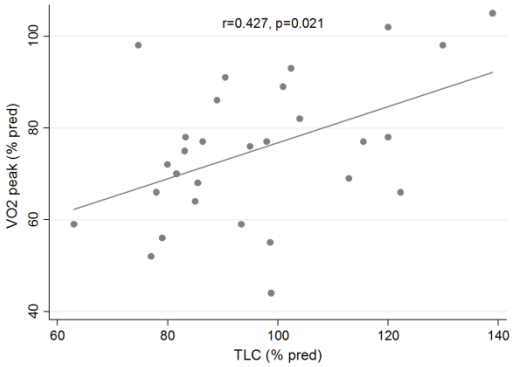
TABLE 3 Results of stepwise multiple regression analysis for VO_2max (ml/kg/min) and Work load max (watts)

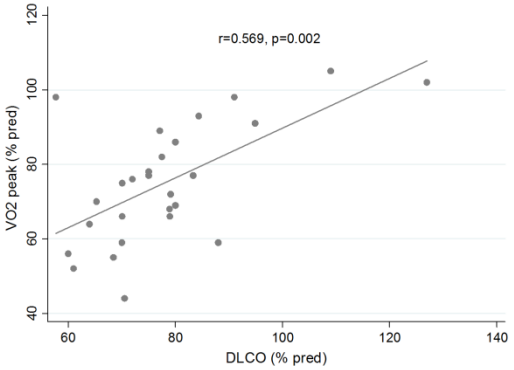
	VO_2max (ml/kg/min)		**Work load max (watts)**	
	Coefficient (95% CI)	p	Coefficient (95% CI)	p
Age (years)	-0.249 (-0.37 – -0.13)	<0.001	-0.24 (-1.17 – 0.69)	0.599
Sex (male)	5.35 (2.19 – 8.51)	0.002	4.72 (-34.75 – 25.30)	0.748
Haemoglobin (g/dL)	--	--	9.62 (2.21 – 17.02)	0.013
FEV_1 (L)	--	--	31.53 (8.88 – 54.17)	0.008
DLCO (% predicted)	0.26 (0.15 – 0.36)	<0.001	--	--
Constant	18.87 (16.80 – 20.95)	<0.001	--	--
Adjusted R^2	0.685		0.580	

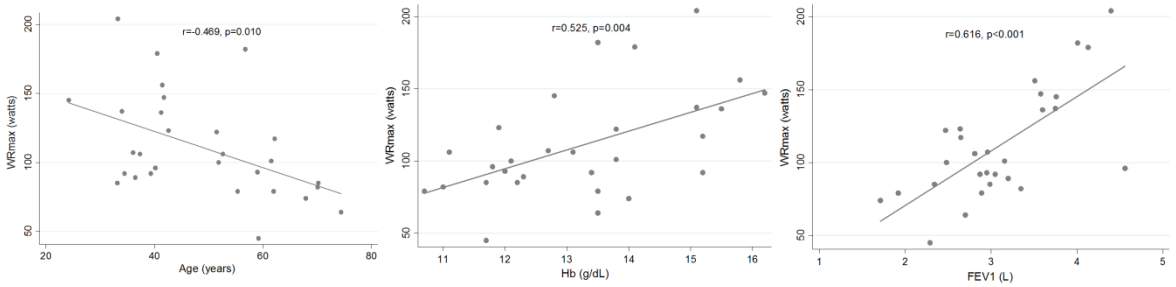
Hb: haemoglobin; FEV1: forced expiratory volume in the first second; DLCO: diffusing capacity for carbon monoxide.

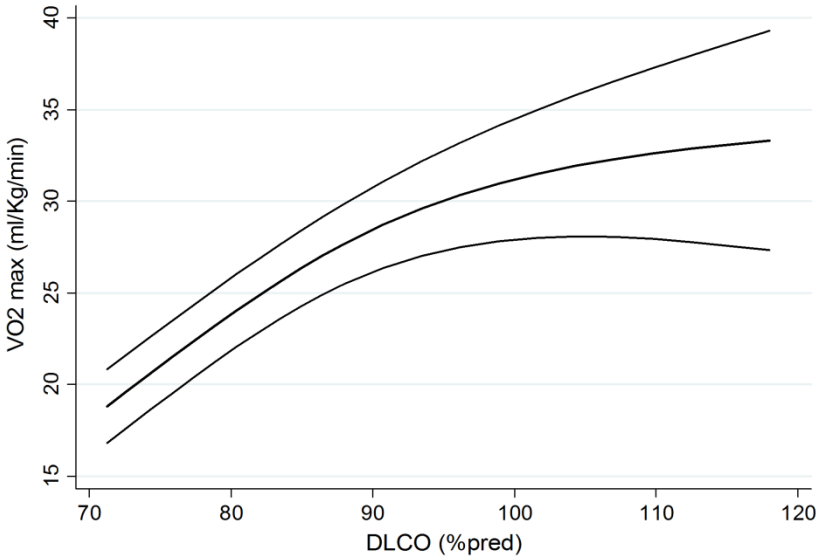

r=0.414, p=0.026
VO2 peak (% pred)
FEV1 (% pred)
40
60
80
100
60
80
100
120
140

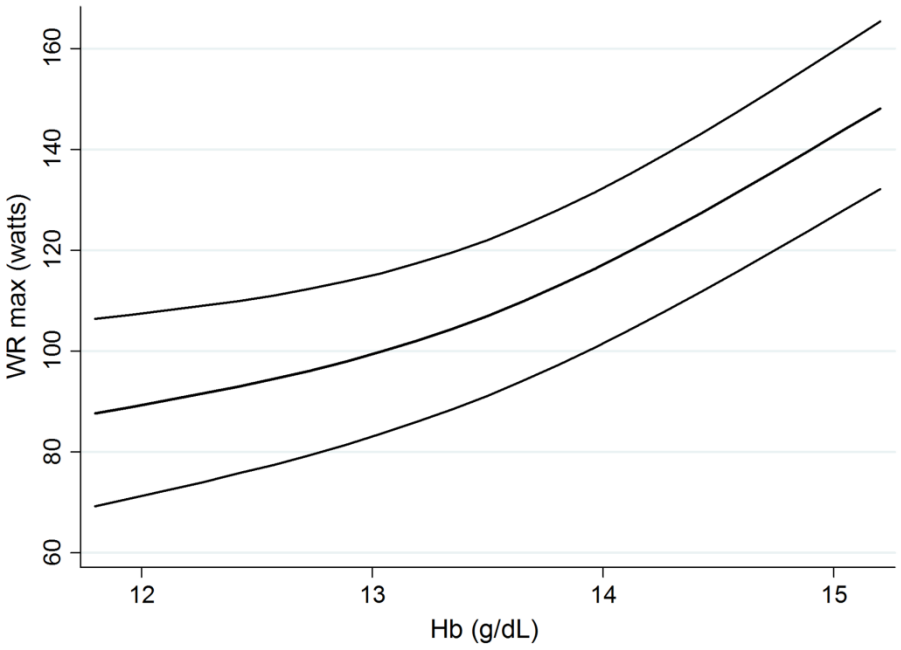

r=0.421, p=0.023
VO2 peak (% pred)
FVC (% pred)
40
60
80
100
60
80
100
120
140


r=0.427, p=0.021
VO2 peak (% pred)
TLC (% pred)
40
60
80
100
60
80
100
120
140


r=0.569, p=0.002
VO2 peak (% pred)
DLCO (% pred)
40
60
80
100
120
60
80
100
120
140


r=-0.469, p=0.010
WRmax (watts)
Age (years)
r=0.525, p=0.004
WRmax (watts)
Hb (g/dL)
r=0.616, p<0.001
WRmax (watts)
FEV1 (L)


VO2 max (ml/Kg/min)
15
20
25
30
35
40
70
80
90
100
110
120
DLCO (%pred)


WR max (watts)
60
80
100
120
140
160
12
13
14
15
Hb (g/dL)