Exercise-Induced Pulmonary Arterial Hypertension

James J. Tolle, MD; Aaron B. Waxman, MD, PhD; Teresa L. Van Horn, BA; Paul P. Pappagianopoulos, MEd; David M. Systrom, MD

Background—The clinical relevance of exercise-induced pulmonary arterial hypertension (PAH) is uncertain, and its existence has never been well studied by direct measurements of central hemodynamics. Using invasive cardiopulmonary exercise testing, we hypothesized that exercise-induced PAH represents a symptomatic stage of PAH, physiologically intermediate between resting pulmonary arterial hypertension and normal.

Methods and Results—A total of 406 consecutive clinically indicated cardiopulmonary exercise tests with radial and pulmonary arterial catheters and radionuclide ventriculographic scanning were analyzed. The invasive hemodynamic phenotype of exercise-induced PAH (n=78) was compared with resting PAH (n=15) and normals (n=16). Log-log plots of mean pulmonary artery pressure versus oxygen uptake (V\(\dot{O}_2\)) were obtained, and a “join-point” for a least residual sum of squares for 2 straight-line segments (slopes m1, m2) was determined; m2<m1=“takeoff” pattern. At maximum exercise, V\(\dot{O}_2\) (55.8±20.3% versus 66.5±16.3% versus 91.7±13.7% predicted) was lowest in resting PAH, intermediate in exercise-induced PAH, and highest in normals, whereas mean pulmonary artery pressure (48.4±11.1 versus 36.6±5.7 versus 27.4±3.7 mm Hg) and pulmonary vascular resistance (294±158 versus 161±60 versus 62±20 dyne · s · cm\(^{-5}\), respectively; \(P<0.05\) followed an opposite pattern. An exercise-induced PAH plateau (n=32) was associated with lower V\(\dot{O}_2\)max (60.6±15.1% versus 72.0±16.1% predicted) and maximum cardiac output (78.2±17.1% versus 87.8±18.3% predicted) and a higher resting pulmonary vascular resistance (247±101 versus 199±56 dyne · s · cm\(^{-5}\); \(P<0.05\)) than takeoff (n=40). The plateau pattern was most common in resting PAH, and the takeoff pattern was present in nearly all normals.

Conclusions—Exercise-induced PAH is an early, mild, and clinically relevant phase of the PAH spectrum. (Circulation. 2008;118:2183-2189.)

Key Words: circulation ■ exercise ■ hemodynamics ■ hypertension, pulmonary ■ physiology

Pulmonary arterial hypertension (PAH) is defined by the National Institutes of Health registry as a mean pulmonary artery pressure (mPAP) of >25 mm Hg at rest or 30 mm Hg during exercise in the absence of pulmonary venous hypertension (PVH). Exercise-induced PAH, which refers to the patient with normal mPAP at rest but >30 mm Hg with exercise, is a poorly understood entity. Some believe that exercise-induced PAH is an early and more treatable phase that precedes resting PAH, whereas others suggest that it may be a stable variant. A recent study of familial PAH relatives demonstrated that exercise-induced PAH can be asymptomatic or “preclinical,” whereas others have described associated exertional intolerance. Whether exercise-induced PAH inexorably progresses to resting PAH is unknown, and whether or not to treat is controversial.

Editorial p 2120
Clinical Perspective p 2189

Most previous descriptions of exercise-induced PAH have been noninvasive, with the use of stress Doppler transthoracic echocardiography. Although it is an established screening modality for resting PAH, echocardiography has not been well validated during exercise, when it is technically difficult to accomplish and is associated with unique pitfalls. Specifically, the components of pulmonary vascular resistance (PVR), which are critical for an accurate diagnosis of pulmonary vasculopathy, cannot be measured directly by stress echocardiography.

There have been surprisingly few direct invasive studies of exercise-induced PAH. Three recent such investigations of a total of 29 patients with suspected PAH found the exercise-induced variant in 5, but all were limited by the failure to exclude PVH.

In the present study, we for the first time fully characterize exercise-induced PAH in a large group of symptomatic patients with direct measurements of central hemodynamics at rest and during maximum cardiopulmonary exercise testing (CPET). We demonstrate that the pattern and severity of the central hemodynamic response to exercise in exercise-induced PAH is intermediate between that of the normal
subject and the patient with resting PAH and provide support for the hypothesis that exercise-induced PAH is a mild yet symptomatic phase of the disease.

Methods

Patients

Four-hundred six complete CPETs performed over a 3-year period in the Massachusetts General Hospital Cardiopulmonary Exercise Laboratory, with radial and pulmonary arterial catheters in place and radionuclide ventriculographic scanning, were analyzed. The study was approved by the Partners Human Research Committee. The CPETs were clinically indicated, with the majority ordered for evaluation of dyspnea or fatigue of unclear etiology or as part of an evaluation for cardiac or pulmonary transplantation.

Cardiopulmonary Exercise Testing

Pulmonary gas exchange and minute ventilation (VE) were measured by breath with a commercially available metabolic cart (Medical Graphics Corporation CPX/D, St Paul, Minn). The pneumotachograph was calibrated with a 3 L syringe at 5 different flow rates, and the zirconia cell O2 analyzer and single-beam CO2 analyzer were calibrated with room air and 5% CO2/12% O2 gas. Radial and pulmonary artery catheters (Edwards Scientific, Irvine, Calif) were placed with the use of standard techniques, the latter by the internal jugular approach. Systemic and pulmonary artery pressures were measured with HP1290A quartz pressure transducers (Hewlett-Packard Co, Andover, Mass). Transducers were interfaced with an MT95K2 recorder (Astro-Med Inc, West Warwick, RI), and mean end-expiratory lung volumes were obtained at right atrial pressure (RAP), mean pulmonary arterial pressure, and mean systemic arterial pressure. Two-milliliter samples of systemic and pulmonary arterial blood were obtained at rest and during exercise and analyzed at 37° for PO2, PCO2, pH (model 1620; Instrumentation Laboratories, Lexington, Mass), hemoglobin concentration ([Hb]), and O2 saturation, with O2 content calculated from the latter 2 (model 482; Instrumentation Laboratories). Right ventricular (RV) and left ventricular (LV) ejection fractions (RVEF, LVEF) and LV end-diastolic volume were measured at rest and near peak exercise by a first-pass cardiac radionuclide scan (Phillips Medical Systems, Valhalla, NY) whose methodology is described elsewhere.

All patients completed a single bout of incremental cycling (Medical Graphics CPE 2000) exercise to exhaustion. Two minutes of rest were followed by 2 minutes of unloaded cycling. Work was then continuously increased by 6.25 to 25 W/min on the basis of the history of exertional tolerance. Mean systemic arterial pressure and end-expiratory RAP and mPAP were measured continuously. End-expiratory pulmonary capillary wedge pressure (PCWP) was obtained at rest and during each minute of exercise. Central pressures associated with an end-expiratory pleural pressure swing that was >10 mm Hg were excluded, or, in select cases, incremental exercise was replicated with an esophageal balloon in place, and end-expiratory pleural pressures were subtracted. Two-milliliter blood samples were simultaneously drawn from the radial and pulmonary arterial catheters during rest and the last 15 seconds of each minute of exercise. At cessation of exercise, patients were asked which of the following symptoms caused them to stop: shortness of breath, leg fatigue or pain, or chest pain, alone or in combination.

Data Analysis

Ventilatory and pulmonary gas exchange data were averaged for the final 30 seconds of the 2-minute rest period and over contiguous 30-second intervals during exercise. Predicted values for VO2,max utilizing age, gender, and height were those of Hansen and colleagues.14 The ventilatory threshold was determined by the V-slope method.16 VE/VO2 was measured at the ventilatory threshold. Cardiac output (Qo) was calculated from the Fick principle: Qo = VO2/(Ca-VO2). Predicted maximal Qo was calculated from predicted VO2,max, and an assumed arterial-venous O2 content difference = ([Hb] × 10).17 PVR was calculated from (mPAP–PCWP)/Qt.

Peak heart rate ≥80% of predicted and peak respiratory exchange ratio ≥1.00 were used as indicators of maximum effort. At maximum exercise, PAH was defined as a mPAP ≥25 mm Hg, PCWP <20 mm Hg,18 and PVR ≥50 dynes · s · cm−5.19 PAH was subdivided subsequently into (1) resting PAH, indicating a mPAP ≥25 mm Hg but a PCWP ≤15 mm Hg at rest, and (2) exercise-induced PAH, with a resting mPAP ≤25 mm Hg. At maximum exercise, PVH was defined as PCWP ≥20 mm Hg. Left ventricular systolic dysfunction was defined as PVH with LVEF <55%, and LV diastolic dysfunction was defined as PVH with LVEF ≥55%. Peripheral limitation was defined as VO2,max <70% of predicted with Qmax >80% of predicted and Ca-VO2<[Hb]. Normal, including detrained, subjects were defined by a VO2,max ≥70% predicted and who met none of the aforementioned abnormal CPET diagnostic criteria. All others were excluded, including those with a primary pulmonary mechanical limitation (VE/maximum voluntary ventilation >0.7 at the ventilatory threshold).

Statistical programs included Excel and GraphPad Prism. Central tendencies were expressed as mean±SD and compared by ANOVA with Newman-Keuls finishing test or unpaired t tests. Continuous variables were analyzed by linear regression. A log-log plot of mPAP versus VO2 was obtained for all patients, and the VO2 “join-point” for a least residual sum of squares for 2 straight-line segments was determined.16,21 In addition, 95% CIs for the slopes of the first (m1) and second (m2) linear regressions were compared; m2<m1 was classified as a “plateau,” and m2≥m1 was classified as a “takeoff” pattern. Identical analyses were performed for mPAP versus Qo and RAP versus VO2. A probability value <0.05 was considered significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Demographics

Of the 406 patients, the indication for testing was known in 340. Of these, 255 (75%) were referred for invasive exercise testing for dyspnea of uncertain etiology, 22 (6%) for fatigue, 28 (8%) to differentiate a cardiac from pulmonary limit to exercise, 28 (8%) had known left-ventricular systolic dysfunction and were being considered for cardiac transplantation, and 7 (2%) had other indications. Thus, 305 patients (90%) were referred to clarify the etiology of exertional intolerance.

All exercise tests were symptom limited; no exercise test was stopped by the supervising technician or physician, and there were no complications related to the pulmonary artery catheter or exercise testing. Patients stopped cycling because of either shortness of breath, leg fatigue, or both, with only 1 patient, in the normal group, additionally experiencing chest pain. CPET diagnoses included 93 cases (23%) of PAH, 196 cases (48%) of PVH or other cardiac limitation, 55 (14%) peripheral limitation, 16 (4%) normal, and 46 (11%) other (Figure 1). Of the 93 PAH cases, 78 had exercise-induced PAH, and 15 had resting PAH. Of the 255 cases referred for dyspnea of uncertain etiology, the 2 most common CPET diagnoses were PAH (n=86) and LV diastolic dysfunction (n=69).

PAH Versus Normal

Thus, 109 subjects constituted the normal and PAH study populations as defined in Methods. One hundred six of 109 subjects (except 1 in the exercise-induced PAH group and 2 in the normal group) demonstrated adequate maximum effort as defined by peak heart rate ≥80% of predicted or peak respiratory exchange ratio ≥1.00.
Exercise-induced PAH and resting PAH groups were older compared with the normal group (Table 1). At maximum exercise, VO_{2\text{max}} (% predicted), Qt_{\text{max}} (% predicted), RVEF, alveolar-arterial difference in partial pressure of O_{2}, mPAP, and PVR were highest in resting PAH, lowest in normals, and intermediate in exercise-induced PAH, whereas PCWP and RAP were not different. There was no difference in ventilatory efficiency, as measured by V_{E}/V_{CO_{2}} at the ventilatory threshold, between the normal and exercise-induced PAH groups, whereas the resting PAH group had a significantly higher value than both.

Takeoff Versus Plateau Patterns of mPAP Versus VO_{2}

Figures 2 and 3 depict representative plateau and takeoff patterns of mPAP versus VO_{2}, respectively. For normals, of 15 interpretable mPAP versus VO_{2} log-log plots, 14 demonstrated a takeoff and 1 a plateau pattern. Of the 78 patients with exercise-induced PAH, 32 had a plateau, 40 had a takeoff pattern, and 6 were uninterpretable. In the resting PAH group, 9 demonstrated a plateau pattern, 2 demonstrated a takeoff pattern, and 4 were uninterpretable. mPAP versus Qt log-log patterns were highly concordant with mPAP versus VO_{2} log-log patterns for all groups.

For the exercise-induced PAH group, a plateau pattern was associated with a reduced maximum exercise work, VO_{2}, and Qt. There was no difference in mPAP, RVEF, or alveolar-arterial difference in partial pressure of O_{2} at peak exercise. The resting PVR was higher, with a trend toward higher PVR at peak exercise, in those with a plateau pattern (Table 2).

For those with takeoff patterns, there was a significant relationship between the VO_{2} at the mPAP breakpoint and that for the ventilatory threshold (\(P<0.05, r=0.52\); Figure 4). No such relationship was found for those with plateau patterns (\(P=0.40, r=0.17\)).

Table 1. Demographic and CPET Variables

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=16)</th>
<th>Exercised-Induced PAH (n=78)</th>
<th>Resting PAH (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>45.9±14.9</td>
<td>58.8±15.1*</td>
<td>58.5±15.7*</td>
</tr>
<tr>
<td>Female gender, %</td>
<td>68.8</td>
<td>65.8</td>
<td>46.7</td>
</tr>
<tr>
<td>Body mass index</td>
<td>25.5±4.2</td>
<td>30.2±5.3*</td>
<td>28.1±6.2</td>
</tr>
<tr>
<td>Work max, W</td>
<td>155.5±43.1</td>
<td>90.3±41.7*</td>
<td>70.0±41.5*</td>
</tr>
<tr>
<td>VO_{2\text{max}}, mL/min</td>
<td>2022±468</td>
<td>1284±58*</td>
<td>1127±507*</td>
</tr>
<tr>
<td>VO_{2\text{max}}, % predicted</td>
<td>91.7±13.7</td>
<td>66.5±16.3*</td>
<td>55.8±20.3*</td>
</tr>
<tr>
<td>Pa(A-a)O_{2}, mm Hg</td>
<td>14.7±7.6</td>
<td>32.0±18.0*</td>
<td>52.7±17.3*</td>
</tr>
<tr>
<td>CaO_{2}, mg/mL</td>
<td>19.0±1.2</td>
<td>18.0±2.5</td>
<td>16.8±3.3</td>
</tr>
<tr>
<td>Paco\text{max}, mm Hg</td>
<td>32.9±4.4</td>
<td>35.1±6.1</td>
<td>37.1±7.6</td>
</tr>
<tr>
<td>VCO_{2\text{max}}, mL/min</td>
<td>2380±722</td>
<td>1561±705*</td>
<td>1310±626*</td>
</tr>
<tr>
<td>mPAP rest, mm Hg</td>
<td>13.9±2.9</td>
<td>18.6±3.2*</td>
<td>30.9±8.9*</td>
</tr>
<tr>
<td>mPAPmax, mm Hg</td>
<td>27.4±3.7</td>
<td>36.6±5.7*</td>
<td>48.4±11.1*</td>
</tr>
<tr>
<td>PCWPmax, mm Hg</td>
<td>14.8±4.5</td>
<td>15.0±2.4</td>
<td>15.2±3.1</td>
</tr>
<tr>
<td>Qmax, L/min</td>
<td>15.5±3.2</td>
<td>11.4±3.0*</td>
<td>10.4±3.6*</td>
</tr>
<tr>
<td>Qmax, % predicted</td>
<td>99.4±11.1</td>
<td>83.1±18.9*</td>
<td>71.8±22.4*</td>
</tr>
<tr>
<td>PVR rest, dyne · s · cm^{-5}</td>
<td>154±61</td>
<td>223±82*</td>
<td>352±141*</td>
</tr>
<tr>
<td>PVRmax, dyne · s · cm^{-5}</td>
<td>62±20</td>
<td>161±60*</td>
<td>294±158*</td>
</tr>
<tr>
<td>RAPmax, mm Hg</td>
<td>9.1±3.5</td>
<td>9.6±3.0</td>
<td>11.0±6.1</td>
</tr>
<tr>
<td>RVEF\text{max} at anaerobic threshold</td>
<td>0.58±0.06</td>
<td>0.53±0.08*</td>
<td>0.43±0.11*</td>
</tr>
</tbody>
</table>

\(P(A-a)O_{2}\) indicates alveolar-arterial difference in partial pressure of O_{2}; VCO_{2}, carbon dioxide production.

\(*P<0.05\) vs normal; \(\dagger P<0.05\) vs exercised-induced PAH.
Takeoff and plateau patterns of RAP versus $V\dot{O}_2$ were equally represented in the 2 groups. There was no difference in RVEF or RV/LV stroke counts ratio.

**Follow-Up Data**
Five subjects with CPET physiological diagnoses of exercise-induced PAH underwent a repeated clinically indicated invasive exercise test following the same protocol. The time to retest was 29.8±10.7 months. Both diagnoses and treatment regimens were heterogeneous (Table 3). At peak exercise, there was a nonsignificant decrease in $V\dot{O}_2$max (69.8±20.2% to 61.2±21.9% predicted) that was associated with a similar change in $Q_{max}$ (86.4±25.6% to 80.0±23.8% predicted; $P>0.05$ for both) but with no change in central hemodynamics (mPAP, 38.4±4.3 to 37.2±7.5 mm Hg; PVR, 175±79 to 131±29 dyne·s·cm$^{-5}$; $P>0.05$ for both).

**Discussion**
We have described a large subset of symptomatic patients who meet the National Institutes of Health registry criteria for PAH during exercise yet do not have an elevated mPAP at rest. At maximum exercise, their overall aerobic capacity and central hemodynamics lie between those of the normal subject and the patient with resting PAH. In these patients, it is only under the stress of incremental cycling exercise that evidence of a pulmonary vasculopathy is uncovered.

**Prior Studies**
Most previous studies describing exercise-induced PAH have utilized noninvasive techniques, particularly stress Doppler transthoracic echocardiography. Although echocardiography has emerged as a useful screening modality for resting PAH, it has not been well validated during exercise, in which there are significant methodological concerns. For instance, during incremental exercise, RAP normally rises well beyond the usual assumed 5 mm Hg. RAP has been utilized noninvasively as a useful screening modality for resting PAH, but it has never been validated during exercise, when venous compliance is known to decrease. Second, the contribution of the PCWP to an exercise-induced RV systolic pressure rise cannot be assessed directly with transthoracic echocardiography. PCWP has been estimated by echocardiography at rest but not during exercise. The former may be critical given that many suspected cases of PAH based on echocardiography actually have PVH, especially in the elderly.

**Table 2. Exercised-Induced PAH: mPAP Takeoff vs Plateau Patterns**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Plateau (n=32)</th>
<th>Takeoff (n=40)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender, %</td>
<td>57.7±15.9</td>
<td>59.6±13.9</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>31.5±5.9</td>
<td>29.4±5.2</td>
<td>NS</td>
</tr>
<tr>
<td>Work max</td>
<td>79.2±38.3</td>
<td>101.7±41.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>$V\dot{O}_2$max, mL/min</td>
<td>1207±507</td>
<td>1373±516</td>
<td>NS</td>
</tr>
<tr>
<td>$V\dot{O}_2$ max, % predicted</td>
<td>60.6±15.1</td>
<td>72.0±16.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(P-A)O$_2$max, mm Hg</td>
<td>36.1±16.9</td>
<td>28.8±18.1</td>
<td>0.09</td>
</tr>
<tr>
<td>P$\rho$O$_2$, mm Hg</td>
<td>23.8±3.7</td>
<td>22.6±4.2</td>
<td>NS</td>
</tr>
<tr>
<td>pHv</td>
<td>7.29±0.04</td>
<td>7.28±0.05</td>
<td>NS</td>
</tr>
<tr>
<td>mPAP rest, mm Hg</td>
<td>19.1±3.5</td>
<td>17.8±2.7</td>
<td>NS</td>
</tr>
<tr>
<td>mPAPmax, mm Hg</td>
<td>35.9±4.2</td>
<td>37.1±6.8</td>
<td>NS</td>
</tr>
<tr>
<td>PCWPmax, mm Hg</td>
<td>15.1±2.8</td>
<td>15.2±2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Qmax, L/min</td>
<td>10.8±3.3</td>
<td>12.0±2.8</td>
<td>0.10</td>
</tr>
<tr>
<td>Qmax, % predicted</td>
<td>78.2±17.1</td>
<td>87.8±18.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PVR rest, dyne·s·cm$^{-5}$</td>
<td>247±101</td>
<td>199±56</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PVRmax, dyne·s·cm$^{-5}$</td>
<td>174±76</td>
<td>150±45</td>
<td>0.12</td>
</tr>
<tr>
<td>RAPmax, mm Hg</td>
<td>9.1±3.1</td>
<td>9.9±2.9</td>
<td>NS</td>
</tr>
<tr>
<td>RVEFmax</td>
<td>0.54±0.08</td>
<td>0.53±0.07</td>
<td>NS</td>
</tr>
<tr>
<td>RV/LV stroke counts ratio</td>
<td>0.8±0.2</td>
<td>0.8±0.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

(P-A)O$_2$ indicates alveolar-arterial difference in partial pressure of O$_2$; P$\rho$O$_2$, mixed venous PO$_2$; and pHv, mixed venous pH.

**Table 3. Patient Diagnosis and Treatment at Times of First and Second CPETs**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>CPET-1</th>
<th>Between CPETs</th>
<th>CPET-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Congenital heart disease</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Idiopathic</td>
<td>None</td>
<td>Bosentan ↑ sildenafil</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>3</td>
<td>Idiopathic</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Mitral valve disease</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>Idiopathic</td>
<td>None</td>
<td>Bosentan ↑ sildenafil</td>
<td>Sildenafil</td>
</tr>
</tbody>
</table>
ent. Finally, the influence of cardiac output on the RV systolic pressure, and therefore the PVR response to exercise, cannot be directly measured by echocardiography. Estimates of cardiac output and PVR have been made recently by transthoracic echocardiography at rest,25 but they have not yet been validated during exercise. The latter is important given a wide range of normal RV systolic pressure at peak exercise, especially in the well-trained athlete.27 In such individuals, both RV systolic pressure and mPAP may be high at peak exercise, but the fall in PVR remains totally normal.18 Thus, although stress echocardiography holds promise in the diagnosis of exercise-induced PAH, it remains to be validated by direct measurements of central hemodynamics.

Noninvasive CPET has also been shown to be useful in the diagnosis and assessment of the severity of resting PAH.28–30 Certain noninvasive exercise testing parameters correlate with an exercise-induced rise in RV systolic pressure by transthoracic echocardiography in breathless patients.31 Our laboratory has recently validated a noninvasive CPET diagnostic algorithm for PAH with direct central hemodynamic measurements.32 We and others13,33 have described CPET-induced exaggerated rise of pulmonary arterial pressure in resting PAH.

We know of 3 recent studies in the English literature employing pulmonary arterial catheters that describe possible exercise-induced PAH. Raeside et al13 reported exercise-induced PAH in 2 of a total of 16 patients with connective tissue disease or idiopathic PAH who cycled at 30% of \( \dot{V}O_2 \) max. They did not, however, include measurements of PCWP during exercise, and PVR is therefore unknown. James and coworkers12 described 3 patients with unexplained exertional dyspnea who had normal resting mPAP and an exaggerated rise at peak cycling exercise. The mean PCWP at peak exercise in that study was >20 mm Hg, however, raising the possibility that some of the patients had diastolic heart failure.

Clinical Significance

The present study confirms, with direct measurements of central hemodynamics during maximum CPET, that exercise-induced PAH exists and is associated with exertional symptoms. As noted above, the 2 most common CPET diagnoses in patients referred for dyspnea of uncertain etiology were exercise-induced PAH and LV diastolic dysfunction. Because all of our patients were referred for symptoms, we can shed no light on whether there are additional patients with exercise-induced PAH who may be asymptomatic or preclinical.5,6

Our data support the notion that exercise-induced PAH represents a mild, intermediate physiological stage of PAH. At maximum exercise, there was evidence of intermediate exercise capacity in exercise-induced PAH, in terms of \( \dot{V}O_2 \) max (% predicted), and measurements of cardiac function, as measured by Q, max (% predicted) and RVEFmax. Likewise, central hemodynamics, namely, mPAP and PVR at both rest and peak exercise, and peak alveolar-arterial PO2 difference, a hallmark of abnormal diffusion in diseased pulmonary vasculature, were highest in resting PAH, lowest in normals, and intermediate in exercise-induced PAH.

The takeoff pattern of mPAP versus \( \dot{V}O_2 \) during exercise testing is most commonly seen in the normal and less severe exercise-induced PAH patients, as measured by maximum exercise \( \dot{V}O_2 \) and cardiac output. Conversely, the plateau pattern of mPAP is typical of the more severely affected exercise-induced PAH patients and of those with resting PAH. Interestingly, Wonisch and associates39 found a similar plateau of invasively measured RV systolic pressure in resting PAH. This suggests a continuum of pulmonary vascular responses to exercise, beginning with the normal takeoff pattern, moving through 2 stages of exercise-induced PAH, and finally reaching the plateau pattern of resting PAH.

If exercise-induced PAH is an early phase of PAH, screening and early detection might facilitate treatment aimed at preventing progression to resting PAH. In our study, exercise parameters, such as \( \dot{V}E/\dot{V}CO_2 \) at the ventilatory threshold and peak alveolar-arterial pressure in partial pressure of \( O_2 \), were not sufficiently sensitive to distinguish exercise-induced PAH from normal. Likewise, resting mPAP, including those in an “indeterminate” range of 21 to 25 mm Hg, did not reliably predict exercise-induced PAH. Thus, at the moment, screening for exercise-induced PAH seems best accomplished with invasive exercise testing.

We do not yet have systematic longitudinal follow-up of our exercise-induced PAH patients. However, our limited longitudinal data suggest that exercise-induced PAH patients may remain relatively stable from a clinical and hemodynamic standpoint over several years. Conversely, 2 patients have been described elsewhere with progressive systemic sclerosis and echocardiographically diagnosed exercise-induced PAH progressing to resting PAH over a 2-year period.10 Clearly, long-term clinical and hemodynamic follow-up is much needed.

Potential Mechanisms

In the normal human, the increase in cardiac output from rest to maximum exercise far outweighs the slight widening of input and outflow pressure difference across the pulmonary vascular bed, ie, PVR falls,35 as a result of both passive and active pulmonary vascular recruitment and distension. Despite being referred for clinical symptoms, the normal subjects in this study were found to have normal oxygen uptake, central hemodynamics, and fall in PVR at peak exercise. These results are similar to those of 2 recent studies of healthy, asymptomatic, physically active male subjects.22,36

In long-standing pulmonary hypertension, intimal proliferation and fibrosis, medial hypertrophy, and in situ thrombosis characterize the pathological findings in the pulmonary vasculature, although at an earlier stage, changes may be confined to the small pulmonary arteries.57–40 These changes, as well as the upstream sequelae such as RV dysfunction, are time dependent and result in progressive symptoms41 and impairment of exercise tolerance.28 Thus, it seems biologically plausible that patients with PAH of varying duration and severity will exhibit very different mPAP responses to exercise.

In this study, the takeoff pattern of mPAP suggests pulmonary vasoconstriction late during incremental exercise in normals and those with mild exercise-induced PAH. The
phenomenon is similar to other well-described “thresholds” described during incremental exercise, including those of arterial blood lactate concentration, ventilation, CO2 output, and humoral catecholamines. The correlation between the VO2 at mPAP takeoff and the ventilatory threshold in the present study suggests either a causal relationship or a shared underlying mechanism. Examples of the former include pulmonary arterial vasoconstrictive effects of desaturated and acid mixed-venous blood, neither of which was related to mPAP pattern in the present study. Alternatively, catecholamines have been postulated to both drive skeletal muscle glycolysis and potentiate PVR. Interestingly, interleukin-6 is the 1 humoral cytokine that rises measurably in proportion to exercise intensity, has been related to catecholamines, and may play a role in the genesis of pulmonary hypertension. Alternatively, intimal proliferation and decreased compliance of the pulmonary vasculature could cause a takeoff of mPAP. However, given that normals most often exhibit a takeoff pattern and resting PAH patients do not, pulmonary vascular stiffness is an unlikely unifying explanation.

Conversely, the plateau pattern of mPAP was typical of more severely compromised exercise-induced PAH and of resting PAH patients. Potential mechanisms include exercise-induced RV dysfunction with or without tricuspid regurgitation. Lower cardiac output in the exercise-induced PAH plateau versus takeoff groups and more severe PAH with a depressed RVEF in resting PAH (dominated by the plateau pattern) support the former. RAP and LV/RV stroke count ratios did not suggest that exercise-induced tricuspid regurgitation was responsible for the plateau pattern, however.

Limitations of the Study
The principal CPET indication at our institution is unexplained dyspnea, which might make our results generally applicable. A very active pulmonary vascular clinic at this institution, however, likely results in the referral of more PAH patients than would be expected in a general medical clinic. Thus, any inferences concerning prevalence of exercise-induced PAH must be made with caution. Mechanisms underlying the 2 mPAP patterns during CPET can only be addressed indirectly in this study, but they have served to generate several testable hypotheses. This study is largely cross-sectional, and systematic longitudinal studies of exercise-induced PAH, with and without treatment, remain to be performed.

Summary
Using invasive maximum cardiopulmonary exercise testing, we have for the first time fully phenotyped the patient with exercise-induced PAH from a large cohort of symptomatic patients and have lent support to the hypothesis that exercise-induced PAH is a mild and clinically relevant phase of the PAH spectrum. If exercise-induced PAH is an early form of a progressive disease, screening and early intervention may prevent the progression of vascular remodeling and development of established PAH in much the same way that we currently approach the diagnosis and treatment of systemic hypertension.

Acknowledgments
The authors would like to acknowledge Shannon Burnham and McKenzie Wessen for their assistance with data collection.

Sources of Funding
This work was supported by grant K24HL04022-05 from the National Institutes of Health.

Disclosures
Dr Waxman has received other research support from Gilead Pharmaceuticals and Epix Pharmaceuticals. He has also served on speakers’ bureaus and consultant/advisory boards for Gilead Pharmaceuticals and United Therapeutics. The authors otherwise report no conflicts.

References
Exercise-Induced Pulmonary Arterial Hypertension
James J. Tolle, Aaron B. Waxman, Teresa L. Van Horn, Paul P. Pappagianopoulos and David M. Systrom

Circulation. 2008;118:2183-2189; originally published online November 3, 2008; doi: 10.1161/CIRCULATIONAHA.108.787101
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 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/118/21/2183

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/