LOW LEVELS OF PHYSICAL ACTIVITY PREDICT WORSE SURVIVAL TO LUNG TRANSPLANTATION AND POOR EARLY POST-OPERATIVE OUTCOMES

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Running title

Physical activity level in lung transplantation

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Severely limited functional status with poor rehabilitation potential is considered an absolute contraindication for lung transplantation.[1] Functional status is a multidimensional measure which includes evaluation of functional capacity and performance. Six minute walk distance (6MWD) is a typical measure of functional capacity and an independent predictor of survival to transplantation.[2] However, pre-lung transplant 6MWD was not associated with intensive care days or mechanical ventilation time.[3] Physical activity level (PAL) is an emerging functional performance measure which can be influenced by both physical and behavioural factors.[4] No studies have evaluated the utility of PAL in predicting pre- and post-transplant outcomes in people being considered for lung transplantation. We hypothesised that PAL, independent of 6MWD, would be a better predictor of survival to transplantation and early post-transplant outcomes including mechanical ventilation duration. To test this hypothesis, we first assessed which patient-specific factors predicted PAL, and then assessed which factors, including PAL, predicted survival to transplantation and early post-transplant outcomes.

Participants undergoing lung transplant assessment at a single institution were evaluated using a prospective observational design. Participants were excluded if they were unable to wear the multi-sensor device for ≥22 hours/day on a minimum of four days in a home environment,[5] or if they had a significant non-respiratory condition (eg musculoskeletal injury) which may influence physical activity. The study was approved by the institutional ethics committee (HREC/11/QPCH/104) and participants gave their written informed consent.

Demographics, lung function (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLco)), and Medical

Research Council dyspnoea scale were measured at transplant assessment. Participants were asked to perform two six minute walk tests[6], with the better 6MWD recorded. Quadriceps strength was measured using hand-held dynamometry and expressed as a percentage by combining the participant's best attempt of each leg and dividing by body weight.[7] Transplant listing status; survival to transplantation (survived; died while listed or delisted); post-operative mechanical ventilation duration, intensive care and hospital admission days were recorded.

Physical activity was assessed using the multi-sensor SenseWear Pro 3 device. This device accurately estimates energy expenditure in people with respiratory diseases when compared to indirect calorimetry.[8, 9] PAL was defined as total energy expenditure in twenty-four hours/basal metabolic rate derived from the average sleeping metabolic rate. Participants were grouped into: extremely sedentary (<1.40), sedentary (1.40-1.69) and active (≥1.70) cohorts.[5]

One hundred and fifty-seven participants were assessed for inclusion. Eleven participants were excluded due to inability to wear the device for the minimum time (n=7) and device failure (n=4). One hundred and forty-six participants (seventy-seven males); mean (± SD) age 49 ± 13 years, FEV_1 36.6 ± 18.7% and DLco 38.4 ± 16.4%; including sixty-one chronic obstructive pulmonary disease (COPD), thirty-three cystic fibrosis and thirty-one idiopathic pulmonary fibrosis patients, were studied. Seventy-one participants (48.6%) were classified extremely sedentary, forty-nine (33.6%) sedentary and twenty-six (17.8%) active. At analysis, eighty-four participants had been transplant listed with sixty-six participants (78.6%) surviving to transplantation, eight participants (9.5%) had either died while listed or been delisted as considered too unwell, and ten participants (11.9%) remained listed. Listing

status was not related to PAL (p=0.374). Of the eight patients (4 idiopathic pulmonary fibrosis, 2 cystic fibrosis, 1 COPD and 1 pulmonary artery hypertension) that either died while listed or had been delisted as too unwell, seven were classified extremely sedentary and one sedentary at time of assessment. Mean post-transplant duration for mechanical ventilation was 3.7 ± 7.8 days, intensive care was 6.1 ± 7.8 days, and hospital admission was 21.2 ± 11.8 days. Mechanical ventilation time was correlated with intensive care (r=0.670, p<0.001); and hospital admission (r=0.528, p<0.001).

Demographic, respiratory function, dyspnea, 6MWD and quadriceps strength were assessed using multivariate linear regression with PAL as the dependent variable. In the univariate analysis, COPD, idiopathic pulmonary fibrosis, age, body mass index, DL_{CO}, 6MWD and quadriceps strength were related to PAL. Only higher DLco (β=0.005, 95% CI% 0.003-0.007, p<0.001) was identified as an independent predictor of increased PAL (r^2=0.223).

Cox survival analysis was used to determine whether age, sex, respiratory diagnosis, FEV_1%, FVC%, DLco, 6MWD, quadriceps strength, body mass index or PAL were risk factors for not surviving to transplantation, or prolonged mechanical ventilation duration. PAL was dichotomised into the extremely sedentary (<1.40) and a more active cohort (≥1.40). In the model (Table 1) assessing survival to transplantation (n=74), PAL <1.40 (extremely sedentary) was the only identified risk factor for death prior to transplantation (Hazard ratio (95% CI): 9.12 (1.10-75.34), p=0.040). In the model (Table 2) assessing prolonged mechanical ventilation (n=66), PAL<1.40 was the only identified risk factor of prolonged duration (Hazard ratio (95% CI): 1.98 (1.16-3.38), p=0.012). No other measure was identified as a risk factor for not surviving to transplantation or prolonged mechanical ventilation.

Physical activity level appears to be an important new measure of functional status, superior to other traditional markers, which may provide additional information when assessing a lung transplantation candidate's suitability. Physical activity was not well described by other measures typically used to assess a candidate's suitability. Other than a weak relationship with DLco, pre-transplant PAL was independent of most measures of disease severity, including 6MWD and quadriceps strength. The present study is the first to demonstrate that individuals who are extremely sedentary are more likely to die while waiting for lung transplantation. Importantly, pre-transplant PAL impacted post-surgical outcomes, with the extremely sedentary cohort more likely to require prolonged mechanical ventilation. Similar to Li et al[3], we found that that pre-transplant 6MWD was not a risk factor for prolonged mechanical ventilation. Our findings confirm that PAL provides valuable prognostic information regarding survival to transplantation and early post-transplant outcomes.

It is important to recognise that as our study was observational we do not know if improving pre-transplant PAL favourably impacts on survival or post-transplant outcomes. Furthermore, our study was uni-institutional. Further study is needed to determine if the results are applicable to other transplant programs.

In conclusion, PAL provides new and important information about the likelihood of a particular individual surviving to transplantation and recovering quickly after transplantation. Our findings suggest that the measurement of PAL should be considered when assessing a candidate's functional status, and that interventions designed to improve PAL while awaiting transplant could improve survival to transplant and post-transplant outcomes.

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Table 1: Cox survival analysis: survival to transplant (n=74)

Univariate analysis	**HR (95% CI)**	**p**
Female sex	6.04 (0.74-49.14)	0.093
Age	1.00 (0.96-1.05)	0.909
Pre-transplant diagnosis: COPD vs CF IPF vs CF Others vs CF	 0.32 (0.03-3.61) 9.43 (1.34-66.45) 0.79 (0.07-8.89)	 0.362 0.024 0.848
FEV_1 (% pred)	1.04 (1.01-1.06)	0.007
FVC (% pred)	0.97 (0.92-1.03)	0.370
DLco (% pred)	0.99 (0.93-1.07)	0.889
6MWD (m)	0.99 (0.98-1.00)	0.021
Quadriceps strength (%)	0.99 (0.96-1.02)	0.417
Body mass index ($kg.m^{-2}$)	1.03 (0.86-1.22)	0.749
PAL: <1.4 vs ≥1.4	9.12 (1.10-75.34)	0.040
Multivariate analysis	**95% CI**	**p**
PAL: <1.4 vs ≥1.4	9.12 (1.10-75.34)	0.040

COPD = chronic obstructive pulmonary disease, CF = cystic fibrosis, IPF = idiopathic pulmonary fibrosis, other = other respiratory diseases, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, DLco = diffusing capacity of the lung for carbon monoxide, 6MWD = six minute walk distance, PAL = physical activity level.

Table 2: Cox survival analysis: time to extubation from mechanical ventilation (n=66)

Univariate analysis	**HR (95% CI)**	**p**
Female sex	1.12 (0.73-1.96)	0.470
Age	0.99 (0.97-1.01)	0.494
Pre-transplant diagnosis: COPD vs CF IPF vs CF Others vs CF	 0.58 (0.31-1.08) 0.71 (0.36-1.41) 0.42 (0.19-0.95)	 0.086 0.330 0.037
FEV_1 (% pred)	0.99 (0.99-1.00)	0.386
FVC (% pred)	1.00 (0.98-1.02)	0.852
DLco (% pred)	1.01 (0.99-1.03)	0.156
6MWD (m)	1.00 (0.99-1.00)	0.705
Quadriceps strength (%)	1.01 (1.00-1.02)	0.143
Body mass index ($kg.m^{-2}$)	0.95 (0.90-1.01)	0.098
PAL: <1.4 vs ≥1.4	1.98 (1.16-3.38)	0.012
Multivariate analysis	**95% CI**	**p**
PAL: <1.4 vs ≥1.4	1.98 (1.16-3.38)	0.012

COPD = chronic obstructive pulmonary disease, CF = cystic fibrosis, IPF = idiopathic pulmonary fibrosis, other = other respiratory diseases, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, DLco = diffusing capacity of the lung for carbon monoxide, 6MWD = six minute walk distance, PAL = physical activity level.

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