Comparison of Progressive Exercise Performance of Normal Subjects and Patients with Primary Pulmonary Hypertension*


The extent of exercise limitation and the mechanisms for that limitation in 11 patients with primary pulmonary hypertension (PPH) were studied by progressive, upright cycle ergometry. All patients had a mean pulmonary artery pressure of 30 mm Hg or higher (mean, 56 ± 15), normal pulmonary function testing, normal pulmonary capillary wedge pressure, and pulmonary angiography consistent with the diagnosis. Rest and exercise data obtained from the patients with PPH were compared with data obtained from 11 matched, sedentary control subjects. Mean maximal oxygen consumption (Vo2) was 13 ± 4 ml/kg/min in the PPH group compared with 28 ± 7 ml/kg/min in the controls. At maximal Vo2, the minute ventilation (Ve) was similar; however, the Ve at any level of carbon dioxide production (Vco2) during rest and exercise was significantly higher in the PPH group. Maximal heart rate and oxygen pulse (Vo2/heart rate) was significantly higher in the control group (148 ± 18 vs 150 ± 24, and 6.3 ± 2.2 vs 9.9 ± 3.9, respectively). Anaerobic threshold occurred earlier during progressive exercise in the PPH group and correlated positively with the maximal oxygen pulse achieved in patients with PPH. In conclusion, patients with PPH have severe exertional limitation due to cardiovascular factors with an inability to maintain appropriate oxygen delivery to the body during exercise. No respiratory impairment was recognized; however, an exaggerated ventilatory response to exercise at any level of Vco2 was found.

Patients with primary pulmonary hypertension have exercise limitation with marked fatigue and dyspnea on even mild exertion.1 Resting hyperventilation as suggested by respiratory alkalosis3 and an excessive ventilatory response to any given exercise load6 has been observed, although serious disturbances in resting and exercise gas exchange have not been found.4,3 In addition, the elevated pulmonary vascular resistance with subsequent right-sided heart dysfunction is likely to further compromise the patient's aerobic capacity and reduce exercise capability.3

To determine the degree of exercise limitation and the physiologic factors responsible for this limitation, the following comparison study was performed.

**MATERIALS AND METHODS**

Primary pulmonary hypertension (PPH) was diagnosed in 11 patients. Each patient had a mean pulmonary artery pressure of 30 mm Hg or higher. The presence of valvular heart disease, intracardiac shunt, and left ventricular failure was excluded during cardiac catheterization. Parenchymal lung disease was excluded by chest x-ray film findings and standard pulmonary function testing. Connective tissue disorders and systemic vasculitides were excluded by the lack of a characteristic clinical history, physical findings, and laboratory studies. Each patient with PPH was compared with a sedentary control subject matched for age, sex, and weight. The age had to match within 18 months and the weight within 3 kg. None of the patients or subjects had a history of drug abuse or smoking.

Measurements of lung volumes and flow rates were made using a dry rolling seal spirometer (Morgan Instruments), and the functional residual capacity was measured in a body plethysmograph (Cardiopulmonary Instrumentation, model 2100). The diffusing capacity for carbon monoxide (Dco) was determined by a modification of the single-breath technique (Morgan Instruments). Normal values for forced vital capacity (FVC) and the one-second forced expired volume are from Kory et al,7 for total lung capacity and residual volume from Goldman and Becklake,8 and for the Dsb are from McGrath and Thomson.9

Pulmonary angiography was performed in each PPH patient. Right and left pulmonary artery contrast injections were followed by more selective magnified views during subsequent injections to determine the anatomy of both the large and small pulmonary arteries. The absence of large vessel obstruction, stricture, and webbing, and the presence of uniform vascular occlusion of vessels less than 1 mm were taken to indicate a diagnosis of PPH.1

Exercise studies for patients and controls were conducted in an air-conditioned laboratory at least two hours after a light meal. Each subject and patient was familiarized with the exercise apparatus prior to testing. A cycle ergometer (Rodby Elektronik AB) was used, and a progressive, one-minute incremental workload test to symptom-limited maximum was performed. Each individual was instructed to exercise as long as possible, until a specific symptom...
limited further performance. With a technician standing behind the patient or subject to ensure maximal patient safety, work was begun and increased in 20-W increments following a one-minute period of unloaded cycling.

The ECG, heart rate, and blood pressure were monitored at rest and throughout exercise. Room air was breathed through a mouthpiece and a low-resistance valve (Hans-Rudolph) connected to a volume turbine (Morgan Instruments), which measured minute ventilation (Ve). Expired air from the turbine was mixed and sampled continuously by rapidly responding oxygen and carbon dioxide analyzers (Morgan Instruments; S-150 and 901-MK2, respectively) coupled in series. All gas and flow measurements were corrected for ambient temperature, barometric pressure, and water vapor. From the expired gas Po2, PCO2, and Ve, oxygen consumption (VO2), and CO2 production (VCO2) were derived. Oxygen pulse (O2P) was calculated by dividing the VO2 by heart rate (HR) and is representative of changes in stroke volume as expressed by the following formula:

\[ \text{VO2/HR} = \left( \text{a-vO2} \right) \times \text{SV} \]

where a-vO2 is the arterial-venous oxygen content difference and SV is the stroke volume. As the limits of a-vO2 difference are small, the O2P mainly relates to SV changes.

In the PPH group, an arterial catheter was placed in the radial artery prior to exercise for intermittent blood sampling. Arterial blood gases were measured using an Instrumentation Laboratories 1303 automated blood gas machine. The O2 saturation was measured with an Instrumentation Laboratories 283 Co-oximeter. The alveolar-arterial difference for oxygen, P(A-a)O2, was calculated as:

\[ P(A-a)O2 = (P(a)O2 - Pco2/R) - Pao2 \]

where P(a)O2 is the inspiratory PO2, PaCO2 is the arterial PCO2, R is the respiratory exchange ratio, and PaO2 is the arterial PO2. The dead space ventilation to tidal volume ratio (Vd/Vt) was calculated as:

\[ \text{Vd/Vt} = \text{PaCO2} / \text{PeCO2/PaCO2} \]

Where PeCO2 is the mixed expired PCO2.

Normal subjects did not have an arterial line placed; therefore, P(A-a)O2 and Vd/Vt calculations were not done. The anaerobic threshold (AT) was chosen as the VO2 at which the Ve/VO2 increased while the Ve/VO2 decreased or remained constant.

**Predicted Exercise Values**

Predicted maximal VO2 values (VO2 max) were determined for each patient and normal subject as follows:

\[ \text{VO2 max} \text{ (males in ml/kg/min) } = W \times (60 - 0.55A) \]

\[ \text{VO2 max} \text{ (females in ml/kg/min) } = W \times (45 - 0.37A) \]

where A = age in years and W = weight in kg. Maximal heart rate (HRmax) was predicted as: HRmax in beats/min = 210 - 0.66A and maximal Ve as: Ve in L/min = 35 × FEV1.

**Statistics**

Two-tailed paired Student's t-tests were used when appropriate to compare differences in maximal exercise parameters between groups, and linear regression analysis was used to correlate parameters when necessary. We accepted p < 0.05 to indicate a significant difference.

**Results**

Demographic, resting pulmonary function, and he-

<table>
<thead>
<tr>
<th>Table 1—Demographic, Resting Pulmonary Function, and Resting Hemodynamic Data in Patients With Primary Pulmonary Hypertension*</th>
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<tbody>
<tr>
<td><strong>Patient No.</strong></td>
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<td>11</td>
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<tr>
<td><strong>Mean</strong></td>
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* Abbreviations: VC, vital capacity; TLC, total lung capacity; FEV1, forced expiratory volume in one second; Db, diffusion capacity of carbon monoxide; PAP, mean pulmonary artery pressure; PCWP, mean pulmonary capillary wedge pressure; CO2, cardiac output; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance. Numbers in parentheses are percentage values representing percent of predicted normal for each value; numbers in brackets are cardiac index values in L/min/m2.
Table 2—Noninvasive Cardiopulmonary Data At Rest and Symptom-Limited Maximal Exercise in Patients with Primary Pulmonary Hypertension*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>$\dot{V}O_2$, L/min</th>
<th>Watts</th>
<th>HR, beats/min</th>
<th>$\dot{V}E$ L/min</th>
<th>$Q_P$, ml/beat</th>
<th>BP, mm Hg</th>
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<tr>
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<td>Rest</td>
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<td>Exercise</td>
<td>Rest</td>
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<tr>
<td>1</td>
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<td>92</td>
<td>158 (86)</td>
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<td>4</td>
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<td>123 (73)</td>
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<td>92</td>
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<td>134 (69)</td>
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<td>6</td>
<td>.26</td>
<td>.56 (35)</td>
<td>40</td>
<td>98</td>
<td>98</td>
<td>145 (82)</td>
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<td>1.47 (78)</td>
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<td>90</td>
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<td>140 (82)</td>
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<td>.38</td>
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<td>60</td>
<td>86</td>
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<td>.25</td>
<td>.56 (28)</td>
<td>60</td>
<td>84</td>
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<td>164 (85)</td>
</tr>
<tr>
<td>Mean</td>
<td>.29</td>
<td>.91 (40)</td>
<td>60</td>
<td>86</td>
<td>86</td>
<td>148 (81)</td>
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<tr>
<td>S/D</td>
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<td>.33 (17)</td>
<td>6</td>
<td>10</td>
<td>10</td>
<td>18 (8)</td>
</tr>
</tbody>
</table>

*Abbreviations: $\dot{V}O_2$, oxygen consumption; HR, heart rate; $\dot{V}E$, minute ventilation; $Q_P$, oxygen pulse; AT, anaerobic threshold; BP, systemic arterial blood pressure. Numbers in parentheses are percentage values representing percent of predicted normal maximum.

modynamic data of the primary pulmonary hypertensive patients are in Table 1. The mean age of the group was 42.2 years (range, 22 to 65 years) and there were eight females and three males. Normal pulmonary function was found in four PPH patients (patients 3, 7, 10, and 11). A total lung capacity less than 85 percent of predicted normal was found in four patients (patients 1, 5, 8, and 9). Mild obstructive disease (%FEV <80 >65) was present in one patient (patient 2). The diffusion capacity for carbon monoxide (Dsb) was reduced below 75 percent of predicted normal in five of ten patients tested (patients 4, 5, 6, 8, and 9). Mean pulmonary artery pressure and total pulmonary vascular resistance ranged from 30 to 75 mm Hg (average, 56±15 mm Hg) and from 4.3 to 34.5 units, respectively.

Rest and symptom-limited maximal cycle exercise data for the PPH patients are shown in Table 2. The resting $\dot{V}O_2$, HR, $Q_P$, and systemic arterial pressure of the PPH patients did not differ significantly from those of normal subjects; however, there was a difference in minute ventilation. The mean resting $\dot{V}E$ for the PPH patients was 11.9 L/min compared with 8.1 L/min (p<0.001) in the control group.

A comparison of maximal exercise performance between patients with PPH and control subjects is found in Figure 1. While the control group universally stopped because of leg heaviness and weakness, the PPH group stopped because of dyspnea and lightheadedness. One patient had syncope but quickly recovered without sequela. Functional limitation, as determined by the $\dot{V}O_2$max was markedly decreased in the pulmonary hypertensive group. The average $\dot{V}O_2$max for the PPH group was 914 ml/min (12.8 ml/kg/min), or 40 percent of predicted maximum, compared with 1,769 ml/min (28.2 ml/kg/min), or 88 percent of predicted maximum for the control group.

Heart rate at maximal exercise (HRmax) was 81 percent of predicted maximum (average of 148 beats/min) in the PPH group and 101 percent of predicted maximum (average of 178 beats/min) in the control group. However, the PPH patients had a higher HR for any submaximal level of work as shown by the $Q_P$. The control subjects achieved 87 percent of their predicted $Q_P$ maximum compared with 51 percent for the pulmonary hypertensive group.

Despite the common complaint of dyspnea, there appeared to be no ventilatory limitation, since neither group exceeded 60 percent of the predicted $\dot{V}E$. While the percent predicted maximal minute ventilation

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21563/ on 04/18/2017)
achieved was similar between the groups (Fig 1), the VE was higher at any level of \( \dot{V}CO_2 \) in the PPH group (Fig 2). In addition, the rate of ventilatory rise with progressive increases in \( \dot{V}CO_2 \) was greater in the pulmonary hypertensive group. This ventilatory difference at rest and during exercise could not be explained solely by either an isolated increase in respiratory rate or tidal volume. Early in exercise, the higher minute ventilation in the PPH group was due more to an increase in respiratory rate than tidal volume, and as \( \dot{V}CO_2 \) increased further, the higher VE was due to a larger tidal volume (Table 3). As a consequence of this increased VE, the respiratory alkalosis present at rest in the PPH patients (mean PaCO\(_2\) of 32±5 mm Hg) was maintained during exercise (PaCO\(_2\)=29±3 mm Hg) (Table 4).

The arterial PO\(_2\) at rest varied from 62 to 95 mm Hg but fell in ten of 11 PPH patients at maximal exercise,

\[
\begin{array}{cccccc}
\text{Table 3—Mean (± SD) Ventilatory Data at Rest and During Progressive Exercise} & \\
& \text{in Control Subjects and Patients with Primary Pulmonary Hypertension (PPH)*} & \\
& \dot{V}CO_2, \text{ ml/kg/min} & & & & \\
\hline
& 5 & 10 & 15 & 25 & 40 \\
\text{VE, (L/min)} & & & & & \\
\text{PPH} & 14.7±9.6 & 34.6±12.0 & 50.0±6.0 & — & — \\
\text{Control} & 9.6±4.0 & 15.9±6.5 & 26.1±7.7 & 40.1±11.6 & 66.5±5.3 \\
\text{P} & <0.001 & <0.001 & <0.002 & — & — \\
\text{VR, ml} & & & & & \\
\text{PPH} & 728±130 & 1138±203 & 1755±5 & — & — \\
\text{Control} & 642±142 & 922±202 & 1216±225 & 1498±186 & 1974±94 \\
\text{P} & NS & <0.05 & <0.01 & — & — \\
\text{fN, breaths/min} & & & & & \\
\text{PPH} & 28±9 & 34±12 & 28±4 & — & — \\
\text{Control} & 18±5 & 21±6 & 24±6 & 29±6 & 34±4 \\
\text{P} & <0.01 & <0.01 & NS & — & — \\
\hline
\end{array}
\]

*Abbreviations: \( \dot{V}CO_2 \), carbon dioxide production; VE, minute ventilation; VR, minute ventilation; fN, respiratory rate; NS, statistical nonsignificance.

\[
\begin{array}{cccccc}
\text{Table 4—Gas Exchange Data at Rest and Symptom-limited Maximal Exercise in Patients with Primary Pulmonary Hypertension*} & \\
& \text{pH} & \text{PO}_2, \text{ mm Hg} & \text{PCO}_2, \text{ mm Hg} & \text{P(A-a)O}_2, \text{ mm Hg} & \text{Vd/VT, %} \\
\hline
\text{Patient No.} & \text{Rest} & \text{Exercise} & \text{Rest} & \text{Exercise} & \text{Rest} & \text{Exercise} & \text{Rest} & \text{Exercise} & \text{Rest} & \text{Exercise} & \text{Rest} & \text{Exercise} \\
1 & 7.46 & 7.40 & 89 & 84 & 30 & 28 & 23 & 31 & 49 & 34 \\
2 & 7.46 & 7.40 & 66 & 53 & 24 & 26 & 52 & 64 & 55 & 46 \\
3 & 7.36 & 7.30 & 88 & 82 & 32 & 26 & 25 & 38 & 54 & 42 \\
4 & 7.42 & 7.40 & 72 & 45 & 28 & 28 & 42 & 70 & 44 & 49 \\
5 & 7.50 & 7.49 & 62 & 53 & 34 & 34 & 49 & 58 & 49 & 58 \\
6 & 7.41 & 7.40 & 86 & 91 & 39 & 31 & 13 & 22 & 36 & 20 \\
7 & 7.46 & 7.40 & 81 & 72 & 31 & 30 & 32 & 42 & 48 & 35 \\
8 & 7.47 & 7.39 & 94 & 67 & 29 & 30 & 20 & 47 & 48 & 26 \\
9 & 7.43 & 7.42 & 72 & 58 & 38 & 32 & 26 & 59 & 64 & 54 \\
10 & 7.42 & 7.41 & 95 & 92 & 36 & 35 & 13 & 17 & 38 & 30 \\
11 & 7.47 & 7.51 & 88 & 78 & 27 & 24 & 23 & 43 & 42 & 39 \\
\text{Mean} & 7.44 & 7.41 & 81 & 70 & 32 & 29 & 29 & 45 & 48 & 39 \\
\text{SD} & 0.04 & 0.05 & 11 & 16 & 3 & 3 & 13 & 17 & 8 & 12 \\
\hline
\text{p} & <0.02 & <0.005 & <0.05 & <0.0005 & <0.02 & \\
\end{array}
\]

*Abbreviations: pH, arterial pH; PO\(_2\), arterial partial pressure of oxygen; PCO\(_2\), partial pressure of carbon dioxide; P(A-a)O\(_2\), alveolar-arterial oxygen gradient; Vd/VT, dead space ventilation to tidal volume ratio.
while the P(A-a)O₂ increased in all patients, and the V̇D/V̇T fell in nine patients (Table 4).

Anaerobic threshold (AT) was identified in all patients and control subjects (Table 2). The pulmonary hypertensive group reached AT at a much lower V̇O₂ and percent predicted maximal V̇O₂ than the control group (Fig 3). A strong positive correlation between the level of AT and maximal O₂P in the PPH patients was found (r = 0.91, p < 0.001) (Fig 4).

**DISCUSSION**

Patients with PPH invariably complain of a reduction in exercise tolerance as one of the earliest manifestations of the disease. In this study we have demonstrated that the reduction in V̇O₂max is due to inadequate cardiac reserve as demonstrated by a lower O₂ pulse and higher heart rate in the PPH group than in control subjects at all levels of oxygen consumption. In addition, we have found that patients with PPH have early development of the anaerobic threshold, which may explain why prolonged exercise can only be accomplished at a low level of work. This reduced anaerobic threshold was correlated with the O₂ pulse and provides further evidence that inadequate cardiac reserve is the major limiting factor to exercise ability.

We have previously shown that when vasodilator therapy is successful in improving cardiac function in these patients, there is a concomitant increase in V̇O₂max and O₂Pmax that mirrors the hemodynamic changes. If the relationship between O₂ pulse and anaerobic threshold continues to hold during treatment in these patients, this should lead to a significant improvement in overall function.

There was clearly no evidence of ventilatory limitation in our PPH patients. The maximal ventilation achieved was similar to that seen in the control population. Minute ventilation at maximal exercise in the PPH group ranged from 24 to 80 percent of the predicted maximum, with a mean value of only 53 percent. In addition, all PPH patients reached anaerobic threshold, a level of exercise not generally attained by patients with ventilatory impairment. However, the ventilation at any level of V̇CO₂, including rest, was higher in the PPH group than in control subjects.

A possible reason for the high ventilatory response at rest and during exercise would be the presence of significant ventilation-perfusion (V̇A/Q) inequality. However, Dantzker and Bower found that patients with PPH have only mild V̇A/Q inequality during rest with no increase observed during moderate exercise. To a great degree, the hypoxemia seen both at rest and during exercise in their patients was due to a low mixed venous PO₂ (ḞV̇O₂) and its impact on the end-capillary PO₂ of the shunt and low V̇A/Q units. The excessive ventilatory response observed during exercise further increased the mean V̇A/Q of the distribution and thus mitigated the fall in PaO₂ that occurred as a result of the further fall in ḞV̇O₂. While the increased ventilation thus served a useful purpose with regard to pulmonary gas exchange, it is hard to believe that this was the primary controlling mechanism. The levels of hypoxemia which would have occurred, even without the exaggerated ventilatory response, would have been lower than normally required for significant stimulation of hypoxic chemoreceptors.

A more likely explanation exists. Patients with PPH have long been known to sustain a resting chronic respiratory alkalosis. While the exact cause of this is...
To control limitation, thus, baroreceptors in normal maintain subjects, not ventilatory alveolar during exercise.

**FIGURE 2**


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**FIGURE 5**

Schematic representation of the relationship among alveolar ventilation ($V_A$), CO$_2$ production ($V_{CO2}$), and arterial CO$_2$ partial pressure (PaCO$_2$) if the resting PaCO$_2$ is to be maintained during exercise. The lower the PaCO$_2$ is at rest, the greater the ventilatory requirements during exercise. (After Oren et al.)

It is not known, it is thought to be due to increased afferent nerve traffic arising from receptors in the lung or baroreceptors in the walls of the pulmonary vasculature or heart. It has been shown that normal subjects, in whom a respiratory alkalosis was induced, maintain the same low resting PaCO$_2$ during exercise, thus, it is not surprising that our patients do the same. To accomplish this, the $V_{FE}$ must increase more than normal for any increase in $V_{CO2}$, even with a normal fall in the $V_{E}$/VT (Fig 5).

Patients with primary pulmonary hypertension have significant exercise limitation secondary to cardiovascular functions with no evidence of ventilatory limitation. However, the ventilatory response is excessive and likely mediated by nonchemoreceptor control mechanisms.