Abnormal Pulmonary Artery Pressure Response in Asymptomatic Carriers of Primary Pulmonary Hypertension Gene

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Background—Familial primary pulmonary hypertension (PPH) is an autosomal-dominant inherited disease with incomplete penetrance and poor prognosis. This study was performed to examine whether asymptomatic carriers of a mutated PPH gene can be identified at an early stage by their pulmonary artery systolic pressure (PASP) response to exercise.

Methods and Results—Stress Doppler echocardiography during supine bicycle exercise and genetic linkage analysis were performed on 52 members of 2 families with PPH. In 4 PPH patients, the mean PASP was increased at rest (73 ± 16 mm Hg). Fourteen additional family members with normal PASP at rest revealed an abnormal PASP response to exercise (from 23 ± 4 to 56 ± 11 mm Hg) without secondary cause (abnormal response [AR] group). Twenty-seven other members (NR group) revealed a normal PASP response (maximal pressure, 40 mm Hg) to exercise (from 24 ± 4 to 37 ± 3 mm Hg, \( P < 0.0001 \)). All 14 AR but only 2 NR members shared the risk haplotype with the PPH patients. The molecular genetic analysis supported linkage to chromosome 2q31-32 with a logarithm of the odds score of 4.4 when the 4 patients and the 14 AR members were classified as affected.

Conclusions—We conclude that the pathological rise of PASP in asymptomatic family members is linked to chromosome 2q31-32 and is probably an early sign of PPH. Therefore, stress Doppler echocardiography may be a useful tool to identify persons at risk for PPH even before pulmonary artery pressures at rest are elevated. (Circulation. 2000;102:1145-1150.)

Key Words: hypertension, pulmonary ■ echocardiography ■ genetics

Primary pulmonary hypertension (PPH) is a rare disease associated with a poor prognosis.1 It is usually diagnosed only after pulmonary artery pressure (PAP) is markedly elevated.2 The disease is thought to develop from reversible vasoconstrictive to irreversible proliferative stages. Although therapy with prostacyclin has improved the symptoms, pulmonary hemodynamics, and prognosis,3,4 treatment of the early stages may be easier, more effective, and less costly if vasoconstriction is predominant, because it may be effectively treated with calcium channel blockers.5 Therefore, it might be of great value to identify latent PPH to start therapy at an early stage. Unfortunately, at present, there are no known clinical signs or markers of the early stages of PPH. Insights derived from the familial form of PPH might be helpful in this regard because the clinical or pathological features are not different from the sporadic form.6 Because familial PPH appears to be a monogenic disease with an autosomal-dominant inheritance,7 one would expect half of the siblings of PPH patients to be affected. However, analysis of 24 families has shown an incomplete age- and sex-related penetrance of the disease, suggesting that some family members are asymptomatic gene carriers.7 Linkage to chromosome 2q31-32 has been reported in 7 families.8,9 The causal gene and identification of family members at risk has not emerged to date. We hypothesized that the clinically asymptomatic gene carriers in PPH families could be identified by a systematic noninvasive assessment of PAP at rest and during exercise.

Therefore, stress Doppler echocardiography (SE) and linkage analysis on members of 2 German PPH families (designated families A and B) were performed.

Methods

Study Population and Design

All 79 living members of 2 families with PPH were invited to participate in a clinical and genetic evaluation. Only 2 declined to be...
Figure 1. Clinical and genetic status of members of families A and B (panels a and b, respectively). Different pedigree symbols indicate clinical status of family members. Filled symbols indicate individuals with manifest PPH (n = 4), half-filled symbols indicate members with normal PASP at rest but pathological PASP during supine bicycle exercise (AR group, n = 14), open symbols indicate unaffected status, open symbols with dot indicate subjects with normal PASP response to exercise (NR group, n = 27), and crossed symbols indicate secondary pulmonary hypertension (n = 3). Chromosome symbols indicate haplotype as derived by analysis of PPH-linked microsatellite markers. Disease haplotype is shown in black.

Table 1. Mean Workload, Cardiac Output, Maximal Rate-Pressure Product, Mean Heart Rate, and Percentage of Age-Predicted Heart Rate

<table>
<thead>
<tr>
<th></th>
<th>AR Members (n = 14)</th>
<th>NR Members (n = 27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>36.9 ± 20</td>
<td>21.3 ± 13</td>
<td>0.02</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>62.4 ± 14</td>
<td>61.2 ± 24</td>
<td>0.88</td>
</tr>
<tr>
<td>Height, cm</td>
<td>164.5 ± 11</td>
<td>162.8 ± 18</td>
<td>0.63</td>
</tr>
<tr>
<td>At maximal exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workload, W</td>
<td>107 ± 36</td>
<td>119 ± 41</td>
<td>0.33</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>12.1 ± 2.6</td>
<td>14.2 ± 4</td>
<td>0.11</td>
</tr>
<tr>
<td>Rate-pressure product, mm Hg/min</td>
<td>24 185 ± 5037</td>
<td>24 312 ± 6008</td>
<td>0.94</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>142 ± 15</td>
<td>151 ± 18</td>
<td>0.08</td>
</tr>
<tr>
<td>Percentage of age-predicted maximal heart rate, %</td>
<td>78 ± 10</td>
<td>76 ± 10</td>
<td>0.69</td>
</tr>
<tr>
<td>At maximal PASP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workload, W</td>
<td>95 ± 39</td>
<td>87 ± 36</td>
<td>0.55</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>9.7 ± 2</td>
<td>10.4 ± 1</td>
<td>0.32</td>
</tr>
<tr>
<td>Rate-pressure product, mm Hg/min</td>
<td>16 135 ± 4 112</td>
<td>15 920 ± 4 789</td>
<td>0.51</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>130 ± 18</td>
<td>127 ± 15</td>
<td>0.6</td>
</tr>
<tr>
<td>Percentage of age-predicted maximal heart rate, %</td>
<td>71 ± 12</td>
<td>63 ± 9</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
studied. From 67 members, blood samples were taken for genetic analysis. Of these, 52 were assessed clinically. They were native-born residents of a low-altitude area and were studied in Heidelberg, Germany, at an altitude of 100 m. The study was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg, and the members gave informed written consent before the study.

Clinical Procedures
Clinical procedures consisted of recording the medical history, physical examination, 12-lead ECG, echocardiography, and SE. Manifest PPH was diagnosed according to the criteria of the World Health Organization16: a mean PAP >25 mm Hg or pulmonary artery systolic pressure [PASP] >35 mm Hg at rest, after excluding secondary reasons for pulmonary hypertension. Secondary pulmonary hypertension (due to left, valvular, or congenital heart disease; chronic thromboembolic disease; pulmonary diseases with emphysema, fibrosis, thoracic cage abnormalities; autoimmune diseases, such as lupus erythematosus, scleroderma, vasculitis, and rheumatoid arthritis; HIV infection; portopulmonary hypertension; and sleep-disordered breathing) was excluded on the basis of clinical examination, chest x-ray, pulmonary function test, lung perfusion scan, right heart catheterization, laboratory testing, and measurement of arterial blood gases.14

Echocardiography
Two-dimensional and Doppler echocardiographic recordings were obtained with the use of 2.5-MHz duplex transducers and conventional equipment (Aloka Vario View 2200). Echocardiographic studies were performed by experienced cardiac sonographers (E.G. and D.M.), who had no knowledge of the molecular genetic data.

Stress Doppler Echocardiography
The participants were examined on a supine bicycle ergometer (model 8420, KHL Corp) as described previously.12,13 After videotape review of echocardiographic images and Doppler signals, measurements were made again with an offline system (Echocom) in random order and in a blinded fashion. PASP was estimated from peak tricuspid regurgitation jet velocities according to the following equation: PASP = 4(V)² + 5 mm Hg, where V is the peak velocity (in m/s) of tricuspid valve regurgitant jet, and 5 mm Hg is the estimated right atrial pressure.14 Maximal tricuspid velocity was measured at the highest coherent boundary on the spectral wave form. Signals were considered technically adequate if they had complete envelopes with well-defined borders. In subjects with inadequate Doppler signals, SE was repeated within 6 to 18 months. PASP values >25 mm Hg at rest and ≤40 mm Hg during exercise were classified as normal.6,13,16 The right ventricular (RV) and atrial areas were obtained in apical 4-chamber views by using planimetry as described by Bommere et al.17 Left ventricular (LV) volumes and ejection fractions were calculated by the disk summation method (modified Simpson’s rule). Cardiac output was estimated from LV volumes in the cardiac cycle.

Right Heart Catheterization
Right heart catheterization was carried out simultaneously with SE in all 4 PPH patients and in 12 family members with the use of a Swan-Ganz balloon-tipped catheter (Baxter) placed in the pulmonary artery. Pressures at rest and during supine bicycle exercise were recorded with a polygraph (Hellige). Cardiac output and mixed venous oxygen saturation were not obtained for all members at rest and during exercise.

Safety
All examinations were performed by 3 physicians: one performed the echocardiographic examinations, the second performed the right heart catheterization, and the third monitored the ECG, heart rates, blood pressures, and oxygen saturation at rest and during exercise.

Linkage Analysis
Genomic DNA was extracted from whole blood by use of standard salt precipitation protocols. Genotypes for chromosome 2–specific microsatellite markers CHRNA1, D2S364, D2S2336, and D2S369 were obtained by polymerase chain reaction, followed by polyacrylamide gel electrophoresis on an ALF express sequencer. For linkage analysis, we studied the data with the use of 2 alternative statistical models. First, we considered only the PPH patients as affected. Second, we considered the PPH patients and all members with abnormal PASP response as affected. Multipoint logarithm of the odds (LOD) scores were calculated by using the program LINKAGE.18 LOD score calculations were performed with an age- and sex-dependent disease penetrance increasing from 10% within 10 years to 70% at age >60 years in men, according to Morse et al.4 The estimated PPH gene frequencies corresponded to a disease prevalence of 1/100 000.

Statistical Methods
Data are given as mean±SD values. All measurements of PASP were calculated as the means of 3 cardiac cycles. Comparisons between groups were analyzed by using the Mann-Whitney-Wilcoxon test. Linear regression analysis was used to correlate invasive and noninvasive PASP measurements. A probability value of P<0.05 was considered significant.

Results

Clinical Data

Study Population
Of 52 family members examined, 3 (mean age 58±13 years) were excluded from further clinical analysis because of elevated mean pulmonary artery wedge pressure (31±3 mm Hg) during exercise secondary to systemic hypertension (maximal systemic arterial systolic pressure 210±10 mm Hg). One member (A:III-18, from family A, shown in Figure 1a) had undergone surgery for an aortic isthmus stenosis in 1968. Four others were excluded because of inadequate Doppler signals during exercise. These 7 family members were assigned to an undefined status (Figure 1).

PPH Patients
Manifest PPH had been diagnosed previously in 4 living patients, aged 28 to 43 years, with a mean PASP of 73±16 mm Hg at rest. In family B, 2 sisters (B:III-2 and B:III-3), aged 28 and 19 years, with an end-stage disease had undergone double-lung transplantation.

Normal PASP Response to Exercise (NR Group)
In 27 members (normal response [NR] group), the PASP was within normal limits at rest (24±4 mm Hg) and during exercise (37±3 mm Hg, ∆PASP 12±2 mm Hg, Figure 2). The physical examination revealed that none of them had cardiopulmonary symptoms or abnormalities. Two had nonspecific ECG changes at rest unchanged during exercise. The results of chest x-ray, pulmonary function test, echocardiogram, and SE were all within normal limits. Right heart catheterization in 2 unaffected members revealed normal PAPs.

Abnormal PASP Response to Exercise (AR Group)
Fourteen members with normal PASP at rest revealed a pathological increase of PASP (>40 mm Hg) during supine bicycle exercise and were classified as the abnormal response (AR) group (Figures 1 and 2). Two of them revealed exertional dyspnea (New York Heart Association class II),
TABLE 2. Hemodynamic Data of Invasively Assessed Family Members

<table>
<thead>
<tr>
<th>Pedigree</th>
<th>Exercise Rest</th>
<th>Exercise Rest</th>
<th>Exercise Rest</th>
<th>PCWP, mm Hg</th>
<th>SASP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Workload, W</td>
<td>PASP, mm Hg</td>
<td>PASP, mm Hg</td>
<td>PASP, mm Hg</td>
<td>PASP, mm Hg</td>
</tr>
<tr>
<td></td>
<td>Rest Exercise</td>
<td>Rest Exercise</td>
<td>Rest Exercise</td>
<td>Rest Exercise</td>
<td>Rest Exercise</td>
</tr>
</tbody>
</table>

PPH

A:III-11 43 ... 80 ... 75 ... 20 ... 38 ... 8 120 ...
A:III-24 38 50 40 55 42 53 16 21 25 32 12 110 130
B:III-2 29 ... 67 ... 65 ... 36 ... 48 ... 11 110 ...
B:III-3 28 ... 61 ... 95 ... 61 ... 72 ... 6 120 ...
Mean ± SD 35 ± 7 62 ± 20 69 ± 22 33 ± 20 46 ± 20 9 ± 3 115 ± 6

AR members

A:II-23 65 100 25 54 25 52 12 26 16 35 10 130 200
A:III-2 51 100 28 48 29 50 10 28 16 35 10 128 140
A:III-4 49 75 19 56 15 45 8 26 10 31 18 120 140
A:III-7 47 200 17 49 15 38 8 25 10 29 12 130 200
A:III-14 41 100 22 50 21 42 8 22 12 29 8 120 160
A:III-28 36 150 23 68 20 58 7 12 11 27 9 120 160
B:III-1 34 125 21 67 19 73 4 18 11 36 10 120 180
Mean ± SD 46 ± 11 121 ± 42 22 ± 4 56 ± 8 21 ± 5 51 ± 12 8 ± 2 22 ± 6 13 ± 3 32 ± 4 11 ± 3 124 ± 5 169 ± 25

NR members

A:III-5 48 125 25 39 15 38 5 25 10 31 2 140 190
A:IV-5 17 150 32 39 17 40 5 11 10 21 3 130 170

Secondary PH

A:III-18 45 100 28 55 12 47 7 31 9 37 16 140 200
A:III-20 58 100 26 65 24 44 10 18 15 27 35 140 220
B:II-2 63 75 21 67 20 46 12 20 15 29 30 145 210
Mean 55 92 25 62 19 46 10 23 13 31 27 142 210

Workload indicates maximal supine bicycle exercise; PADP, pulmonary artery diastolic pressure; PAMP, pulmonary artery mean pressure; PCWP, pulmonary capillary wedge pressure; SAPS, systemic arterial systolic pressure; SADP, systemic arterial diastolic pressure; SAMP, systemic arterial mean pressure; RAP, right atrial pressure; SaO2, systemic arterial oxygen saturation; and PH, pulmonary hypertension.

Exercise Capacity

The AR and NR groups were similar in body weight, height, and exercise parameters (Table 1). The exercise capacity was similar in the AR and NR groups (107 ± 36 and 119 ± 41 W, respectively) and was within the normal range, considering the supine exercise position and the fact that 3 AR and 14 NR members were children aged 6 to 16 years. The mean age of the NR group (21 ± 13 years) was lower than that of the AR group (36.9 ± 20 years, P = 0.02). However, if the comparison of the AR and NR groups was restricted to members <40 years of age, the PASP differences were still significant, indicating that they were not age-related.

At rest, both groups had similar cardiac outputs, heart rates, and systemic blood pressures (Table 1). During exercise, the mean PASP increased to significantly higher levels in AR subjects (from 23 ± 4 to 56 ± 11 mm Hg, ΔPASP 32 ± 11 mm Hg) than in NR subjects (from 24 ± 4 to 37 ± 3, ΔPASP 13 ± 4 mm Hg; P < 0.001; Figure 2). Right heart catheterization was performed in all 4 PPH patients, in 3 members with secondary pulmonary hypertension, and in 2 NR and 7 AR members (Table 2). PASP at rest and during exercise estimated with SE correlated closely with the results obtained by right heart catheterization (at rest: n = 16, r = 0.95, P < 0.0001, and standard error of estimate [SEE] 5.3 mm Hg; during exercise: n = 13, r = 0.63, P = 0.019, and SEE 8.0 mm Hg; and overall: n = 29, r = 0.927, P < 0.0001, and SEE 7.0 mm Hg). In 27 of the NR and AR members, Doppler signals became inadequate at maximal workloads corresponding to a heart rate >135 bpm. Despite these technical limitations, both groups could be discriminated according to their PASP response at submaximal levels of exercise (50 to 125 W).

LV and RV Function at Rest and During Exercise

The 4 patients with PPH revealed dilated and impaired RV. All other examined family members had normal RV and right atrial diameters and normal RV and LV function at rest and during exercise. LV ejection fraction did not correlate with PASP at rest or during exercise. RV end-diastolic and
The 2 carriers (A:IV-14 and A:IV-25 [in carriers of the disease-associated haplotype was 82.4% (95% CI 87.2 to 100) and 87.5% sensitivity in identifying asymptomatic carriers with the PPH gene.

Discussion

The present study is the first report on a systematic clinical assessment of PAPs at rest and during exercise in members of families with PPH. Our results indicate that asymptomatic gene carriers can be identified clinically by their pathological pulmonary artery response to exercise with high specificity and sensitivity.

Although there are few studies involving the normal limits of PAP in healthy individuals, previous invasive15,16,19 and noninvasive12,20 studies have shown that at sea level in normoxia, PASP does not exceed 40 mm Hg in normal subjects even during heavy exercise, with the exception of some extremely well-trained individuals during a workload of 300 W and an increase of cardiac output of >25 to 30 L/min.21,22 In 14 members of the 2 families, a pathological rise of PASP during normoxic supine bicycle exercise was documented by continuous-wave Doppler at a workload of 50 to 150 W. In all 14 AR members, secondary causes of pulmonary hypertension could be excluded. The values obtained by continuous-wave Doppler correlated closely with the PAPs measured invasively. Although all 14 members were carriers of the disease haplotype, only 3 had nonspecific symptoms. The factors that may trigger symptomatic pulmonary hypertension in asymptomatic carriers are unknown. Only further follow-up studies can clarify at what stage of the disease these findings occur and whether the findings represent susceptibility or an early stage of PPH. These studies

TABLE 2. Continued

<table>
<thead>
<tr>
<th>SADP, mm Hg</th>
<th>SAMP, mm Hg</th>
<th>RAP, mm Hg</th>
<th>SaO2, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>Exercise</td>
<td>Rest</td>
<td>Exercise</td>
</tr>
<tr>
<td>90</td>
<td>100</td>
<td>7</td>
<td>...</td>
</tr>
<tr>
<td>60</td>
<td>80</td>
<td>77</td>
<td>97</td>
</tr>
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<td>80</td>
<td>...</td>
<td>90</td>
<td>...</td>
</tr>
<tr>
<td>70</td>
<td>...</td>
<td>87</td>
<td>...</td>
</tr>
<tr>
<td>75 ± 13</td>
<td>88 ± 10</td>
<td>10 ± 4</td>
<td></td>
</tr>
</tbody>
</table>

End-systolic areas were normal in all AR and NR subjects and did not change significantly during exercise (Table 3).

Genetic Studies

Pedigree analysis indicated an autosomal-dominant mode of inheritance with incomplete penetrance in both families. Positive LOD scores for linkage between manifest PPH and chromosome 2q31-32 markers were found in families A and B (LOD score 0.83 at D2S364). Although not significant in itself, this score indicated cosegregation of PPH with the disease locus mapped by Morse et al8 and Nichols et al9 and adds to the evidence for linkage. A disease haplotype was identified in all 4 PPH-patients, in all 14 AR members, in 2 NR subjects, and in 2 members with unknown disease status due to inadequate Doppler signals (Figure 1). If the AR members were considered to be affected, the multipoint LOD score increased to 4.4 at a locus 2.5 cM proximal to D2S364 and 1.5 cM distal to CHRNA1. If PASP of 40 mm Hg was used as a cutoff level, the sensitivity of SE for identifying the carriers of the disease-associated haplotype was 82.4% (95% CI 68.3 to 98.8). The 2 carriers (A:IV-14 and A:IV-25 [in family A]) that showed a normal PASP response to exercise

were 11 and 17 years old, respectively. In family A, PASP increased from 21 to 37 mm Hg in one member (A:IV-14) and from 19 to 38 mm Hg in another (A:IV-25). Because we could not attribute their unaffected disease status to recombination events, a reduced penetrance of the AR trait at young ages appears to be the best explanation for the incomplete sensitivity of carrier identification by SE. Within this study population, SE had a 100% specificity (95% CI 87.2 to 100) and 87.5% sensitivity in identifying asymptomatic carriers with the PPH gene.

TABLE 3. Changes in LV and RV Areas and LVEF During Exercise

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Maximal Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR members</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDA, cm²</td>
<td>32±5</td>
<td>31±5</td>
</tr>
<tr>
<td>LVESA, cm²</td>
<td>16±4</td>
<td>12±3</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>69±8</td>
<td>78±6</td>
</tr>
<tr>
<td>RVEDA, cm²</td>
<td>13±2</td>
<td>12±2</td>
</tr>
<tr>
<td>RVESA, cm²</td>
<td>6±1</td>
<td>4±1</td>
</tr>
<tr>
<td>NR members</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDA, cm²</td>
<td>28±7</td>
<td>28±8</td>
</tr>
<tr>
<td>LVESA, cm²</td>
<td>13±4</td>
<td>11±3</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>68±5</td>
<td>77±5</td>
</tr>
<tr>
<td>RVEDA, cm²</td>
<td>13±4</td>
<td>13±5</td>
</tr>
<tr>
<td>RVESA, cm²</td>
<td>6±2</td>
<td>5±3</td>
</tr>
</tbody>
</table>

Values are mean±SD. LVEDA indicates LV end-diastolic area; LVESA, LV end-systolic area; LVEF, LV ejection fraction; RVEDA, RV end-diastolic area; and RVESA, RV end-systolic area. P=NS for AR vs NR.
may also evaluate the factors underlying manifestation of the disease.

Whether early diagnosis will allow an increased number of patients to be effectively treated with simpler therapeutic interventions, such as chronic oral calcium channel blockade as opposed to continuous prostanoïd therapy, remains unknown. SE may allow the noninvasive investigation of such a question.

Our molecular genetic analysis provides evidence that manifest PPH and abnormal PASP response to exercise are inherited as a dominant trait, localized on chromosome 2q31-32. The lack of evidence for genetic heterogeneity in the linkage analyses reported so far suggests that a single major gene may account for all cases of familial PPH. The gene defect was nonpenetrant with respect to the AR trait in 2 members (A:IV-14 and A:IV-25), aged 11 and 17 years. This was expected in light of the previously documented low penetrance for PPH at young ages. In contrast, Loyd et al have reported genetic anticipation, with this disease being more manifest at younger ages. Therefore, these carriers might have been missed clinically with the use of noninvasive estimation of PASP. On the other hand, all AR members shared the disease haplotype with the 4 PPH patients. Therefore, the pathological PASP response to exercise in members of PPH families may be one of the first clinical manifestations of PPH and may indicate carriers of the PPH gene. Relaying this information to family members is a very delicate issue. Family assessment and genetic counseling should be performed only in conjunction with an experienced counselor as well as with the pulmonary hypertension medical team and other family members involved. The risks of exercise testing in family members of PPH patients, despite being very low, necessitate that during performance of the exercise test, all members will be carefully monitored by an experienced team including either 2 physicians or 1 physician and a nurse.

Identification of susceptibility to PPH by estimation of a pathological pulmonary artery response to exercise and by molecular genetic analysis opens new insights into the natural course of the disease and may lead to an earlier treatment. It may also improve the possibility of linkage analysis, even in small families. Further molecular genetic analysis of additional families may help to narrow the identified genetic region on chromosome 2q31-32. SE during supine bicycle exercise may be a useful screening method to identify members with pathological PASP response in families with PPH. Therefore, SE should be offered at least to all first-degree family members of PPH patients even if they reveal normal resting PASP.

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References
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