Distinguishing Pulmonary Hypertension in Interstitial Lung Disease by Ventilation and Perfusion Defects Measured by Cardiopulmonary Exercise Testing

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Key Words
Cardiopulmonary exercise test · Interstitial lung disease · Lung transplantation · Pulmonary hypertension · Ventilation/perfusion defects

Abstract

Background: Pulmonary hypertension (PH) is common in interstitial lung disease (ILD). Since cardiopulmonary exercise testing (CPET) is useful in understanding the pathophysiology of respiratory disorders and can distinguish between ventilation and perfusion (V/Q) defects, it may have a role in the detection of PH in ILD. We evaluated whether CPET can detect PH through analysis of V/Q defects in ILD. Objectives: We aimed to use CPET to determine if there are changes in the ventilation and the activity pattern of mixed-expired carbon dioxide pressure (PECO\textsubscript{2}) and end-tidal carbon dioxide pressure (PetCO\textsubscript{2}) in ILD patients with and without PH. Methods: A retrospective chart review was done of all patients who received lung transplants at the Columbia University Medical Center between 2000 and 2011 with the diagnosis of ILD. CPETs were performed during the 2 years prior to transplantation; right heart catheterizations and pulmonary function tests were performed within 4 months of CPET. Results: The ILD patients with PH demonstrated significantly lower PetCO\textsubscript{2} and PECO\textsubscript{2} during certain levels of exercise with a distinctive activity pattern for PECO\textsubscript{2}/PetCO\textsubscript{2}. Conclusions: Evaluation of V/Q defects through the PECO\textsubscript{2} and PetCO\textsubscript{2} patterns on CPET in ILD patients can distinguish between patients with and without PH.

Introduction

Interstitial lung disease (ILD) often leads to pulmonary hypertension (PH) through mechanisms of pulmonary arteriolar vasoconstriction, vascular remodeling, inflammation and destruction due to progressive parenchymal architectural distortion, perivascular fibrosis, thrombotic angiopathy and associated left-sided cardiac disease [1, 2].

Hansen et al. [3] have previously shown that ventilation/perfusion (V/Q) mismatch caused by airway defects could be differentiated from perfusion defects using non-invasive measures of mixed-expired carbon dioxide pressure (PECO\textsubscript{2}) and end-tidal carbon dioxide pressure (PetCO\textsubscript{2}) in heart failure, primary PH, and chronic obstructive lung disease patients. Since cardiopulmonary exercise testing (CPET) is often useful in understanding...
the pathophysiology of respiratory disorders [4], prior studies have assessed how to determine the domain and mechanism of these diseases, particularly when two disorders such as PH and ILD might coexist [3]. In addition to the actual values of PE CO2 and PetCO2, the activity pattern of PECO2 to PetCO2 was shown to differ as patients go through the stages of exercise-rest, unloaded pedaling, ventilatory threshold (VT), and peak performance. The differences in activity patterns can be striking when looking at the phases of exercise to allow for separation of patients based on their underlying physiology when plotted. We hypothesized that there may be similar changes in ventilation and the activity pattern of PECO2 to PetCO2 in patients with ILD that may be helpful in distinguishing between patients with and without PH.

The main objective of this study was to determine if PECO2, PetCO2, PECO2/PetCO2, and the activity pattern of PECO2 versus PetCO2 could differentiate between abnormal V/Q due to ventilatory disorders alone and abnormal V/Q caused by airway and perfusion disorders during increasing work rates in severe ILD patients with and without PH.

Patients and Methods

Patients

A retrospective chart review was performed of all patients who received a lung transplant at the Columbia University Medical Center between December 2000 and September 2011 with the diagnosis of ILD, and who had CPETs during the 2 years prior to transplantation and right heart catheterizations (RHCs) and pulmonary function tests (PFTs) performed within 4 months of CPET. Patients with known left heart failure, known cardiac disease, ischemic or valvular heart disease determined by echocardiography, nuclear cardiology study, or left heart catheterization and RHC were excluded. Further reasons for exclusion included missing or incomplete CPETs and RHCs or testing far from the transplant date; RHCs done outside of our hospital, or a mean pulmonary arterial pressure (mPCWP) >15. Subjects were verified to have ILD according to the diagnostic criteria established by the American Thoracic Society (ATS)/European Respiratory Society [5]. The Institutional Review Board of the New York Presbyterian-Columbia University Medical Center approved this study.

Cardiopulmonary Exercise Testing

CPET was performed on an electronically braked cycle ergometer (Ergometrics 800; SensorMedics Inc., Yorba Linda, Calif., USA) with a Viasys Encore Metabolic Cart (Viasys Corporation, Loma Linda, Calif., USA); prior to 2005, a SensorMedics Vmax 229 series workstation was used. The equipment was calibrated prior to every test. Continuous 12-lead telemetry was monitored via CardioSoft electrocardiogram software (GE/CardioSoft, Houston, Tex., USA); prior to 2005, a model Max-1 electrocardiogram was used (Marquette Medical Systems, Milwaukee, Wisc., USA). The exercise protocol was ramping and followed the exercise protocol used in the National Emphysema Treatment Trial [6] and ATS guidelines [7, 8]. An individualized ramping protocol was determined by the maximal voluntary ventilation (MVV) test. Individuals who achieved ≤40 l/min MVV performed a 5-watt per minute ramping protocol, and those attaining >40 l/min MVV performed a 10-watt ramping protocol. Oxygen was administered if used daily or with exercise at 30.00 ± 0.20% via a closed system; all calibrations were two-point calibrations with hyperoxic and hypoxic points and included hypercarbic and absent carbon dioxide levels of calibration. The metabolic system was validated for use with hyperoxic testing and was stable for measurement of fraction of expired carbon dioxide at hypoxic situations. CPET variables were collected breath by breath and included the rate of carbon dioxide production by weight (VCO2 in ml/kg/min), maximal oxygen consumption by weight (VO2 in ml/kg/min), percent of predicted VO2 (VO2%), minute ventilation (Ve; in l/min), tidal volume (Vt; in liters), respiratory exchange ratio, and PetCO2 (in mm Hg). The predicted watts and VO2% were calculated for males and females as described by Jones et al. [9]. Each VT was determined independently by three exercise physiologists and then averaged. PECO2 was calculated as a result of dividing 863 by the Vt/VO2 ratio [3].

Pulmonary Function Tests

All PFTs were performed according to the ATS criteria [10]. This included the forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), residual volume (RV), total lung capacity (TLC), diffusion capacity of the lung for carbon monoxide (DlCO), and forced expiratory flow (FEF). Percentages of predicted FEV1 (FEV1%), FVC (FVC%), DlCO (DlCO%), TLC (TLC%), and FEF (FEF%) were calculated for males and females as described in prior publications [11–13]. Arterial blood gases were taken at rest and included arterial oxygen pressure (PaO2) and acidity.

Right Heart Catheterization

Catheterization was performed at rest with a Swan-Ganz catheter. PH was defined as mean pulmonary arterial pressure ≥25 mm Hg at rest with a normal mPCWP (≤15) [14, 15]. Other variables collected included mean right arterial pressure, mean mPCWP, cardiac output, and cardiac index when available in the chart.

Statistics

Normal distribution was assessed using the Kolmogorov-Smirnov test. Variables that were normally distributed are presented as means ± SD or as mean percent of predicted ± SD. Variables that deviated from normal are presented as medians and interquartile ranges (25–75%). Between-group comparisons were performed using unpaired Student t or the Mann-Whitney U test for normal and nonnormal data, respectively. Equal distribution was not assumed. A χ2 test was used to analyze 2 × 2 tables. Analysis of variance was used to determine significant differences between time periods with the Gabriel post hoc test. Receiver-operating characteristic analyses were used to find sensitivities and specificities. Both univariate and multivariate analyses were performed to determine variables associated with PH. All analyses were completed using SPSS version 19 (SPSS, Chicago, Ill., USA). All tests were two tailed; statistical significance was set at p ≤ 0.005, and 95% confidence intervals were determined.
Results

Between December 2000 and September 2011, there were 175 lung transplantations for ILD. A total of 75 patients with ILD who met the inclusion criteria were analyzed. There were 42 patients with idiopathic pulmonary fibrosis, 5 with sarcoidosis, 12 with parenchymal lung disease, 8 with hypersensitivity pneumonitis, and 8 with fibrosis due to connective tissue disease. Patient demographic, hemodynamic, and PFT parameters are shown in Table 1. According to hemodynamic criteria, 34% of the patients were classified as having PH. Age, sex, and body mass index distributions were similar between those with and without PH. Except for DLCO, the PFT parameters were similar between the two groups.

The CPET parameters for both groups are presented in Table 2. All patients with PH and 90% of patients without PH were on supplemental oxygen during CPET. There were no significant differences in CPET variables between those on and off supplemental oxygen.

Figure 1a shows the PEO2 values for the two groups at each of the four activity stages. The PH group significantly differed from the no PH group during the unloaded, VT, and peak stages. Those without PH significantly increased their PEO2 from rest to each level of exercise; from rest to unloaded p = 0.008, from rest to VT p < 0.001, and from rest to peak p < 0.001. Those with PH did not significantly change their PEO2.

Figure 1b shows the PetCO2 values for the same activity stages for both groups. The two groups differed significantly during rest, unloaded pedaling, and peak exercise. Neither group significantly changed its PetCO2 from rest.

Figure 1c shows the PEO2/PetCO2 ratios for the activity stages in both groups. Surprisingly, the groups were not significantly different in any of the activity stages as compared to the Hansen study. Those with PH significantly increased their PEO2/PetCO2 ratio between rest and unloaded.
and peak exercise ($p < 0.001$). The group without PH significantly increased their PE CO$_2$/Pet CO$_2$ ratio from rest to each level of exercise; from rest to unloaded $p = 0.001$, from rest to VT $p < 0.001$, from rest to peak $p < 0.001$, and from unloaded to peak $p = 0.005$.

Next we performed univariate and multivariate analyses with known variables that are associated with PH, namely D LCO$_{\%}$ [16–18], 6-min walk distance [18–21], Pa O$_2$ [17], and V E/V CO$_2$ [22, 23] along with PE CO$_2$ and Pet CO$_2$. We chose to only perform univariate analyses on PE CO$_2$ and Pet CO$_2$ since the PE CO$_2$/Pet CO$_2$ ratio did not show any difference between activity stages. The results of the univariate analyses (table 3) reveal that PE CO$_2$ had the most significant and strong hazard ratios at all activity levels.

In the multivariate analysis, we used two main models. The first model included either PE CO$_2$ (at rest, unloaded, VT, or peak), Pet CO$_2$ (at rest, unloaded, VT, or peak) or PE CO$_2$ and Pet CO$_2$ (at rest, unloaded, VT, or peak) with D LCO$_{\%}$, 6-min walk distance, and Pa O$_2$ with V E/V CO$_2$ at
VT. The second model included these variables but used \( \text{Ve/VCO}_2 \) at peak instead of at VT. None of the multivariate analyses showed PE\(_{CO_2}\) or Pet\(_{CO_2}\) to be significant at the \( p \leq 0.005 \) level. However, in the model with \( \text{Ve/VCO}_2 \) at peak, Pet\(_{CO_2}\) at peak had a significance of \( p = 0.037 \) with a hazard ratio of 0.845 (95% confidence intervals: 0.722–0.990); when both PE\(_{CO_2}\) at rest and Pet\(_{CO_2}\) at rest were entered, Pet\(_{CO_2}\) had a significance of \( p = 0.038 \) with a hazard ratio of 0.806 (95% confidence intervals: 0.658–0.988), PE\(_{CO_2}\) was not significant. Interestingly, in every model, DLCO% was significant at least at the \( p \leq 0.05 \) level, while no other variables were significant.

When the pattern of activity for PE\(_{CO_2}\) to Pet\(_{CO_2}\) was plotted (fig. 2), there was a distinctive activity pattern for patients with PH versus those without PH. Those without PH showed a progressive increase, while those with PH...
demonstrated a bowed appearance with reversion to the left. Subgroup analysis by diagnosis for those diagnoses with more than 2 patients (idiopathic pulmonary fibrosis, nonspecific fibrotic lung disease, and connective tissue-associated ILD) showed preservation of this pattern (plots not shown). Receiver-operating characteristic analysis revealed that a peak PE CO\textsubscript{2} of 22.59 had a sensitivity of 0.920 and a specificity of 0.667 while a peak Pet CO\textsubscript{2} of 39.10 had a sensitivity of 0.920 and a specificity of 0.479.

**Discussion**

This study demonstrated that there were clear ventilatory differences between severe ILD patients evaluated for lung transplantation who had PH and those who did not have PH. Patients with PH had lower PetCO\textsubscript{2} and PE CO\textsubscript{2} values with higher VE/VCO\textsubscript{2} ratios, as would be anticipated [16]. Although there were no clear differences between the PE CO\textsubscript{2}/Pet CO\textsubscript{2} ratios, there was a distinctive pattern of activity for PE CO\textsubscript{2} versus Pet CO\textsubscript{2} for patients with PH versus those without PH.

The lower values of PetCO\textsubscript{2} and PE CO\textsubscript{2} throughout exercise in the patients with PH compared to those without PH are similar to the known ventilatory inefficiencies seen in patients with pulmonary vascular limitations [3] and suggest an inability to increase pulmonary perfusion in exercise. Supporting that perfusion is mainly involved are the findings that ventilation and dead space/V\textsubscript{T} were not different between the two groups. The fact that neither those with nor those without PH were able to significantly decrease their Pet CO\textsubscript{2} above the VT reflects a similar difficulty in increasing ventilation in response to lactic acidemia [3]. In ILD patients without PH, all levels of exercise had a higher PE CO\textsubscript{2} than at rest, while those with PH did not significantly change their PE CO\textsubscript{2}. This may suggest an alteration in ventilation that is exaggerated in patients with PH. Notably, the lower VCO\textsubscript{2} values in patients with PH may possibly indicate worse lung function. Additional support for this finding is the relationship between DlCO\% and PH. The lack of change in the PE CO\textsubscript{2}/Pet CO\textsubscript{2} ratios may reflect the relative relationship of the changes in ventilation, with both the Pet CO\textsubscript{2} and PE CO\textsubscript{2} moving in similar directions in all ILD patients.

The interesting finding is that the pattern of activity of PE CO\textsubscript{2} versus Pet CO\textsubscript{2} seen in our group of patients with ILD is similar to published data from Hansen et al. [3]. ILD patients without PH showed a progressive increase in PE CO\textsubscript{2} versus Pet CO\textsubscript{2} values going from rest to peak exercise. This pattern is similar to and in the same range of values described for patients with chronic obstructive pulmonary disease (a gradual mild increase) in their study. In contrast, for patients with ILD and PH, the values showed a bowed appearance with reversion to the left, a pattern similar to the values seen in patients with primary PH in the Hansen study. These similarities between the pattern of activity of PE CO\textsubscript{2} versus Pet CO\textsubscript{2} and the results of published data in patients with isolated lung disease and isolated primary PH indicate that the pattern of activity of PE CO\textsubscript{2} to Pet CO\textsubscript{2} may be sensitive for detecting the presence of V/Q mismatching due to PH in ILD. Further evidence for this can be seen in the PFTs. There were no significant differences in the FEF 25–75%, FEF 25% or RV/TLC ratio between those with and without PH. This indicates that the alteration in V/Q matching is due to perfusion changes and not due to other associated ventilatory alterations such as the presence of small airway obstruction/distortion.

There are several limitations to this study, including its retrospective nature and the relatively smaller numbers of subjects, which also did not allow for complete analysis based on diagnostic subgroups. Some of the subjects were tested on room air, and this may have introduced a degree of error and also increased the standard deviations of the data, limiting the sensitivity of the study to detect more
subtle changes. However, this was adjusted for through the use of V̇CO₂ and V̇O₂ was not a main outcome of our study. The analysis of the pattern of activity of PECO₂ to PetCO₂ is also somewhat limited because quantification of these values is somewhat difficult. We did not collect arterial blood gases with exercise so PaCO₂ or pH measurements could not be used in order to detect changes in dead space/V̇T.

In conclusion, the ventilation of patients evaluated for transplantation with ILD and PH is different from that of patients with ILD but no PH. There are unique patterns of activity of PECO₂ versus PetCO₂ for one group of patients versus the other. Further elaboration of the activity pattern with objectification of the findings may help to distinguish the presence of perfusion defects caused by PH from the ventilatory limitations in patients with ILD.

Acknowledgments

This research was supported in part by the VIDDA foundation. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Financial Disclosure and Conflicts of Interest

The authors have no conflicts of interest.

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