Primary pulmonary hypertension (PPH) is a rare, life-threatening illness that is typically diagnosed a year or more after patients become symptomatic (1–4). It begins with alterations to the pulmonary arterioles and capillaries that lead to increased pulmonary vascular resistance, right ventricular hypertrophy and/or dilation, decreased systemic and pulmonary perfusion, and an increase in dead-space ventilation. Both the increased ventilatory requirement and the decreased cardiac output response to exercise contribute to the predominant symptoms of exercise dyspnea and fatigue (5,6), symptoms common to many disorders, either organic or functional. Unfortunately, most patients with PPH are diagnosed in advanced stages of their disease, when the mean survival rate is less than three years without treatment (5,6). Because of the lack of distinctive physical, radiographic, and electrocardiographic findings in PPH, cardiac catheterization is required to establish and confirm the diagnosis (5,7).

Several studies (6–12) have found that simple, noninvasive lung function measurements, especially the gas transfer index or diffusing capacity for carbon monoxide (DLCO), can also be abnormal in PPH patients. This is not surprising considering that the pathology of PPH primarily involves the small pulmonary arteries and capillaries, and that the DLCO is dependent on the access and transfer of inhaled carbon monoxide to the hemoglobin in the pulmonary capillaries. However, none of the above studies have shown significant correlations of DLCO with the severity of the disease as measured by New York Heart Association (NYHA) class, resting hemodynamic measurements, or cardiopulmonary exercise test (CPET) parameters. The CPET can be safely performed in PPH patients to: 1) detect patterns of gas exchange abnormalities that are typical of PPH, 2) quantify disease severity, and 3) identify the presence of right-to-left shunting (2,3,13,14). Specifically, the severity of PPH has been shown to be correlated with several CPET parameters, including peak O2 uptake (maximal aerobic capacity), peak O2 pulse, and anaerobic threshold (maximal sustainable exercise level) (2). We hypothesized that the DLCO and perhaps other lung function measurements, would be significantly correlated with the severity of PPH assessed in other ways. Thus, in 79 patients with well-documented diagnoses of PPH and 20 control subjects, resting lung function measurements (including spirometric, lung volume, and DLCO values) were correlated with CPET parameters, resting hemodynamic variables (measured during cardiac catheterization), and NYHA symptom class.

**METHODS**

**Subjects.** After we obtained Human Subjects Committee approval, the resting lung function and CPET measurements of 79 consecutive patients referred for such tests with
well-documented diagnoses of PPH seen between 1996 and 2001 in our PPH clinic were analyzed. The diagnosis of PPH was based on clinical and laboratory data, including cardiac catheterization, according to currently accepted criteria (4). Many patients had used appetite suppressants. Secondary causes of pulmonary hypertension, such as portal hypertension, interstitial lung disease, thromboembolic, and infectious diseases were excluded by history, physical examination, cardiac catheterization, ventilation/perfusion scans, and computerized tomography. All patients’ diagnoses were made or confirmed by the PPH referral clinic cardiologist in charge, who also assigned the NYHA class independently of CPET and resting lung function data. The patients were nonsmokers at the time of study; most had never smoked. This report includes only the first lung function and exercise test measurements made after referral to our PPH clinic, nearly always prior to the initiation of pulmonary vasodilator therapy.

For comparison purposes, the CPET and resting lung function data of 20 sedentary age- and gender-matched control individuals, without detectable cardiorespiratory disorders, were measured during the same time period and analyzed.

Resting lung function measurements. Each patient underwent resting measurements of forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), maximum voluntary ventilation (MVV), DLco, and effective alveolar volume (VA') using standard equipment and methodology meeting American Thoracic Society standards (15,16). Total lung capacity (TLC) was assessed by multiple breath nitrogen washout or plethysmographic measurements (17,18) in 41 patients.

CPET measurements. On the same day as resting lung function testing, each patient underwent CPET after familiarization with the exercise apparatus. The exercise protocol consisted of a progressively increasing work rate test to maximum tolerance on an electromagnetically braked cycle ergometer (2,3,12). Gas exchange was measured using the MedGraphics (St. Paul, Minnesota) CPET equipment that calculated heart rate, ventilation, CO2 output, O2 uptake, and other gas exchange variables, breath-by-breath (2,3,19). From these data, peak O2 uptake, anaerobic threshold, peak O2 pulse, and other parameters were analyzed by standard techniques (2,3,19–22).

Calculation of percent predicted values. All resting lung function and CPET values were reported in absolute terms and normalized to percent of predicted (%pred). Predicted spirometry values were calculated using accepted equations for Caucasians, Hispanics, and Blacks (23), with Asian values considered equal to Blacks (24). Predicted DLco and VA' were calculated using nonsmoker equations for Caucasians and Hispanics (25); and 0.93 and 0.88 of the Caucasian values for Asian and Black adult patients, respectively (26). Separate predicting equations were used for those under age 20 (27). Predicted DLco values were corrected for measured hemoglobin concentration (28). All predicted values of CPET parameters were calculated as previously reported (2,3,19,29).

### Table 1. Demographics and Cardiopulmonary Exercise Testing Parameters in PPH Patients and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>PPH Patients (n = 79)</th>
<th>Control Subjects (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>44 ± 13</td>
<td>45 ± 12</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>71/8</td>
<td>15/5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164 ± 9</td>
<td>169 ± 9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73 ± 18</td>
<td>81 ± 24</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27 ± 6</td>
<td>28 ± 8</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14.9 ± 2.0*</td>
<td>13.6 ± 1.5</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.7 ± 0.6</td>
<td>—</td>
</tr>
<tr>
<td>mPAP (mm Hg)</td>
<td>60 ± 18</td>
<td>—</td>
</tr>
<tr>
<td>Peak O2 uptake, l/min (%pred)</td>
<td>0.78 ± 0.26 (45 ± 13)‡</td>
<td>1.87 ± 0.48 (97 ± 18)</td>
</tr>
<tr>
<td>Peak work rate, W (%pred)</td>
<td>47 ± 24 (37 ± 17)‡</td>
<td>151 ± 45 (104 ± 24)</td>
</tr>
<tr>
<td>Anaerobic threshold, l/min (%pred)</td>
<td>0.59 ± 0.18 (59 ± 15)‡</td>
<td>0.98 ± 0.20 (89 ± 14)</td>
</tr>
<tr>
<td>Peak O2 pulse, ml/beat (%pred)</td>
<td>5.9 ± 1.9 (69 ± 17)‡</td>
<td>12.0 ± 3.2 (108 ± 16)</td>
</tr>
<tr>
<td>Peak heart rate, beats/min (%pred)</td>
<td>133 ± 21 (76 ± 11)‡</td>
<td>156 ± 16 (89 ± 8)</td>
</tr>
<tr>
<td>Peak ventilation, l/min (%MVV)</td>
<td>43 ± 15 (47 ± 13)*</td>
<td>72 ± 19 (58 ± 10)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD and percentage of measured to predicted values (%pred).

*P < 0.05, †P < 0.001, ‡P < 0.0001, vs. controls using unpaired t test.

mPAP = mean pulmonary artery pressure; %MVV = percentage of maximum voluntary ventilation; NYHA class = New York Heart Association heart failure classification; PPH = primary pulmonary hypertension; %pred = percent predicted.

### Abbreviations and Acronyms

- CPET = cardiopulmonary exercise test
- DLco = diffusing capacity of the lung for carbon monoxide or gas transfer index
- FEV1 = forced expiratory volume in 1 second
- FVC = forced vital capacity
- MVV = maximum voluntary ventilation
- NYHA = New York Heart Association
- %pred = percent predicted
- PPH = primary pulmonary hypertension
- TLC = total lung capacity
- VA' = effective alveolar volume
Table 2. Resting Lung Function in PPH Patients and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>PPH Patients (n = 79)</th>
<th>Control Subjects (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value</td>
<td>% Abnormal</td>
</tr>
<tr>
<td>FVC, l (%pred)</td>
<td>2.86 ± 0.72 (80 ± 15) †</td>
<td>54 §</td>
</tr>
<tr>
<td>FEV1, l (%pred)</td>
<td>2.30 ± 0.63 (79 ± 17) †</td>
<td>54 §</td>
</tr>
<tr>
<td>FEV1/FVC (%pred)</td>
<td>0.80 ± 0.07 (98 ± 9)</td>
<td>8</td>
</tr>
<tr>
<td>VA', l (%pred)</td>
<td>4.26 ± 0.98 (83 ± 14) †</td>
<td>42 §</td>
</tr>
<tr>
<td>DLco, ml/mm Hg/min (%pred)</td>
<td>16.24 ± 4.54 (68 ± 17) §</td>
<td>78</td>
</tr>
<tr>
<td>DLco/VA’, ml/mm Hg/min/l (%pred)</td>
<td>3.87 ± 0.92 (81 ± 19) †</td>
<td>49 §</td>
</tr>
<tr>
<td>MVV, l/min (%pred)</td>
<td>92 ± 25 (80 ± 19)*</td>
<td>53 §</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD and percentage of measured to predicted values (%pred). *p < 0.05, †p < 0.01, §p < 0.001, ‡p < 0.0001, vs. controls using unpaired t test or chi-square test.

DLco = gas transfer index or diffusing capacity for carbon monoxide; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; MVV = maximum voluntary ventilation; VA’ = effective alveolar volume. Other abbreviations as in Table 1.

Statistical analyses. Parameters were expressed as mean ± SD, except where specifically noted. Individual values within two-tailed 95% confidence limits were considered normal. The Student-Newman-Keuls tests were performed for the repeated-measures analyses of variance. Individual linear regression analyses were performed. Pearson correlation coefficients were performed for all pulmonary function and exercise values, which were normally distributed, whereas Spearman rank correlation coefficients were performed for NYHA class. To ascertain the relative significance of resting lung function parameters to CPET parameters, multicollinearity analyses were done. Stepwise regression with forward selection and backward elimination was used, eliminating variables with an alpha of p > 0.05.

RESULTS

Demographics of PPH patients and controls. The female-to-male ratio of the PPH patients in this study was 9:1 (Table 1). The control population, by design, had a similar female-to-male ratio. The resting lung function and CPET parameters of the control group were within normal limits (Tables 1 and 2). Using arabic numerals to grade NYHA class, the PPH patients both had an average NYHA class of 2.7. The hemoglobin concentration in the PPH group was significantly higher than the controls.

All individuals completed their CPET studies without incident or untoward effects. Nearly all patients stopped exercise because of dyspnea and/or leg fatigue; uncommonly, patients noted palpitations or lightheadedness. The magnitude of the absolute and percent of predicted peak O2 uptake, and all of the other measured parameters of cardiovascular function and ventilatory efficiency was strikingly abnormal, and similar to those seen in a smaller group of PPH patients previously reported (2).

Resting lung function. Mean FVC (80 %pred), FEV1 (79 %pred), and VA’ (83 %pred) showed mild, albeit highly significant reductions (p < 0.001 to p < 0.0001) in the PPH group (Table 2), with values ranging from 46% to 118%, 40% to 121%, and 55% to 126 %pred, respectively. Approximately half of the FVC measurements, as well as the FEV1, VA’, and TLC values, were below 80 %pred, a level approximating the lower limit of normal (Table 1). In Figure 1, the regression lines (solid lines) of
FEV$_1$-versus-FVC and VA'/versus-TLC had nonsignificant intercepts (p > 0.05 vs. 0) and similar slopes to the line of identity (dotted lines, p > 0.05). The ratio of directly measured MVV to the FEV$_1$ was 39 ± 9 (Fig. 2, upper right). This MVV/FEV$_1$ ratio is similar to that found in the control group and in patients with obstructive lung disease, but lower than that found in patients with interstitial lung disease (19).

Only two patients could not perform the necessary
maneuvers for measurement of DL_{CO} and VA' in slightly over three-fourths of the remaining PPH patients, the DL_{CO} values were below 80% of predicted, that is, the lower limit of normal (Fig. 1, lower) and generally reduced to a greater extent than the FVC (Fig. 2, lower right). The mean DL_{CO} was 68 ± 17%pred (p < 0.0001) with a range of 32% to 114%pred (Table 2 and Fig. 2, lower right) Methodologically, when a patient has a good inspiratory volume (at least 90% of the vital capacity) during the single breath maneuver required for the DL_{CO} measurement and a normal hemoglobin concentration (as did these PPH patients), a reduced DL_{CO} can be due only to a real reduction in pulmonary alveolar capillary bed or maldistribution of ventilation to the alveoli during the single breath maneuver, or both. The near equality of VA' and TLC (VA'/TLC = 96 ± 3%, Fig. 2, lower left) demonstrate that maldistribution of ventilation does not account for the low DL_{CO}.

In contrast to the PPH patients who, on average, demonstrated mild restriction and moderate loss of diffusing capacity (Fig. 1 and 2), the resting lung function measurements in the controls were rarely outside of the 95% confidence limits for normal subjects (Table 2 and Fig. 1).

Despite the frequency of dyspnea as a symptom and the reduced FVC, FEV₁, and MVV in the PPH patients, the ratio of peak exercise ventilation to MVV was significantly lower than that of the controls (Table 1), indicating that the decreased ventilatory capacity of the PPH group (Table 2) did not appear to limit their maximal exercise capacity.

Correlations of resting lung function to CPET, NYHA class, and resting cardiac catheterization measurements.

Because patients and controls varied in age, gender, and size, and because all correlations were higher using %pred than with absolute values, only %pred values are used to establish correlation (Table 3). The DL_{CO} was most highly correlated with peak O₂ uptake (peak O₂ uptake = 24 + 0.32 × DL_{CO}, r = 0.42, SD = 12, n = 77, p = 0.0001), anaerobic threshold (anaerobic threshold = 31 + 0.43 × DL_{CO}, r = 0.50, SD = 13, n = 76, p < 0.0001), and peak O₂ pulse (peak O₂ pulse = 32 + 0.41 × DL_{CO}, r = 0.41, SD = 16, n = 77, p = 0.0002), although DL_{CO} also correlated significantly with peak work rate and NYHA class. The relationships of %pred peak O₂ uptake, anaerobic threshold, and peak O₂ pulse to DL_{CO} are shown for the PPH patients as shown in Figure 3. Although other PFT parameters (FVC, FEV₁, MVV, and VA') correlated significantly with many CPET parameters and NYHA class, the highest r values and most significant p values were those for DL_{CO}. There were no significant correlations of any resting lung function parameter with resting mean pulmonary artery pressure, cardiac output, pulmonary vascular resistance, or other values obtained during right heart catheterization.

Multicollinearity regression analysis of resting lung function and CPET measurements of aerobic function.

Using all resting lung function factors for stepwise regression analysis, the only significant independent factor that was a determinant for peak O₂ uptake, anaerobic threshold, or peak O₂ pulse was DL_{CO} (Fig. 3). The equations were similar to the equations derived using simple regression correlation.

Physiologic severity. The PPH patients were divided into four categories of severity (Table 4) according to their %pred peak O₂ uptake: 1) mild, 65 to 79 %pred; 2) moderate, 50 to 64 %pred; 3) severe, 35 to 49 %pred; and 4) very severe, <35 %pred, as was done in a previous analysis of CPET in PPH patients (2). Clearly shown is the tendency to a progressive decrease in the resting lung function measures, especially DL_{CO}, as the severity of PPH increases, using either %pred peak O₂ uptake or NYHA class (p < 0.05 to p < 0.001).
PPH clinic. These resting lung function findings are moderate reductions in D\textsubscript{LCO} and mild, albeit statistically significant, reductions in FVC, FE\textsubscript{V}\textsubscript{1}, MVV, TLC, and VA’.

Conversely, airway obstruction and maldistribution of ventilation are uncommon.

Restriction, as evidenced by reductions in FE\textsubscript{V}\textsubscript{1}, FVC, VA’, TLC, and D\textsubscript{LCO} have been reported in other series (6,10,30) of patients with PPH, but the degree and proportion of patients with these abnormalities are generally larger in our study. Because reference values derived from normal populations have a large variance for FVC and TLC, the finding of a VA’ within normal limits in 58% of the PPH patients does not exclude a developing restrictive process in some patients, as sequential measurements were not made. However, any developing restrictive process, per se, is not a likely explanation for the exercise dyspnea of our PPH patients since, at peak exercise, PPH patients had both a lower ratio of ventilation relative to their resting MVV and a proportionally larger breathing reserve than did our control population. In addition, their symptoms were generally well out of proportion to their degree of ventilatory restriction.

The finding that the VA’ measured by a single breath averaged 96% of the TLC measured by plethysmography or nitrogen washout, with a standard deviation of only 3%, is strong evidence against maldistribution of ventilation in the PPH patients. If maldistribution of ventilation were part of PPH, the TLC would have been considerably higher than the VA’. In comparing resting lung function values in a normal population, ratio values have a much lower coefficient of variation than do absolute values (31). Therefore, the nearly universally normal FE\textsubscript{V}\textsubscript{1}/FVC ratio (Fig. 1) indicates that obstructive airways disease was uncommonly present in our patients with PPH. The fact that the FE\textsubscript{V}\textsubscript{1}/FVC was rarely increased and that the overall MVV-to-FEV\textsubscript{1} ratio was not appreciably or significantly increased over the normal value of 40 (Fig. 2) is evidence against lung fibrosis with increased elastic recoil, as is commonly found in patients with interstitial lung disease (19). These resting lung function findings fit with those from other reports in PPH patients (6–8,10), except that prior reports did not find significant correlations between resting lung function and disease severity.

**Probable causes of reduction in D\textsubscript{LCO}**

Importantly, the overall reduction in mean resting D\textsubscript{LCO} in most of our PPH patients (Figs. 1 and 2, Table 2) strongly suggests that, even at rest, pulmonary capillary blood volume was reduced. This reduction fits the pathological findings typical of PPH, described by Meyrick and Reid (32)—that is, muscularization of smaller, more peripheral pulmonary arteries, medial thickening of the muscular arteries, intimal thickening, and a reduction in peripheral vascular bed. The possible effect of smoking causing the low D\textsubscript{LCO} values in the eight men in this study was investigated because the prediction equations of Miller et al. (25) indicate a reduction in D\textsubscript{LCO} in men, but not women, smokers. For these eight men, the D\textsubscript{LCO}

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**Figure 3.** Correlations and regression equations for gas transfer index (D\textsubscript{LCO}) versus three cardiopulmonary exercise test parameters of aerobic function (upper = peak O\textsubscript{2} uptake; middle = anaerobic threshold; lower = peak O\textsubscript{2} pulse) in primary pulmonary hypertension (PPH) patients. Each symbol indicates an individual PPH patient. All values and equations are in units of % predicted (%pred). Dotted lines approximate the 95% confidence limits of controls.
were 77%, 75%, and 65% of predicted in the three never-smokers and 68%, 66%, 63%, 53%, and 49% in the ex-smokers. Using Miller’s predicting equations (25) for men smoking one and a half packs per day (though none of these five men had smoked this heavily), their % predicted DLCO all remained abnormal, increasing an average of 9%. Thus, smoking was unlikely to be more than a minor factor in the overall reduction in DLCO in this study. The reduction in DLCO cannot be attributed to maldistribution of ventilation, because the VA’ (measured concurrently with the DLCO during 10-s breathholding at full inspiration) was approximately 96% of the separately measured TLC. Hence, all the study findings support the concept that the reduced DLCO in PPH patients must be attributable to a reduction in perfused pulmonary capillary bed rather than maldistribution of ventilation or anemia. Furthermore, the lung function findings in this study do not fit the pattern found in patients with interstitial lung disease and secondary pulmonary hypertension, as in such patients the restriction tends to be more severe, with the FEV1/FVC and MVV/FEV1 ratios abnormally increased (10, 19).

Possible causes of restriction. What are the possible causes of lung restriction in PPH? The PPH patients were not more overweight than the controls or general population, and no evidence was observed for chest wall disease, lung fibrosis, pleural effusions, or left ventricular failure in these patients. Patients with severe left ventricular failure commonly have lung restriction (32–34), but following heart transplant, the TLC may increase by 400 to 1,000 ml, presumably due to the fact that the transplanted heart is smaller (34). We conjecture that cardiomegaly with right ventricular hypertrophy and dilation may account for some of the reduction in lung volume in the PPH patients. Additionally, because lung expansion depends on the distensibility (compliance) of all lung tissues including the pulmonary vasculature, loss of the normal distensibility of the smaller arteries radiating out into the lung periphery may be an important factor causing lung restriction in these patients.

Clinical implications. The positive correlations of the DLCO, FVC, FEV1, and VA’ values with multiple CPET parameters and NYHA class support the hypothesis that a close relationship exists between the processes that causes each to become abnormal (Table 4, Fig. 3). However, the greater proportional reduction in DLCO than in FVC (Fig. 2) and TLC in our PPH patients supports the findings that the primary pathological process involves the blood vessels of the lungs. These simple, safe, and patient-friendly resting lung function measurements can be clinically useful in suspecting (but not excluding) the diagnosis of PPH in patients who have unexplained dyspnea on exertion. Whether or not they are useful in following the course of the disease remains to be seen.

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REFERENCES


Table 4. Resting Lung Function in PPH Patients Grouped by Severity of Reduction in Peak VO2

<table>
<thead>
<tr>
<th>Peak O2 Uptake Range (%pred)</th>
<th>Mild PPH (n = 5)</th>
<th>Moderate PPH (n = 24)</th>
<th>Severe PPH (n = 33)</th>
<th>Very Severe PPH (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (%pred)</td>
<td>92 ± 12</td>
<td>88 ± 13</td>
<td>75 ± 14†</td>
<td>74 ± 15†</td>
</tr>
<tr>
<td>FEV1 (%pred)</td>
<td>94 ± 19</td>
<td>86 ± 16</td>
<td>76 ± 15§</td>
<td>73 ± 16</td>
</tr>
<tr>
<td>FEV1/FVC (%pred)</td>
<td>100 ± 10</td>
<td>97 ± 8</td>
<td>100 ± 7</td>
<td>96 ± 10</td>
</tr>
<tr>
<td>VA’ (%pred)</td>
<td>89 ± 13</td>
<td>90 ± 13</td>
<td>79 ± 12‖</td>
<td>79 ± 15</td>
</tr>
<tr>
<td>DLCO (%pred)</td>
<td>87 ± 10</td>
<td>74 ± 18*</td>
<td>66 ± 14†</td>
<td>56 ± 15§†‡</td>
</tr>
<tr>
<td>DLCO/VA’ (%pred)</td>
<td>100 ± 22</td>
<td>80 ± 18</td>
<td>84 ± 14</td>
<td>72 ± 20</td>
</tr>
<tr>
<td>MVV (%pred)</td>
<td>101 ± 17</td>
<td>92 ± 10</td>
<td>87 ± 18§</td>
<td>72 ± 21§‡</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1.9 ± 0.4</td>
<td>2.4 ± 0.6</td>
<td>2.9 ± 0.5</td>
<td>3.2 ± 0.5</td>
</tr>
</tbody>
</table>

* p < 0.05, † p < 0.01, ‡ p < 0.001 vs. mild PPH. § p < 0.05 vs. moderate PPH. † p < 0.05 vs. severe PPH using repeated analysis of variance.

 Abbreviations as in Tables 1 and 2.


