Exercise Pathophysiology in Patients With Primary Pulmonary Hypertension

Xing-Guo Sun, MD; James E. Hansen, MD; Ronald J. Oudiz, MD; Karlman Wasserman, MD, PhD

Background—Patients with primary pulmonary hypertension (PPH) have a pulmonary vasculopathy that leads to exercise intolerance due to dyspnea and fatigue. To better understand the basis of the exercise limitation in patients with PPH, cardiopulmonary exercise testing (CPET) with gas exchange measurements, New York Heart Association (NYHA) symptom class, and resting pulmonary hemodynamics were studied.

Methods and Results—We retrospectively evaluated 53 PPH patients who had right heart catheterization and cycle ergometer CPET studies to maximum tolerance as part of their clinical workups. No adverse events occurred during CPET. Reductions in peak O₂ uptake (VO₂), anaerobic threshold, peak O₂ pulse, rate of increase in VO₂, and ventilatory efficiency were consistently found. NYHA class correlated well with the above parameters of aerobic function and ventilatory efficiency but less well with resting pulmonary hemodynamics.

Conclusions—Patients with PPH can safely undergo noninvasive cycle ergometer CPET to their maximal tolerance. The CPET abnormalities were consistent and characteristic and correlated well with NYHA class. (Circulation. 2001;104:429-435.)

Key Words: oxygen ■ hypertension, pulmonary ■ ventilation ■ exercise ■ hemodynamics

Primary pulmonary hypertension (PPH) is a progressive and usually fatal disease of unknown etiology that leads to increased pulmonary vascular resistance and loss of the pulmonary vasodilator response to exercise. Because of inefficient lung gas exchange and the inability of the right ventricle to adequately increase pulmonary blood flow (cardiac output [CO]) for the O₂ exercise demand, dyspnea and/or fatigue ensues. The increased right ventricular work ultimately causes pulmonary hypertension at rest, at which time cardiac catheterization and/or echocardiography is used to establish the diagnosis and to grade the severity.

Cardiopulmonary exercise testing (CPET) with gas exchange has the potential of noninvasively grading the severity of exercise limitation, quantifying the hypoperfusion of the lung and systemic circulation, and assessing responses to therapy before overt right ventricular failure and pulmonary hypertension are evident at rest.

The objective of the present study was to quantify the exercise abnormalities in aerobic function and ventilatory efficiency in PPH patients and to relate them to traditional measurements, such as resting hemodynamics and New York Heart Association (NYHA) symptom class.

Methods

Patients and Normal Control Subjects

The medical records of 53 patients with PPH who systematically underwent echocardiography, right heart catheterization, and CPET for clinical evaluation were retrospectively studied. The diagnosis of PPH was based on clinical and laboratory data, which included right heart catheterization to satisfy diagnostic criteria described by a National Institutes of Health registry of PPH and by the World Health Organization. Patients with other disorders were excluded. For comparison purposes, the CPET findings of 20 normal subjects of similar age, sex, and body size were also analyzed. The institution’s Human Subjects Committee approved the project.

Measurements

Right heart catheterization with standard hemodynamic measurements was performed within 1 month of each patient’s CPET study. Just before their CPET studies, patients had standard pulmonary function tests.

Each patient performed a physician-supervised, standard, progressively increasing work rate (WR) CPET to maximum tolerance on an electromagnetically braked cycle ergometer. Gas exchange measurements (Cardiopulmonary Metabolic Cart, Medical Graphics) were made during 3 minutes of rest, 3 minutes of unloaded leg cycling at 60 rpm followed by a progressively increasing WR exercise of 5 to 15 (10 ± 5) W · min⁻¹ to maximum tolerance, and 2 minutes of recovery. Pulse oximetry (SpO₂), heart rate (HR), 12-lead ECG, and cuff blood pressure were monitored and recorded.

Minute ventilation (Ve, BTPS), O₂ uptake (VO₂, STPD), CO₂ output (VCO₂, STPD), and other exercise variables were computer-calculated breath by breath, interpolated second by second, and averaged over 10-second intervals. The anaerobic threshold (AT), ratio of O₂ uptake to WR increase (∆VO₂/∆WR), and oxygen pulse (O₂ pulse) were determined as previously described. Ventilatory efficiency during exercise was expressed as the ratio of ventilation to CO₂ output at AT (Ve/VCO₂@AT) and the slope of Ve versus VCO₂ over the linear component of the plot of Ve versus VCO₂. The rate of change has the potential of noninvasively grading the severity of exercise limitation, quantifying the hypoperfusion of the lung and systemic circulation, and assessing responses to therapy before overt right ventricular failure and pulmonary hypertension are evident at rest.
of VO2 increase during unloaded cycling was expressed as the mean response time (MRT) for a monoexponential curve fit to the second-by-second VO2 measurements during the 3 minutes of unloaded cycling.10 If the first breath VO2 equaled the 3-minute VO2, the MRT was considered equal to the duration of the first breath.

### Statistical Analysis

Standard equations were used to predict actual and percent predicted (%Pred) values for maximal voluntary ventilation and CPET parameters.3,11 The predicted value for VO2/VO2 AT was calculated as 24.71 – 4.04 × sex (female = 0, male = 1) + 0.115 × age (data from 41 normal subjects). Resting CPET values were compared with their predicted values by using paired 2-tailed t tests. A significant change was defined as an α level of P < 0.05. Correlation and regression analyses were performed by ANOVA. Simple individual linear regression analyses were performed by the Pearson correlation coefficient (r) between individual variables and each of the other variables. Multicolinearity analyses were performed to predict NYHA class by using stepwise regression with an α level of P = 0.05 for tolerance level.12,13

### Results

#### Pulmonary Hemodynamics and Cardiopulmonary Exercise Analyses

Most of the 53 PPH patients were middle-aged women (Table 1) of NYHA class 3. Their symptoms were dyspnea (87%), fatigue (42%), lower extremity edema (21%), syncope (13%), light-headedness (11%), chest pain or tightness (8%), and palpitations (6%).

At cardiac catheterization, all patients had resting pulmonary hypertension (mean pulmonary artery pressure 64 ± 18 mm Hg), increased mean right atrial pressure and pulmonary vascular resistance, reduced CO and cardiac index, and normal left ventricular ejection fraction (Table 1). On echocardiography, all patients had an enlarged right ventricle and/or right atrium, 89% had tricuspid valve regurgitation, and approximately one third had a patent foramen ovale.

All patients completed CPET without incident. Two patients completed only 2 to 3 minutes of unloaded pedaling; the duration of exercise in all others averaged 8 ± 2 (range 3.5 to 14) minutes. All subjects exercised above their ATs; this finding and their high end-exercise respiratory exchange ratio (1.23 ± 0.11)
indicate that they had developed a significant metabolic acidosis and had exercised to a heavy, if not maximal, work intensity. The dominant symptoms described for stopping cycle exercise were leg fatigue (49%), dyspnea (43%), palpitations (4%), and light-headedness (2%).

**Pattern of Exercise Gas Exchange**

The parameters of exercise gas exchange were systematically abnormal in the PPH patients (Table 1). Peak VO₂, peak WR, peak O₂ pulse or VO₂/HR, the ratio of VO₂ to increase in WR increase (ΔVO₂/ΔWR), AT, and MRT were all moderately to severely reduced. There was a marked increase in the slope of VE versus VCO₂ and a moderate decrease in peak HR in all patients. Compared with the control group, the differences between actual and predicted values for all of these variables were significant (P<0.0001) (Table 1). The typical abnormal pattern of CPET findings for 2 PPH patients, 1 with moderate and 1 with severe exercise limitation, and a normal control subject are shown in Figure 1. The exercise pathophysiology is reflected in the reduced peak VO₂, AT, ΔVO₂/ΔWR, and peak O₂ pulse and high VE/ VCO₂.

**Correlations**

Table 2 summarizes multiple correlations between CPET and other variables. NYHA class was significantly correlated with exercise parameters of aerobic function and ventilatory efficiency and better with %Pred values than either per kilogram or absolute values. NYHA class was significantly, but weakly, correlated with resting CO and pulmonary vascular resistance but not with pulmonary artery pressure. Peak WR, AT, and O₂ pulse (VO₂/HR), slope of VE versus VCO₂, and VE/VCO₂@AT were also significantly correlated with NYHA class (P<0.01 to P<0.0001 for all) (Table 2).

Peak VO₂ and VE/VCO₂@AT correlated well with NYHA class (P<0.0001) (Figure 2). Peak VO₂ and VO₂/HR also correlated well with AT (P<0.0001, Figure 2), showing that the latter can be used as a submaximal parameter for grading aerobic function. The good correlation between peak VO₂/HR and AT suggests that the latter is highly influenced by stroke volume (SV).

The MRT of VO₂ for PPH patients during unloaded cycling exercise averaged 48±17 seconds versus 14±9 seconds for the control subjects (P<0.0001) (Figure 3). MRT was positively correlated with NYHA class and negatively correlated with peak VO₂, AT, and peak O₂ pulse (all P<0.001).

By use of stepwise regression analysis of multiple factors, NYHA class could be estimated from peak VO₂ (%Pred) and the slope of VE versus VCO₂ (%Pred) (R=0.64, P<0.0001).

**Physiological Severity of PPH**

The physiological responses to exercise were abnormal in all patients. Table 3 categorizes the PPH patients into 4 groups on the basis of the severity of reduction in their %Pred peak VO₂ rather than the less discriminating gradations in NYHA class or pulmonary hemodynamic data. By use of this method of grading disease severity, there is virtually no overlap in any of the key parameters of aerobic function (peak VO₂, AT, ΔVO₂/ΔWR, peak O₂ pulse, and MRT of VO₂) or ventilatory efficiency (VE/VCO₂@AT and slope of VE versus VCO₂) when the control subjects and the PPH patients of mildest severity are compared. Peak VE became a lesser fraction of the actual maximal voluntary ventilation as disease severity increased.

---

**Figure 1.** CPET measurements of 2 PPH patients and normal control subject (open circles; female, aged 28 years, height 162 cm, and weight 55 kg). Patients with moderate PPH (×; female, aged 35 years, height 161 cm, and weight 84 kg) and severe PPH (solid squares; female, aged 27 years, height 160 cm, and weight 58 kg) are illustrated. All have similar predicted values. Protocol consisted of 3 minutes of rest, 3 minutes of unloaded cycling at 60 rpm (Unl.), and ramp WR of 15, 10, and 5 W·min⁻¹, respectively, to maximal tolerance. a, VO₂ vs VO₂ with arrows at the respective AT of each subject. b, Change in VO₂ vs change in WR, with dotted line indicating normal slope of 10 mL·min⁻¹·W⁻¹. c, HR vs VO₂, with diagonal dotted lines indicating O₂ pulse in mL·beat⁻¹. d, Ventilatory equivalent for CO₂ (VE/ VCO₂) vs time, with vertical dashed lines separating rest, unloaded, and ramp exercise. Characteristic abnormalities of PPH patients depicted are low values for peak VO₂, AT, peak WR, ΔVO₂/ΔWR, peak HR, and peak O₂ pulse. With PPH, resting VE/VCO₂ values are elevated and tend to remain relatively constant or increase during exercise, contrasting with lower resting and decreasing VE/VCO₂ during exercise in normal control subject.
Discussion

Basis for CPET Abnormalities in PPH

The breathlessness of PPH patients during exercise can be related to the relative hypoperfusion of their well-ventilated alveoli (increased “dead space”). In normal subjects, the ventilatory response (Ve) to exercise is tightly related to CO₂ output (VCO₂). In PPH, the ventilation of underperfused alveoli causes an increase in dead space ventilation, manifested by a hyperbolic increase in Ve relative to the VCO₂.

Table 2. r Matrix of Selected Simple Regressions for Multiple Factors in Patients With PPH

<table>
<thead>
<tr>
<th>Variable</th>
<th>Peak VO₂</th>
<th>AT</th>
<th>Peak VO₂</th>
<th>AT/AVO₂</th>
<th>Cardiac Index</th>
<th>PVR, U Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA</td>
<td>-0.54*</td>
<td>-0.49*</td>
<td>-0.44†</td>
<td>-0.45*</td>
<td>-0.44†</td>
<td>-0.39‡</td>
</tr>
<tr>
<td></td>
<td>-0.35‡</td>
<td>0.44‡</td>
<td>0.37‡</td>
<td>0.26§</td>
<td>0.23</td>
<td></td>
</tr>
</tbody>
</table>

Selected exercise parameters

| Peak VO₂ | -0.54* |
| AT       | -0.45*  | 0.92* |
| Peak WR  | -0.42†  | 0.78*  | 0.77* |
| Peak O₂ pulse | -0.43‡ | 0.86*  | 0.82*  | 0.56* |
| ΔVO₂/ΔWR | -0.24  | 0.56*  | 0.42†  | 0.46† |
| VCO₂@AT  | 0.49*   | -0.49* | -0.44†  | -0.36‡ |
| Ve-VCO₂ slope | 0.39‡  | -0.30§ | -0.26§  | -0.23§ |
| AT/peak VO₂ | 0.35†  | -0.52* | -0.15  | -0.37‡ |
| Peak VE   | -0.31§  | 0.38§  | 0.33§   | 0.47§ |
| Peak HR   | -0.05   | 0.41†  | 0.36†   | 0.38‡ |
| MRT       | 0.41‡   | -0.62* | -0.61*  | -0.50* |

Selected resting hemodynamics

| CO       | -0.31§  | 0.32§  | 0.33§   | 0.27§  |
| PVR      | 0.27§   | -0.25§ | -0.29§  | -0.19  |

U index indicates Wood unit index (mm Hg · L⁻¹ · min⁻¹ · m²).

*P<0.0001, †P<0.001, ‡P<0.01, and §P<0.05.
increase during exercise. In addition, the lactic acidosis at low WRs and hypoxemia can act as additional stimuli to breathing\(^7\) and contribute to the sensation of dyspnea in PPH patients, even though their peak \(\dot{V}O_2\) was well below their maximal voluntary ventilation. Concurrently, the inability to adequately increase pulmonary (and therefore systemic) blood flow during exercise results in the failure to meet the exercise \(O_2\) requirement.

A brief description of 5 parameters of aerobic function (peak \(\dot{V}O_2\), peak \(O_2\) pulse, AT, \(\Delta\dot{V}O_2/\DeltaWR\), and MRT) that reflect the inability of pulmonary blood flow to increase adequately in PPH patients follows.

**Peak \(\dot{V}O_2\)**

Peak \(\dot{V}O_2\) assesses the subject’s maximal work ability and the maximal ability of the circulatory system to increase \(CO\). In PPH, this relates to the pulmonary vasculopathy, which limits blood flow through the lung (and thus through the body).

**Peak \(O_2\) Pulse**

From the Fick principle, \(\dot{V}O_2\) equals \(CO \times C(a\_\bar{v})O_2\). \(C(a\_\bar{v})O_2\) denotes content difference between arterial and mixed venous blood. Because \(CO\) is the product of HR and SV, dividing both sides of the Fick equation by HR discloses that the \(O_2\) pulse (\(\dot{V}O_2/HR\)) at any given time equals \(SV \times C(a\_\bar{v})O_2\). As noted previously,\(^{16-18}\) a low peak \(O_2\) pulse usually indicates a low peak SV.

**Anaerobic Threshold**

The AT, which describes the highest \(\dot{V}O_2\) that the patient can sustain without developing a lactic acidosis, appears to be an independent marker of PPH severity.

\(\Delta\dot{V}O_2/\DeltaWR\)

\(\Delta\dot{V}O_2/\DeltaWR\) also characterizes PPH severity\(^7\) (Table 3). Values progressively lower than 10 mL/min per watt disclose a higher than normal dependence on anaerobic metabolism and,

![Figure 3. \(\dot{V}O_2\) kinetics in response to 3 minutes of unloaded cycling exercise in PPH patients and normal control subjects.](image-url)

TABLE 3. Resting and Exercise Values in Normal Subjects and PPH Patients Categorized According to Severity of Reduction in CPET Aerobic Capacity

<table>
<thead>
<tr>
<th></th>
<th>Normal* (n=20)</th>
<th>Mild PPH (n=3)</th>
<th>Moderate PPH (n=14)</th>
<th>Severe PPH (n=22)</th>
<th>Very Severe PPH (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak (\dot{V}O_2) range, % pred</td>
<td>82–132</td>
<td>65–79</td>
<td>50–64</td>
<td>35–49</td>
<td>&lt;35</td>
</tr>
<tr>
<td>Peak (\dot{V}O_2), % pred</td>
<td>101±19</td>
<td>70±4</td>
<td>58±4</td>
<td>42±5</td>
<td>27±4</td>
</tr>
<tr>
<td>Peak (\dot{V}O_2), ml/(\text{min} \cdot \text{kg}^{-1})</td>
<td>29.5±6.6</td>
<td>14.5±3.3</td>
<td>12.5±2.2</td>
<td>11.2±2.6</td>
<td>8.1±1.7</td>
</tr>
<tr>
<td>AT, % pred</td>
<td>104±16</td>
<td>85±7</td>
<td>75±10</td>
<td>57±9</td>
<td>41±7</td>
</tr>
<tr>
<td>AT, ml/(\text{min} \cdot \text{kg}^{-1})</td>
<td>16.3±3.9</td>
<td>10.4±2.3</td>
<td>9.7±1.3</td>
<td>8.7±2.2</td>
<td>6.8±1.3</td>
</tr>
<tr>
<td>Peak (O_2) pulse, % pred</td>
<td>108±25</td>
<td>86±11</td>
<td>73±8</td>
<td>56±11</td>
<td>39±5</td>
</tr>
<tr>
<td>Peak HR, % pred</td>
<td>96±13</td>
<td>83±12</td>
<td>80±8</td>
<td>77±12</td>
<td>70±13</td>
</tr>
<tr>
<td>(\Delta\dot{V}O_2/\DeltaWR), ml/(\text{min} \cdot \text{W}^{-1})</td>
<td>9.6±0.9</td>
<td>8.3±0.5</td>
<td>7.0±1.5</td>
<td>6.0±1.0</td>
<td>5.6±1.3</td>
</tr>
<tr>
<td>(\dot{V}O_2/\dot{V}O_2@AT), % pred</td>
<td>99±12</td>
<td>142±22</td>
<td>149±21</td>
<td>161±25</td>
<td>219±76</td>
</tr>
<tr>
<td>(\dot{V}O_2/\dot{V}O_2@AT), absolute</td>
<td>29±4</td>
<td>43±6</td>
<td>45±7</td>
<td>46±8</td>
<td>62±20</td>
</tr>
<tr>
<td>(\dot{V}e)-vs-(\dot{V}CO_2), slope, % pred</td>
<td>88±11</td>
<td>164±49</td>
<td>148±27</td>
<td>141±32</td>
<td>215±123</td>
</tr>
<tr>
<td>(\dot{V}e)-vs-(\dot{V}CO_2), slope, absolute</td>
<td>25±3</td>
<td>49±14</td>
<td>45±9</td>
<td>40±10</td>
<td>60±32</td>
</tr>
<tr>
<td>Peak (\dot{V}e), as % MVV</td>
<td>70±15</td>
<td>63±19</td>
<td>54±9</td>
<td>47±11</td>
<td>43±16</td>
</tr>
<tr>
<td>MRT, s</td>
<td>12±10</td>
<td>34±9</td>
<td>37±14</td>
<td>47±13</td>
<td>64±15</td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>...</td>
<td>48±17</td>
<td>63±14</td>
<td>70±18</td>
<td>57±17</td>
</tr>
<tr>
<td>CO, L/(\text{min}^{-1})</td>
<td>...</td>
<td>5.1±1.1</td>
<td>4.4±1.4</td>
<td>3.5±1.0</td>
<td>3.8±1.2</td>
</tr>
<tr>
<td>PVR, mm Hg · (\text{L}^{-1} \cdot \text{min}^{-1})</td>
<td>...</td>
<td>8±4</td>
<td>15±8</td>
<td>18±5</td>
<td>14±6</td>
</tr>
<tr>
<td>NYHA class</td>
<td>...</td>
<td>2.0±0.4</td>
<td>2.5±0.5</td>
<td>2.8±0.6</td>
<td>3.3±0.4</td>
</tr>
</tbody>
</table>

*Each CPET parameter of all PPH patients is significantly different from that of normal control subjects (\(P<0.001\)).
circulation stimulates ventilation profoundly because it has not only a low $P_{O_2}$ but also a high $P_{CO_2}$ and high $H^+$ concentration.

**Fatigue**

In PPH, aerobic regeneration of ATP is impaired, with more work being done anaerobically at relatively low WRs, as reflected by the reduced peak $V\dot{O}_2$, AT, and $\Delta V\dot{O}_2/\Delta WR$ in our patients (Figure 4, right branch). Because the mechanism of anaerobic ATP regeneration stimulates anaerobic glycolysis, a prominent lactic acidosis results. Probably the most important mechanism leading to muscle fatigue in PPH is the reduction in the rate of aerobic regeneration of ATP.

**Light-Headedness**

The light-headedness with exercise that some PPH patients experience is probably related to their inability to adequately maintain CO and systemic blood pressure with exercise and/or sudden arterial hypoxemia via a patent foramen ovale.

**Resting Pulmonary Hemodynamics in PPH Patients**

There were significant but modest correlations between resting CO and pulmonary vascular resistance with NYHA class and several of the CPET measures of aerobic function (Table 2). Cardiac catheterization is invasive and carries a significant risk of morbidity and mortality in PPH, although it is essential in making the diagnosis. In contrast, CPET measures of aerobic function and gas exchange efficiency might be better for determining disease severity and tracking the clinical course, especially in view of the better correlations of these measures with NYHA symptom class.

**Grading of Physiological Impairment in PPH**

All of the CPET parameters of aerobic function and gas exchange efficiency in our patients correlated well with their NYHA symptom class. Because NYHA class correlated best with %Pred peak $V\dot{O}_2$, we chose the latter parameter to physiologically grade the impairment in PPH (Table 3), as did Weber et al\textsuperscript{18} for chronic heart failure. The absence of overlap in the predicted peak $V\dot{O}_2$ of our PPH patients (18 to 75 %Pred) and our 20 control subjects (82 to 132 %Pred) (Table 3) indicates the discriminating power of CPET even in "mild" PPH. Two thirds of our PPH patients had peak $V\dot{O}_2$ levels of <50% predicted value, a level associated with a 60% 2-year mortality in patients with chronic left heart failure.\textsuperscript{51}

Peak $O_2$ pulse and AT decreased in parallel fashion within the grading established by the peak $V\dot{O}_2$ in our patients (Table 3). Because $O_2$ pulse equals $SV\times(C(a-V)O_2$, the progressively decreasing peak $O_2$ pulse likely reflects a progressive reduction in peak SV paralleling disease severity. The AT becomes a higher fraction of peak $V\dot{O}_2$ as disease severity (peak $V\dot{O}_2$) worsens, suggesting a decrease in cardiovascular reserve as PPH worsens (Table 3).

**Conclusions**

The pathophysiologic CPET findings that we have described in PPH appear to be consistent and characteristic. CPET is of great potential value for evaluating patients with dyspnea and fatigue safely, reproducibly, and noninvasively.\textsuperscript{8,22,23} It may become as useful in assessing the pro-
nosis of PPH patients as it has been in patients with chronic heart failure, or it may be used for the purpose of prioritizing patients for lung transplantation and for evaluating drug therapy. The need to categorize disease severity accurately and noninvasively in PPH patients makes it desirable that physicians responsible for diagnosis and management of these patients become familiar with CPET and the information that can be derived from it.

References
Exercise Pathophysiology in Patients With Primary Pulmonary Hypertension
Xing-Guo Sun, James E. Hansen, Ronald J. Oudiz and Karlman Wasserman

Circulation. 2001;104:429-435
doi: 10.1161/hc2901.093198

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/104/4/429