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THE IMPACT OF PULMONARY HYPERTENSION ON EXERCISE PERFORMANCE IN PATIENTS WITH INTERSTITIAL LUNG DISEASE UNDERGOING EVALUATION FOR LUNG TRANSPLANTATION

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Abstract

Background and objective—Pulmonary hypertension (PH) is a known complication in patients with interstitial lung disease (ILD). Cardiopulmonary exercise testing (CPET) is an essential tool for the assessment of patients with cardiac and pulmonary diseases due to its prognostic and therapeutic implications. Few studies have evaluated the relationship between CPET response and mean pulmonary artery pressures (mPAP) in interstitial lung disease (ILD). The purpose of the present study was to determine and compare the potential correlations between CPET, 6-minute walk test (6MWT), pulmonary function testing (PFT) and PH in patients with ILD being evaluated for lung transplantation.

Methods—The present study reviewed patients with ILD who received lung transplantations and had CPETs within two years before transplantation, right heart catheterizations, PFTs and 6MWTs within 4 months of CPET.

Results—A total of 72 patients with ILD were analyzed; 36% had PH. There were significant correlations between mPAP and CPET parameters in patients with PH; but mPAP had no impact on DLCO% or 6MWD. CPET parameters were able to detect differences between levels of severity of PH through the use of the ratio of minute ventilation to rate of carbon dioxide production ($\dot{V}_E/\dot{V}_{CO_2}$) and the partial pressure of end-tidal carbon dioxide ($P_{et}CO_2$).

Conclusions—This is the first study that analyzes 6MWD, PFT and CPET in patients with ILD awaiting lung transplantation with and without PH. The present study demonstrates the significant impact of PH on exercise capacity and performance in patients with ILD awaiting lung transplantation.

Keywords

Cardiopulmonary exercise test; Interstitial lung disease; Lung Transplantation; Pulmonary hypertension; Respiratory insufficiency

INTRODUCTION

Interstitial lung disease (ILD) includes a diverse group of primary and secondary lung diseases with comparable clinical, radiographic and physiologic symptoms.^{1, 2} With a prevalence of 30-40%, pulmonary hypertension (PH) is a known complication in patients with ILD^{2, 3} and highly associated with morbidity and mortality.^{4, 5} To date, studies that have evaluated PH in ILD have focused on subgroups of lung transplant candidates including idiopathic pulmonary fibrosis^{6, 7} and sarcoidosis.^{8, 9} However, the cohorts of patients with ILD followed in lung transplant centers are a variety of several subtypes of ILD.¹⁰

Cardiopulmonary exercise testing (CPET) is important for assessing patients with cardiac and pulmonary diseases due to its prognostic and therapeutic implications. Additionally, a joint statement by the American Thoracic Society (ATS) and American College of Chest Physicians advocates the use of CPET in assessing patients with PH.¹¹ Recently, there has been increased recognition that CPET plays a valuable role in evaluating patients with PH because of the abnormalities seen in the physiologic response to exercise.^{12, 13} Exercise assessment provides a non-invasive way to assess the cardiopulmonary system and the interaction between heart and lung function.¹³ Another exercise assessment, the 6-minute walk test (6MWT) has been used to assess exercise capacity in patients with ILD;^{7, 10, 14} however, a direct comparison of 6MWT, CPET and PFT for correlation with mPAP has not been done to date. We hypothesized that variables on CPET would be more highly associated with mPAP than 6MWT in patients with ILD who have PH.

Given the paucity of data, this study attempts: (i) to determine the relationship between PH and exercise capacity, gas exchange and ventilatory inefficiency in patients with ILD awaiting lung transplantation; and (ii) to determine and compare the potential correlation between mean pulmonary artery pressure (mPAP), PFT, CPET and 6MWT parameters in patients with ILD who have PH.

METHODS

Study Cohort

A retrospective chart review was performed of all patients who received a lung transplant at Columbia University Medical Center between December 2000- September 2011 with the diagnosis of ILD, who had CPET within two years prior to transplantation and RHC and PFTs within 4 months of CPET. When available, 6MWTs within 4 months of CPET were chosen. Patients with known left heart failure, known cardiac disease, ischemic or valvular heart disease as determined from echocardiography, nuclear cardiology study or left and right heart catheterization were excluded. Additionally, to have a clean dataset, those who were tested on room air (5 patients) were excluded. Subjects were verified to have ILD

according to the diagnostic criteria established by the ATS/European Respiratory Society criteria.¹⁵ The Institutional Review Board of the New York Presbyterian-Columbia University Medical Center approved this study.

Cardiopulmonary Exercise Testing

A CPET was performed on an electronically braked cycle ergometer (Ergometrics 800, SensorMedics Inc., Yorba Linda, CA) with a Viasys Encore metabolic cart (Viasys Corporation, Loma Linda, CA); prior to 2005 a Sormedics Vmax 229 series workstation (SensorMedics Inc., Yorba Linda, CA) was used. The equipment was calibrated prior to every test. Continuous 12-lead telemetry was monitored via CardioSoft electrocardiogram software (GE/CardioSoft, Houston, TX); prior to 2005 a model Max-1 electrocardiogram was used (Marquette Medical Systems; Milwaukee, WI). Oxygen was administered if used daily or with exercise at $30.00 \pm 0.20\%$ 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 $\dot{V}\text{CO}_2$ at hyperoxic situations. The exercise protocol was ramping and followed the exercise protocol used in the National Emphysema Treatment Trial¹⁶ and ATS guidelines.¹¹ Individualized ramping protocol was determined by the maximal voluntary ventilation (MVV) test. Individuals who achieved $> 40 \text{ L} \cdot \text{min}^{-1}$ MVV performed a 5-watt per minute ramping protocol, and those attaining $> 40 \text{ L} \cdot \text{min}^{-1}$ MVV performed a 10-watt ramping protocol. CPET variables were collected breath-by-breath and included the rate of carbon dioxide output ($\dot{V}\text{CO}_2$ in $\text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$), workload (peak watts), oxygen uptake ($\dot{V}\text{O}_2$ in $\text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$), oxygen saturation (SpO_2), minute ventilation ($\dot{V}\text{E}$) in liters per min ($\text{L} \cdot \text{min}^{-1}$), tidal volume (V_t) in liters (L), respiratory exchange ratio (RER), partial pressure of end-tidal CO_2 (PetCO_2) in millimeters of mercury (mmHg), heart rate (HR) in beats per minute (bpm), volume of O_2 uptake per heartbeat (O_2 pulse) in milliliters per beat ($\text{mL} \cdot \text{beat}^{-1}$) and rate of CO_2 output per heartbeat (CO_2 pulse) in $\text{mL} \cdot \text{beat}^{-1}$. Each ventilatory threshold (VT) was determined independently by three exercise physiologists and then averaged. The predicted watts and $\dot{V}\text{O}_2$ were calculated for males and females as described by Jones et al.¹⁷

Pulmonary Function Tests

All PFTs were performed according to the ATS criteria.¹⁸ This included the forced vital capacity (FVC), forced expiratory volume in one second (FEV1), total lung capacity (TLC), and diffusion capacity of the lung for carbon monoxide (DLCO). Percent of predicted FEV1 (FEV1%), FVC (FVC%), DLCO (DLCO%) and TLC (TLC%) were calculated for males and females as described in prior publications.¹⁹⁻²¹

Right Heart Catheterization

Right heart catheterization was performed at rest with a Swan-Ganz catheter. PH was defined as $\text{mPAP} \geq 25 \text{ mmHg}$ at rest with a normal mean pulmonary capillary wedge pressure ($\text{mPCW} \leq 15$).^{22, 23} Other variables collected were mean right arterial pressure (mRAP), mean pulmonary capillary wedge pressure (mPCWP), cardiac output and cardiac index when available.

Statistical Analysis

Normal distribution was assessed using the Kolmogorov-Smirnov test. Variables that were normally distributed are presented as mean $\pm$ standard deviation. Variables that deviated from normal are presented as median and interquartile range (IQR) (25 – 75%). Between PH group comparisons were performed using unpaired Student's *t*-test or the Mann-Whitney *U* test for normal and non-normal data, respectively. Equal variance was not assumed. Chi-square testing was used to analyze sex distribution between PH groups. One-way analysis of variance was used to compare parameters between the groups of PH severity. The Gabriel post-hoc test was used to compare groups of different sizes. Quadratic polynomial regression models were fitted as they provided a low residual mean squared error when compared to other models considered. We purposely selected covariates that are known prognostic factors for PH in patients with ILD: 6 minute walk distance (6MWD) and DLCO %. We examined the ability of CPET variables and other known factors to detect the presence of PH using receiver operating characteristic (ROC) curves. All analyses were completed using SPSS version 20 (SPSS, Chicago, IL). All tests were two-tailed and statistical significance was set a priori at an $\alpha=0.05$ and 95% confidence intervals (CI₉₅) were determined.

RESULTS

Patient characteristics

A total of 72 patients with ILD were analyzed. There were 39 patients with idiopathic pulmonary fibrosis, 6 with sarcoidosis, 7 with hypersensitivity pneumonitis, 8 with fibrosis due to connective tissue disease and 12 with ILD of unknown origin. According to hemodynamic criteria, 36% of the patients were classified as having PH. Table 1 compares the demographic, hemodynamic, and PFT parameters of patients with and without PH. Except for DLCO, the PFT parameters were similar between the two groups.

Exercise capacity and gas exchange

The maximal CPET parameters for both groups can be seen in Table 2. Exercise capacity, as measured in Watts% was significantly lower in patients with PH. Ventilatory inefficiency, seen by the $\dot{V}_E/\dot{V}_{CO_2}$ ratio at VT and maximal exercise, was significantly higher in the patients with PH.

Additionally, the 6MWT variables that differed between the groups are also listed in Table 2. In patients with PH, there were significant correlations between mPAP and CPET parameters (Table 3), but mPAP had no impact on DLCO% ($r^2=0.061$, $p=0.516$) or 6MWD ($r^2=0.055$, $p=0.524$). Overall, the mPAP of patients with PH had the largest impact on PetCO₂ at all levels of exercise. Figure 1 shows the correlation between mPAP and peak PetCO₂.

Pulmonary Hypertension Severity

We then subcategorized our cohort into normal (mPAP: <25 mm Hg), mild to moderate PH (25-39 mm Hg) and severe PH (≥ 40 mm Hg) (Table 4). Comparing the three groups revealed significant differences between patients with severe PH and those without PH in

regards to DLCO%, $\dot{V}\text{CO}_2$ (mL·kg·min), RER, CO_2 pulse (mL·beat) and the average supplemental O_2 used during the 6MWT. The patients with severe PH had significantly higher $\dot{V}\text{E}/\dot{V}\text{CO}_2$ and lower PetCO_2 at maximal exercise compared to patients with mild to moderate or no PH reflecting disproportionate ventilation with worsening mPAP (Figure 2). No patient with severe PH reached the ventilatory threshold; therefore, these variables could not be compared.

Strength of Association with Pulmonary Hypertension

Figure 3 presents the ROC curves for severe PH comparing maximal PetCO_2 , 6MWD, and DLCO%. The C-statistic (area under the ROC curve) was 98% for PetCO_2 ($p<0.001$), 82% for DLCO% ($p=0.018$), and 62% for 6MWD ($p=0.375$).

DISCUSSION

Our findings demonstrate the significant impact of PH on ventilatory efficiency and show that exercise capacity expressed as Watts% on CPET is reduced in patients with ILD awaiting lung transplantation. Furthermore, this is the first study that analyzes and compares PFT, 6MWT and CPET in patients with ILD awaiting lung transplantation, with and without PH.

Our cohort revealed that 36% of patients with ILD had PH, which is similar to a prospective study that found 32% of patients with ILD to have PH.²⁴ Our findings show that those with PH tend to have a lower DLCO%²⁵ and shorter 6MWD^{7, 14, 26} which is consistent with prior studies that analyzed ILD patients with and without PH. In contrast to those prior studies,^{7, 25} we did not find the SpO_2 nadir on the 6MWT or at peak exercise capacity on CPET to be different between patients with and without PH. Our patients with PH also had a higher resting supplemental oxygen requirement, which was not reported in prior studies. Although testing on supplemental oxygen reduces submaximal ventilation and affects exercise performance in ILD, our data assessment was restricted to testing with supplemental oxygen in those patients because the patients were hypoxemic before transplantation and our study was designed to test those at risk prior to surgery.

Our present study shows that peak exercise capacity is significantly lower in patients with ILD and PH compared to patients with ILD without PH, in agreement with prior studies.^{3, 27} While age, gender, resting lung volumes and ventilatory measurements such as $\dot{V}\text{E}$, breathing reserve, and Vt were not different between the two groups,³ measures of exercise capacity including Watts% and $\dot{V}\text{CO}_2$ were significantly lower for patients with ILD and PH. However, exercise capacity alone is not sufficient to describe the complex pathophysiology or differentiate causes of reduced exercise capacity, so other measurements beyond the 6MWD and peak Watts% should be assessed.²⁸ In our study, the $\dot{V}\text{E}/\dot{V}\text{CO}_2$ ratio at VT was higher, indicating more ventilatory inefficiency in patients with PH. Patients with severe PH showed significantly more impaired maximal PetCO_2 and $\dot{V}\text{E}/\dot{V}\text{CO}_2$ compared to those with mild to moderate or no PH, confirming an incremental increase related to the severity in the impact of mPAP. PetCO_2 and $\dot{V}\text{E}/\dot{V}\text{CO}_2$ are important non-invasive measurements of ventilation-perfusion mismatching due to loss of normal pulmonary vasculature.²⁸

The main premise advocating the use of CPET for detecting PH is that CPET variables observe the degree of ventilation/perfusion mismatch secondary to altered pulmonary hemodynamics.¹³ The increased ventilatory response to exercise, measured by the higher $\dot{V}_E/\dot{V}_{CO_2}$ ratio and lower $P_{et}CO_2$, shows the degree to which ventilation is heightened relative to the demands of the work rate and is caused by ventilation/perfusion mismatch - usually from impaired cardiac output, increased chemo- and muscle-receptor sensitivity, hypoxemia, metabolic demands such as early lactate accumulation and/or increased pulmonary pressure causing decreased alveolar-capillary membrane conductance.^{25, 29, 30} Mechanisms that may explain the amplified ventilatory requirements include the increase in functional intrapulmonary right-to-left shunt.^{3, 13} Supporting this theory, we found decreased CO_2 pulse and $P_{et}CO_2$ and an increased $\dot{V}_E/\dot{V}_{CO_2}$ in patients with PH. Although the precise mechanisms remain unclear, ventilatory inefficiency increases the respiratory burden of patients with ILD and PH.³ Additionally, it is known that the increased dead space ventilation in patients with ILD fails to decrease with exercise (increased physiological dead space fraction).³¹ Furthermore, the ventilation-perfusion mismatch, metabolic demands, shallow breathing pattern, and other factors stimulating ventilatory drive such as systemic and local hypoxia³ and acidemia may account for the increased ventilatory response.²⁵

Historically, the 6MWT has been the exercise assessment of choice for PH in pulmonary populations,³² but CPET is developing as a more precise way to quantify cardiopulmonary limitations in patients with suspected or confirmed PH.^{12, 13} The CPET parameters on our study were able to show differences between levels of severity of PH with the use of maximal $P_{et}CO_2$ and $\dot{V}_E/\dot{V}_{CO_2}$. None of the 6MWT parameters correlated, suggesting that CPET is more closely associated than 6MWT with mPAP. Additionally, compared to the 6MWD and DLCO%, $P_{et}CO_2$ had the highest sensitivity and specificity for association with severe PH.

Limitations of the study include that this is a retrospective review of patients at a single center. Statistically, multiple tests were performed on numerous variables which could result in potential issues of multiplicity. Since only those patients undergoing lung transplant evaluation with complete data were included, the average age of our population may be lower and the results might not reflect the parameters in older adults or non-transplant candidates.⁷ The 6MWT was also not performed on the same day as the CPET, but rather within 4 months and there is a possibility that patients may have improved or declined within this timeframe. Additionally, the presence of more advanced disease in a transplant referral population possibly resulted in overestimation of the prevalence of PH. Finally, even though this study included all subjects with ILD regardless of etiology, the numbers were too small for subgroup analysis, so the differences between underlying disease process and the presence of PH could not be assessed.

In conclusion, this is the first study to analyze exercise capacity in patients with ILD with and without PH for comparison of PFT, 6MWT and CPET variables and to correlate those findings with the presence of PH. Our study suggests that CPET variables, specifically maximal $P_{et}CO_2$ and $\dot{V}_E/\dot{V}_{CO_2}$, are highly correlated with mPAP compared to DLCO%, 6MWD, or supplemental oxygen used on the 6MWT. For patients awaiting lung

transplantation, the detection of early signs of mild to moderate PH with CPET may have implications for pre-transplant survival, as well as pre- and peri-transplant management.

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Summary at a Glance

A direct comparison of the 6-minute walk test, cardiopulmonary exercise testing (CPET) and pulmonary function tests for correlation with mean pulmonary arterial pressure is unknown in interstitial lung disease patients with pulmonary hypertension. CPET variables are strongly associated with presence or absence of pulmonary hypertension, independent of resting lung volumes.

Figure 1. Peak partial pressure of end-tidal carbon dioxide (PetCO₂) as a function of mean pulmonary arterial pressure (mPAP) in patients with pulmonary hypertension
The curve through the data points was determined by quadratic modeling.

Figure 2. Patients with ILD-Peak $\dot{V}\dot{E}/\dot{V}\dot{C}\text{O}_2$ and PetCO₂ according to severity of resting pulmonary hypertension

The peak ratio of minute ventilation to rate of carbon dioxide produced ($\dot{V}\dot{E}/\dot{V}\dot{C}\text{O}_2$) and partial pressure of end-tidal carbon dioxide (PetCO₂) were significantly different (* $p < 0.05$) between the patients with severe pulmonary hypertension (≥ 40 mmHg) compared to those with mild to moderate (25-39 mmHg) or no pulmonary hypertension (<25 mmHg). With increasing severity of pulmonary pressures, the $\dot{V}\dot{E}/\dot{V}\dot{C}\text{O}_2$ increased while the PetCO₂ decreased.

Figure 3. ROC Curves

Receiver operating characteristic (ROC) curves for severe pulmonary hypertension at rest. The area under the curve was 98% (p-value<0.001) for partial pressure of end-tidal carbon dioxide (PetCO₂), 82% (p-value=0.018) for percent of predicted diffusion capacity of the lung for carbon monoxide (DLCO %), and 62% (p-value=0.375) for 6-minute walk distance (6MWD).

Table 1

Baseline characteristics, pulmonary function and hemodynamic values in patients with ILD, comparing those with and without pulmonary hypertension

Patient Characteristic	ILD, PH n=26	ILD, No PH n=46	p-value
Demographics			
Age (yr)	57 ± 8	59 ± 7	0.192
% Female	31%	46%	0.216
BMI (kgm ⁻²)	28.5 ± 4.7	27.0 ± 3.4	0.167
Pulmonary Function			
FVC %	51% (44 - 66%)	44% (37 - 56%)	0.119 *
FEV1 %	53 ± 14%	50 ± 15%	0.499
TLC %	53 ± 15%	50 ± 16%	0.429
DLCO %	21 ± 6%	31 ± 14%	<0.001
Hemodynamics			
mPAP (mmHg)	34.3 ± 8.1	19.1 ± 4.2	<0.001
mRAP (mmHg)	4.0 (2.0 – 7.3)	2.0 (1.0 – 4.0)	0.008 *
mPCWP (mmHg)	7.8 ± 4.2	6.4 ± 3.5	0.159
Cardiac Output (l/min)	4.6 ± 1.3	5.1 ± 1.4	0.174
Cardiac Index (l-min-m ⁻²)	2.4 ± 0.6	2.7 ± 0.7	0.083
Time between CPET and RHC (days)	3 (–9 – 31)	2 (–8 – 4)	0.215 *

Values are means±SD unless otherwise specified. Unpaired Student t used unless otherwise specified.

Bold p-values indicate significance; statistical significance is set at p 0.05.

BMI- body mass index. FVC %- percent of predicted forced vital capacity. FEV1 %- percent of predicted forced expiratory volume in 1 second. TLC %- percent of predicted total lung capacity. DLCO %- percent of predicted diffusion capacity of the lung for carbon monoxide. mPAP- mean pulmonary arterial pressure. mRAP- mean right atrial pressure. mPCWP-mean pulmonary capillary wedge pressure.

Five patients with PH and seven patients with no PH did not have TLC % available; Two patients with PH and nine patients with no PH did not have DLCO % available; One patient with no PH did not have mRAP available; One patient with PH did not have mPCWP available; Six patients with PH and four patients with no PH did not have cardiac output available; Seven patients with PH and five patients with no PH did not have cardiac index available

* Mann-Whitney U test used and values presented as median (interquartile range).

Table 2

Cardiopulmonary exercise and six minute walk test inpatients with ILD, comparing those with and without pulmonary hypertension

Patient Characteristic	ILD, PH n=26	ILD, No PH n=46	p-value
Cardiopulmonary Exercise			
Maximal $\dot{V}O_2$ (mL·min ⁻¹ ·kg ⁻¹)	13.88 ± 3.62	15.79 ± 5.00	0.067
$\dot{V}O_2$ % predicted	53 ± 14%	60 ± 18%	0.063
Watts % predicted	24 ± 12%	35 ± 18%	0.002
Maximal $\dot{V}CO_2$ (mL·min ⁻¹ ·kg ⁻¹)	13.20 ± 3.38	16.23 ± 4.82	0.003
Maximal $\dot{V}E$ (L·min ⁻¹)	51 ± 13	45 ± 13	0.065
Resting $\dot{V}E/\dot{V}CO_2$	56 ± 13	49 ± 9	0.018
VT $\dot{V}E/\dot{V}CO_2$	43 ± 3	36 ± 7	0.004
Maximal $\dot{V}E/\dot{V}CO_2$	44 (40 – 50)	36 (31 – 44)	<0.001
Breathing Reserve	19 ± 41%	24 ± 42%	0.626
Resting SpO ₂	96% (94 – 98%)	97% (95 – 98%)	0.281
Maximal SpO ₂	89% (85 – 94%)	92% (90 – 95%)	0.058
Maximal HR (bpm)	122 ± 11	121 ± 17	0.712
Maximal RER	0.97 ± 0.23	1.05 ± 0.18	0.140
Maximal O ₂ Pulse (mL·beat ⁻¹)	9.50 ± 2.67	10.12 ± 3.10	0.375
Maximal CO ₂ Pulse (mL·beat ⁻¹)	9.00 ± 2.60	10.36 ± 2.85	0.045
Resting PetCO ₂ (mmHg)	30.4 ± 5.9	36.4 ± 5.1	0.001
VT PetCO ₂ (mmHg)	31.7 ± 5.6	40.0 ± 6.5	0.015
Maximal PetCO ₂ (mmHg)	28.6 ± 7.8	38.6 ± 6.7	<0.001
Maximal Vt (L)	1.08 ± 0.34	0.93 ± 0.39	0.265
Time from CPET to LTx (days)	155 (81 – 297)	192 (124 – 346)	0.281
Six Minute Walk Test			
6MWT distance (feet)	868 ± 296	1136 ± 434	0.003
Resting SpO ₂	98% (97 - 99%)	97% (96 - 98%)	0.035
Nadir SpO ₂	83 ± 9%	85 ± 8%	0.337
Change SpO ₂	15 ± 9	12 ± 8	0.131
Average Suppl O ₂ (Lmin ⁻¹)	6.00 (4.00 - 15.00)	4.00 (2.00 - 6.00)	0.004*
Time from CPET to 6MWT (days)	-1 (-18 – 4)	-1 (-5 – 8)	0.696

Values are means±SD unless otherwise specified. Unpaired Student t used unless otherwise specified.

Bold p-values indicate significance; statistical significance is set at p 0.05.

$\dot{V}O_2$ - volume of oxygen consumed. $\dot{V}O_2$ % pred.- percent of predicted volume of oxygen consumed. Watts % pred.- percent of predicted watts attained. VT-Ventilatory threshold. $\dot{V}CO_2$ -rate of carbon dioxide produced. $\dot{V}E$ - minute ventilation. SpO₂- saturation of peripheral oxygen. HR- heart rate measured in beats per minute. RER- respiratory exchange ratio. O₂ pulse- volume of oxygen consumed in milliliters per heartbeat. CO₂ pulse- rate of carbon dioxide produced per heartbeat. PetCO₂- partial pressure of end-tidal carbon dioxide. Vt- tidal volume. 6MWT- six minute walk test. SpO₂- saturation of peripheral oxygen.

One patient with no PH did not have peak RER, CO₂ pulse, resting VE/VCO₂, resting and maximal PetCO₂, Vt, or V̇CO₂ data available; One patient with PH did not have Vt, resting and maximal PetCO₂, or resting VE/VCO₂ data available; there were only 6 patients with PH and 20 without PH that had VT data available; there were 43 patients with no PH that had 6MWT data available.

* Mann-Whitney U test used and values presented as median (interquartile range).

Table 3

Quadratic correlations between mean pulmonary artery pressure (mPAP) and cardiopulmonary exercise testing variables in patients with pulmonary hypertension

Patient Characteristic	R ²	p-value
Cardiopulmonary Exercise Variable		
Maximal $\dot{V}O_2$ (mL·min ⁻¹ ·kg ⁻¹)	0.220	0.057
Maximal $\dot{V}CO_2$ (mL·min ⁻¹ ·kg ⁻¹)	0.582	<0.001
Maximal $\dot{V}E/\dot{V}CO_2$	0.267	0.028
Maximal CO ₂ Pulse (mL·beat ⁻¹)	0.339	0.009
Resting PetCO ₂ (mmHg)	0.427	0.002
Warmup PetCO ₂ (mmHg)	0.487	0.001
Maximal PetCO ₂ (mmHg)	0.448	<0.001

Bold p-values indicate significance; statistical significance is set at p 0.05.

$\dot{V}O_2$ - volume of oxygen consumed. $\dot{V}CO_2$ - rate of carbon dioxide produced. CO₂ pulse- rate of carbon dioxide produced per heartbeat. PetCO₂- partial pressure of end-tidal carbon dioxide.

Table 4

Patients with ILD categorized according to severity of resting pulmonary hypertension

Patient Characteristic	mPAP <25 mm Hg n= 46	mPAP 25-39 mm Hg n= 19	mPAP ≥ 40 mm Hg n= 7
Age (yr)	59 ± 7	58 ± 8	53 ± 8
% Female	46%	21%	57%
BMI (kg·m ⁻²)	27.0 ± 3.4	28.0 ± 3.7	29.8 ± 7.0
DLCO %	31 ± 14% [#]	21 ± 5%	19 ± 6% [#]
Maximal $\dot{V}O_2$ (mL·min ⁻¹ ·kg ⁻¹)	15.79 ± 4.78	14.37 ± 4.00	12.54 ± 1.89
Maximal $\dot{V}O_2$ % pred.	60 ± 18%	54 ± 14%	50 ± 15%
Maximal Watts % pred.	35 ± 18%	25 ± 13%	20 ± 10%
Maximal $\dot{V}CO_2$ (mL·min ⁻¹ ·kg ⁻¹)	16.23 ± 4.82 [#]	14.16 ± 3.35	10.61 ± 1.79 [#]
Maximal $\dot{V}E$ (L·min ⁻¹)	45 ± 13	52 ± 14	50 ± 8
Maximal $\dot{V}E/\dot{V}CO_2$	37 ± 7 [*]	45 ± 9 [*]	59 ± 16 [*]
Breathing Reserve	24 ± 42%	18 ± 42%	22 ± 39%
Maximal RER	1.05 ± 0.18 [#]	1.02 ± 0.24	0.85 ± 0.11 [#]
O ₂ Pulse (mL·beat ⁻¹)	10.12 ± 3.10	9.99 ± 2.83	8.17 ± 1.67
CO ₂ pulse (mL·beat ⁻¹)	10.36 ± 2.85 [#]	9.80 ± 2.56	6.84 ± 1.05 [#]
Maximal PetCO ₂ (mmHg)	38.7 ± 6.7 [*]	31.2 ± 6.5 [*]	20.2 ± 5.4 [*]
Maximal Vt (L)	0.93 ± 0.39	1.03 ± 0.36	1.22 ± 0.24
6MWD (feet)	1136 ± 434	885 ± 300	824 ± 302
Avg. Supp. O ₂ on 6MWT (L·min ⁻¹)	5.24 ± 4.86 [#]	8.00 ± 5.21	10.00 ± 5.03 [#]

One-way analysis of variance was used to compare parameters between the groups of PH severity. The Gabriel post-hoc test was used to compare groups of different sizes. Values are means±SD. Statistical significance is set at p 0.05

BMI-body mass index. FVC %- percent of predicted forced vital capacity. FEV1 %- percent of predicted forced expiratory volume in 1 second. TLC %- percent of predicted total lung capacity. DLCO %- percent of predicted diffusion capacity of the lung for carbon monoxide. $\dot{V}O_2$ - volume of oxygen consumed. $\dot{V}O_2$ % pred.- percent of predicted volume of oxygen consumed. Watts % pred.- percent of predicted watts attained. $\dot{V}CO_2$ - rate of carbon dioxide produced.

$\dot{V}E$ - minute ventilation. RER- respiratory exchange ratio. O₂ pulse- volume of oxygen consumed in milliliters per heartbeat. CO₂ pulse- rate of carbon dioxide produced per heartbeat. PetCO₂- partial pressure of end-tidal carbon dioxide. Vt- tidal volume. 6MWD-6-minute walk distance.

* p 0.05 for comparing the group with severe pulmonary hypertension (PH) and the other two groups

p 0.05 for comparing the group with severe PH and the group without PH