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Cardiopulmonary exercise factors predict survival in patients with advanced interstitial lung disease referred for lung transplantation

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ABSTRACT

Background: The purpose of this work was to determine if parameters assessed during Cardiopulmonary Exercise Testing (CPET) while using supplemental oxygen can independently predict one-year transplant-free survival in patients with Interstitial Lung Disease (ILD) referred for lung transplant evaluation.
Methods: We performed a chart review of patients with ILD who completed CPET with 30% FiO_2 and gathered spirometry, pulmonary hemodynamic, six-minute walk, and CPET data. The primary end-point was death or lung transplantation within one-year of CPET.
Results: The final data set included 192 patients. 79 patients died/underwent transplant, 113 survived transplant-free. Multivariable Cox regression revealed peak workload % predicted, nadir CPET SpO_2, and FVC% predicted as independent predictors of one-year transplant-free survival. Of the independent predictors of survival, receiver operating characteristics analysis revealed peak workload %predicted cutoff of 35% to be highly discriminatory, more so than nadir CPET SpO_2 or FVC % predicted in identifying patients at risk for one-year mortality or transplant (peak workload % predicted < 35% HR = 4.71, 95% CI = 2.64–8.38 and area under the curve (AUC) = 0.740, nadir CPET SpO_2 < 86% HR = 2.27, 95%CI = 1.41–3.68, AUC = 0.645, FVC %predicted <45% HR = 1.82, 95% CI = 1.15–2.87, AUC = 0.624).
Conclusion: Peak workload % predicted, nadir CPET SpO_2, and FVC% predicted in ILD patients referred for lung transplant evaluation are independently predictive of one-year mortality or need for transplant.

1. Introduction

The median lung transplant waitlist time in the United States is 3.4 months [1] and UNOS guidelines currently allocate lungs primarily based on mortality risk within one year of listing [2]. Therefore, predicting one-year transplant-free survival in patients with advanced lung disease is useful in the determination of timing of referral, the need for an expedited evaluation and/or listing for lung transplantation. Prediction of one-year survival is especially relevant to patients with Interstitial Lung Disease (ILD) due to the heterogeneity among disease phenotypes and patient outcomes [3]. Certain cardiopulmonary exercise testing (CPET) parameters have been reported as indicators of poor prognosis in patients with ILD; however, 80% of the patients in prior studies survived beyond a year and results only gave insight into predicting 3–5 year survival [4–6]. As patients with ILD generally have a less than 5-year life expectancy [5], the prediction of 3–5 year survival does not provide more prognostic insight than the diagnosis itself. Furthermore, prior studies generally focused on a healthier patient population who did not need supplemental oxygen during testing, leading to small sample sizes in the non-surviving group ($n \leq 10$) [6–8]. Lastly, a great deal of research has been performed using field tests, such as the six-minute walk test (6MWT) to identify patients with a higher likelihood of short-term mortality [9–11]. Unlike field tests, CPET is a well-controlled laboratory test that measures parameters indicative of various physiological changes in the cardiovascular,

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respiratory and musculoskeletal systems. The ATS/ERS guidelines [3] bring into question the reproducibility of 6MWT results, strengthening the rationale to study well-controlled laboratory testing that standardizes for FiO_2 and effort for identifying changes in functional measures that may predict a poor prognosis.

We hypothesized that CPET parameters would be independently associated with one-year transplant-free survival in patients with ILD undergoing lung transplant evaluation.

2. Material and methods

This was a cross-sectional observational study of survival in patients undergoing lung transplant evaluation between January 1, 2011 and July 30, 2014, which was approved by our institution's human ethics committee/internal review board (IRB #AAAO4254).

2.1. Study population

Data were collected from a chart review of patients diagnosed with ILD (idiopathic pulmonary fibrosis (IPF), sarcoidosis, hypersensitivity pneumonitis, nonspecific interstitial pneumonia (NSIP) and ILD associated with connective tissue disease), who had undergone CPET as part of their lung transplant evaluation. We chose to investigate the outcomes of patients whose CPET was performed on supplemental oxygen for the following reasons: 1) To focus our investigation on patients with more advanced ILD for better evaluation of 1-year outcomes; 2) Most patients referred for lung transplantation need supplemental oxygen with activity and therefore results are applicable to the majority of this patient population; and 3) The use of supplemental oxygen during exercise may alter physiologic responses to exercise. Patients were excluded if they were not being evaluated for lung transplantation, did not require oxygen with exercise, or their status could not be confirmed within one-year of CPET. We confirmed each patient's vital status by chart review and/or the social security database. The status of living patients was confirmed at one year of their CPET by chart review or last point of contact.

2.2. Measurements and clinical variables

2.2.1. Exercise testing

Peak exercise aerobic capacity (VO_2 ml/kg/min, % predicted), workload (watts, % predicted), ventilatory equivalent for CO_2 slope ($V'_E/V'CO_2$ slope, % predicted), end tidal CO_2 ($ETCO_2$ mmHg), and oxygen delivery per heartbeat (O_2 pulse) were measured using a Vmax Encore 29 metabolic cart and Viasprint 2900 cycle ergometer (Carefusion, Palm Spring, CA 92887) during a symptom-limited CPET. The protocol consisted of a five minute baseline of ECG data, one minute baseline of metabolic data, three minutes of 5–10 W resistance warm-up and then a ramping protocol of either five or ten watts per minute. A five watt ramping protocol was used for patients with maximal voluntary ventilation (MVV) of <40 and ten-watt ramping protocol was used for patients with a MVV of ≥40. Percent predicted reference normals were obtained from age- and sex-adjusted equations [12]. Patients received supplemental oxygen throughout testing via Hans Rudolph 2-way valve and Bird mixing chamber to 30% FiO_2 being delivered into the flow sensor. Oxyhemoglobin saturation was monitored with pulse oximetry (SpO_2, Nellcor N-600× Pulse Oximeter with Oximax, Covidien-Nellcor, Boulder, CO 80301). Heart rate was collected using a 12-lead electrocardiogram (Cardio V4 MDL37 ECG, Cardiosoft, Houston, TX 77056). Blood pressure was collected via a manual blood pressure cuff (Welch-Allen, Skaneateles Falls, NY 13153).

Six-minute walk test distance (6MWD), oxygen saturation at minute six of the walk (6 MW SpO_2) and supplemental oxygen used were collected by chart review if test was performed within 6 months of CPET.

2.2.2. Pulmonary function tests

Pulmonary function tests (PFT) were performed using ATS criteria [13]. Data were used from tests performed within six months of CPET. PFT variables collected consisted of forced vital capacity (FVC (L), FVC % predicted), and single breath diffusion capacity for carbon monoxide (DL_{CO}, DL_{CO} % predicted).

2.2.3. Pulmonary hypertension

The presence of pulmonary hypertension (PH) was confirmed by resting right heart catheterization (RHC) or echocardiography (ECHO). Data were included if RHC or ECHO was performed within 6 months of the CPET. PH was considered present if the mean pulmonary artery was ≥25 mmHg [14] by RHC or estimated systolic pulmonary artery pressure (SPAP) was >40 mmHg by ECHO [14]. If SPAP could not be estimated by ECHO and a RHC was not available, than the presence of right ventricular (RV) hypertrophy, decreased RV function, and presence of RV pressure overload, with normal left ventricular function, were considered as surrogate markers and confirmation of PH.

2.2.4. Exercise regimen

Recent or current exercise regimen was assessed by review of physician and/or physical therapist notes at the time of the CPET to determine the exercise regimen of patients within the previous 3 months.

2.2.5. Lung allocation score

The lung allocation score (LAS) was reported at the time of listing and at the time of transplant in the population of patients listed for transplant and in those who received a lung transplant.

2.3. Statistical analysis

Our primary outcome was survival without the need for lung transplantation. Descriptive statistics were used to summarize data: means and standard deviations for continuous and counts and percentages for categorical variables. The differences in continuous variables between patients who died or underwent lung transplant (D/LTx group) and those who survived transplant-free (S group) were compared using a two-sample independent *t*-test. The differences in continuous variables between patients who died versus those who received a transplant were also compared similarly. Chi squared tests were performed to determine differences in all categorical variables. Peak VO_2 ml/kg/min was collected as a continuous variable but due to the skewed distribution it was categorized (VO_2 ml/kg/min >15.0 and VO_2 ml/kg/min ≤15.0). DL_{CO} was also analyzed as a categorical variable to account for the high percentage of patients unable to complete the DL_{CO} maneuver (moderately reduced (>30% predicted), severely reduced (≤30% predicted), and unable to perform DL_{CO} maneuver).

Survival time was calculated from time of CPET to death or lung transplantation (D/LTx) up to one year with follow-up censored at the last contact using the Kaplan-Meier method. D and LTx groups were combined for two reasons: 1) Patients who underwent lung transplantation were so sick that had they not been transplanted, death would have likely occurred within months of their transplant date. This is supported by the mean LAS of 57 at the time of their transplant. 2) Our goal was to determine if CPET data could help identify patients who were more likely to rapidly deteriorate and die. Therefore, death or transplant were taken as indicators of rapid (within 1 year) clinical deterioration regardless of the patient's ability to receive a transplant. Univariable Cox regression analysis