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Frailty and maximal exercise capacity in adult lung transplant candidates

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ABSTRACT

Background: Frail lung transplant candidates are more likely to be delisted or die without receiving a transplant. Further knowledge of what frailty represents in this population will assist in developing interventions to prevent frailty from developing. We set out to determine whether frail lung transplant candidates have reduced exercise capacity independent of disease severity and diagnosis.

Methods: Sixty-eight adult lung transplant candidates underwent cardiopulmonary exercise testing (CPET) and a frailty assessment (Fried's Frailty Phenotype (FFP)). Primary outcomes were peak workload and peak aerobic capacity ($\dot{V}O_2$). We used linear regression to adjust for age, gender, diagnosis, and lung allocation score (LAS).

Results: The mean ± SD age was 57 ± 11 years, 51% were women, 57% had interstitial lung disease, 32% had chronic obstructive pulmonary disease, 11% had cystic fibrosis, and the mean LAS was 40.2 (range 19.2–94.5). In adjusted models, peak workload decreased by 10 W (95% CI 4.7 to 14.6) and peak $\dot{V}O_2$ decreased by 1.8 mL/kg/min (95% CI 0.6 to 2.9) per 1 unit increment in FFP score. After adjustment, exercise tolerance was 38 W lower (95% CI 18.4 to 58.1) and peak $\dot{V}O_2$ was 8.5 mL/kg/min lower (95% CI 3.3 to 13.7) among frail participants compared to non-frail participants. Frailty accounted for 16% of the variance (R^2) of watts and 19% of the variance of $\dot{V}O_2$ in adjusted models.

Conclusion: Frailty contributes to reduced exercise capacity among lung transplant candidates independent of disease severity.

1. Introduction

Lung transplantation is widely considered to be an effective treatment for chronic respiratory failure, yet the vast majority of those affected by advanced lung disease are deemed ineligible for transplantation based on their perceived risk for serious complications following transplantation. Reduced exercise capacity and "poor functional status" have long been considered to be contraindications to transplantation, since physical stamina is required to tolerate transplant surgery and thrive despite post-operative complications [1]. The requirement for physical "fitness" is a challenge for many, since advancing disease severity greatly limits exercise capacity, definitions for fitness in this population are lacking, and advanced lung disease impedes the ability to maintain one's functional status.

Recently, frailty, defined conceptually as a physical vulnerability to stressors, has risen to attention as an important phenotype in lung transplant candidates. Frail lung transplant candidates are almost twice as likely to be delisted or die without receiving a transplant [2]. Frailty using the Fried frailty phenotype [3], is measured on a 0–5 scale with 5 being the frailest and encompasses

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measures of muscle strength, daily activity levels, and fatigue [3], and therefore may represent an objective measure of "fitness" for surgery. Yet its relationship to maximal exercise capacity, a metric used by transplant centers to determine candidacy, remains unknown. It is possible that lower exercise capacity in lung transplant candidates can be largely explained by greater disease severity. Alternatively, frailty may capture unique information impacting exercise capacity that is independent of disease severity, a finding which would have important consequences for transplant candidacy decisions. Therefore, we hypothesized that frailty in lung transplant candidates would be associated with reduced exercise capacity, independent of disease severity and other confounding factors of exercise capacity.

We tested whether frailty was associated with reduced peak aerobic capacity ($\dot{V}O_2$ peak) and peak workload during cardiopulmonary exercise testing in adults with advanced lung disease undergoing lung transplant evaluation [4], while controlling for disease severity. We also examined whether frailty was associated with a number of other measures of exercise performance found to be predictive of reduced exercise capacity and/or poor surgical outcomes in those with pulmonary disease, including: oxygen economy ($\dot{V}O_2$/Work rate slope), heart rate-oxygen uptake relationship (HR/$\dot{V}O_2$ slope), reduced breathing reserve, minute ventilation ($\dot{V}_E$), oxygen saturation (SpO_2), ventilatory equivalent for carbon dioxide slope ($\dot{V}_E/\dot{V}CO_2$ slope), end tidal CO_2 ($ETCO_2$ mmHg), heart rate reserve (HRR) and systolic blood pressure (SBP) [5–9].

2. Materials and methods

2.1. Study design, participants, and setting

We conducted a single center cross-sectional study of adults undergoing outpatient evaluation for lung transplantation at Columbia University Medical Center between December 22, 2010 and September 24, 2015, who were enrolled in the Lung Transplant Body Composition Study (LTBC) [2,10–12] (Fig. 1). CPET within CPET was performed as a standard clinical assessment for lung transplant evaluation. Analysis of the CPET data was performed post hoc to the original study. Inclusion criteria was enrollment in the LTBC study. Exclusion criteria for the study was a lack of a CPET within 3 months of the participant's frailty assessment. All participants provided informed consent for participation and the Columbia University Medical Center Institutional Review Board approved the study (IRB protocol #AAAI1000).

2.2. Measurement of frailty

The primary exposure of interest was the 5-point Fried Frailty Phenotype score (FFP) [3]. Briefly, the FFP is an aggregated score that consists of five components: shrinking (>10 lb. unintentional weight loss in the past year), muscle weakness (grip strength measured by dynamometer), exhaustion (using two questions from the Center for Epidemiological Studies Depression scale (CESD) [13]), slowness (time to walk 4.57 m), and low physical activity level (<270 Kcals for women and <383 Kcal for men expended per week based on the Minnesota Leisure Time Activity questionnaire [14]). Each of the 5 components is scored as "frail" or "not frail" based on established criteria [3]. The FFP is calculated by summing the total number of components scored as frail, with a range of 0–5. To achieve an adequate sample size a window of 3 months between tests was allotted.

2.3. Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) testing is a cardiac stress test that also measures gas exchange and ventilatory parameters, used to determine the primary limitation to exercise, $\dot{V}O_2$ peak, and peak aerobic power output (workload/watts) [4,15]. The primary outcomes of interest were peak workload (watts, % predicted) and peak oxygen utilization ($\dot{V}O_2$, ml/kg/min and % predicted), obtained by a symptom-limited CPET testing using a Vmax Encore 29 metabolic cart and Viasprint 2900 cycle ergometer (Carefusion, Palm Spring, CA 92887). Secondary measures of interest were: $ETCO_2$ mmHg, SpO2%, HRR, SBP, $\dot{V}_E/\dot{V}CO_2$ slope, HR/$\dot{V}O_2$ slope and $\dot{V}O_2$/work rate slope. Data from the last 20 s of the ramped exercise phase were considered "peak". The $\dot{V}_E/\dot{V}CO_2$ slope, HR/$\dot{V}O_2$ slope and $\dot{V}O_2$/work rate slope were measured from the onset of the ramping exercise phase and ending at the last data point before recovery. HRR was calculated by determining the change in HR from rest to peak exercise divided by the difference of the resting HR and the age predicted maximum HR (220-age) [16].

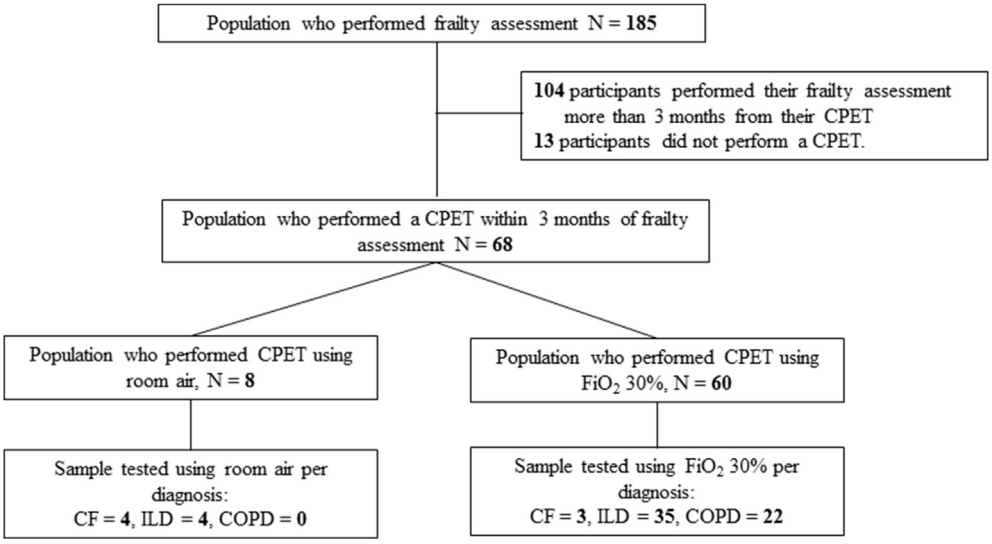

Fig. 1. Study population flow diagram.
FFP; Fried Frailty Phenotype, COPD; Chronic Obstructive Pulmonary Disease, CF; Cystic Fibrosis, ILD; Interstitial Lung Disease.