Primary Pulmonary Hypertension in Children: Clinical Characterization and Survival

JULIO SANDOVAL, MD, FACC, OTTO BAUERLE, MD, ARTURO GOMEZ, MD, ANDRES PALOMAR, MD, MARIA LUISA MARTINEZ GUERRA, MD, MARIA ELENA FURUYA, MD

Mexico City, Mexico

Objectives. This study characterized mortality in a group of Mexican children (n = 18, mean ±SD age 9.9 ± 3 years) with primary pulmonary hypertension and investigated the factors associated with their survival.

Background. Primary pulmonary hypertension is a progressive, fatal disease of unknown cause. Establishing the diagnosis earlier in life may influence prognosis.

Methods. A dynamic cohort of children with primary pulmonary hypertension were enrolled between December 1977 and May 1991 and followed up through September 1992. Measurements included hemodynamic and pulmonary function variables in addition to demographic data, medical history and response to vasodilator treatment. We also compared the survival estimates of these children with those of our adult patients with primary pulmonary hypertension (n = 42, mean age 27.9 ± 8.5 years).

Results. Baseline mean (±SD) pulmonary artery pressure was similar in children and adults (66 ± 15 vs. 65 ± 18 mm Hg, p = NS), but a higher cardiac index resulted in a lower mean pulmonary vascular resistance index in children (18 ± 7 vs. 26 ± 12 U/m², p < 0.01). The proportion of patients who had a positive hemodynamic response to vasodilator treatment was higher in children than in adults (41% vs. 25%). Estimated median survival in children was 4.12 years (95% confidence interval [CI] 0.75 to 8.66) and 3.12 years in adults (95% CI 0.5 to 13.25, chi-square log-rank 0.81, p = NS). Elevated right atrial pressure (rate ratio 10.2) and decreased stroke volume index (rate ratio 32.9) were the only significant predictors of mortality (Cox proportional hazards model).

Conclusions. Children with primary pulmonary hypertension have a poor survival expectancy, which does not appear to differ from that in adults with primary pulmonary hypertension. Mortality in childhood primary pulmonary hypertension is also associated with variables that assess right ventricular dysfunction.

(J Am Coll Cardiol 1995;25:466-74)
Methods

Patients. The study series included 18 children <16 years of age (range 4 to 15) in whom primary pulmonary hypertension was diagnosed at our institution between December 1977 and May 1991 and who were followed up through September 1992. These patients are among the 61 who comprise the institutional registry for primary pulmonary hypertension (13). The diagnostic as well as therapeutic approach in these patients has followed strict clinical and hemodynamic criteria that have remained basically unchanged over the years. As in other studies (3,4,8), every patient has had a thorough workup, including clinical history and physical examination, laboratory tests, chest roentgenography, electrocardiography, pulmonary function tests when feasible, echocardiography, radionuclide perfusion lung scan and cardiac catheterization. All procedures were approved by our local committee for clinical investigation. They were explained to the parents of the children, and their written consent was obtained.

Criteria used to establish the diagnosis of primary pulmonary hypertension included the presence of elevated mean pulmonary artery pressure (Ppa) >22 mm Hg at rest, a normal pulmonary capillary wedge pressure when measurable and the absence of other diseases known to cause or to be associated with secondary pulmonary hypertension (3,4,8). Particular care was taken to exclude patients with evidence of congenital heart disease or acquired valvular or myocardial disease; obstructive or restrictive lung disease, or both; parasitic disease involving the lungs; pulmonary thromboembolic and clearly defined collagen vascular disease; and the antiphospholipid syndrome. Also, the patients were not in the age range for, nor did they have any evidence of, persistent pulmonary hypertension of the newborn (17).

Hemodynamic measurements. Our procedure for cardiac catheterization at rest has been described elsewhere (18,19). In brief, cardiac output was measured in triplicate by the thermodilution method, and pressures were obtained by a Swan-Ganz catheter positioned in the main trunk of the pulmonary artery. This catheter was also used for sampling mixed venous oxygen tension. In most patients, the brachial artery was also cannulated with a Coumad-Potts needle for systemic pressure recording and arterial blood sampling. Standard formulas were used to calculate cardiac index, stroke volume index, pulmonary vascular resistance index and systemic resistance. We also calculated the pulmonary/systemic vascular resistance ratio.

Vasodilator drug testing and long-term treatment. Most patients in this study had at least one short-term trial with a vasodilator, and many of them are still under treatment with these agents. Before testing, we tried to ensure steady state by waiting ~15 min to obtain baseline hemodynamic values. Afterward, the hemodynamic response to 100% oxygen breathing was evaluated in most of the patients. The protocol for vasodilator testing has remained basically unchanged, but the selected vasodilator drug for short-term challenge has changed over the years. We have used the following drugs: isoproterenol (3 to 5 µg) infused into the pulmonary artery for 1 min (19); hydralazine (0.33 mg/kg body weight infused into the pulmonary artery over 3 min (18); and nifedipine (10 to 20 mg) administrated sublingually (20). On the basis of hemodynamic response to the short-term vasodilator trial, we classified the patients into two groups: responders and nonresponders. The criteria for a favorable response to vasodilator treatment included 1) a significant decrease in mean pulmonary artery pressure or pulmonary vascular resistance index (>20% from baseline); 2) a predominant pulmonary vasodilatory response, as assessed by the decrease in the pulmonary/systemic vascular resistance ratio; and 3) absence of a deleterious effect on pulmonary gas exchange. Only when these three criteria were met was the patient considered for vasodilator drug treatment. In most patients the response to oral medication was evaluated on the ward and reassessed again 1 week later. After evaluation of a satisfactory immediate and short-term response, the patient was considered for long-term vasodilator treatment.

Other therapeutic measures. Routine anticoagulation was not used in our patients until recently. Digitalis was only occasionally used, and mild diuretic therapy was utilized for the treatment of symptomatic right-sided cardiac failure.

Statistical analysis. 1) We analyzed the clinical and hemodynamic characteristics of our patients at entry for the whole group (n = 18) and separately in those patients with (n = 10) and without (n = 8) long-term vasodilator treatment. 2) For survival analysis we used the initial diagnostic catheterization as an index for determining survival. The Kaplan-Meier method was used to estimate overall survival distribution. Univariate analysis based on the Cox proportional hazards model (22-24) was used to examine the relation between survival and selected demographic, medical history, pulmonary function, laboratory and hemodynamic variables measured at initial catheterization. Results are expressed as rate ratio with 95% confidence interval. Multivariate analysis based on the Cox proportional hazards regression analysis was used to examine the adjusted independent effect on survival of each variable, controlling for possible confounders (23,24). For both survival analysis and Cox proportional hazards models we used STATA software (22). 3) We compared the clinical, functional, hemodynamic and survival results for patients <16 years old with primary pulmonary hypertension with those found in our adult patients (n = 42, mean age 27.9 ± 8.5 years) with primary pulmonary hypertension (13).

For all other statistical analyses we used paired and unpaired t tests and linear regression. Results are expressed as mean value ± 1 SD. A p value < 0.05 was significant in all comparative analysis.

Results

Demographic characteristics. All 18 patients are Hispanic (mean [±SD] age 9.9 ± 3 years, range: 4 to 15; 11 girls, 7 boys, female/male ratio 1.6:1), and 11 of the 18 were born and raised in Mexico City and are current residents there (2,240 m above
ponent of the second heart sound (P2) was reported in all
Association functional class I, 33.3% in class II, 38.8% in class
pulmonary hypertension. An increase in the pulmonary com-
syncope or near syncope in 61% and chest pain in 5.5%.
patients, and in 2 (11%) of the 18 patients, generalized seizures
were part of the presenting symptoms. None of the patients
reported symptoms of Raynaud's phenomena. Mean time from
onset of the first symptom to diagnosis of primary pulmonary
hypertension was 2.06 ± 1.93 years (range 0 to 8.2). At
diagnosis 5.5% of the patients were in New York Heart
Association functional class I, 33.3% in class II, 38.8% in class
III and 22.2% in class IV.

Physical findings in the patients with primary pulmonary hypertension were those usually found in any patient with
pulmonary hypertension. An increase in the pulmonary com-
ponent of the second heart sound (P2) was reported in all
patients. A soft systolic pulmonary murmur was found in 33%
patients (11%) had a history of familial pulmonary hyperten-
sea level). The other seven patients are from different parts of
Mexico.

Medical and family history. None of the patients had a
history of appetite suppressant or hormonal drug use. Two
patients (11%) had a history of familial pulmonary hyperten-
sion. One of the two was diagnosed as asymptomatic during the
routine family screening study that all patients underwent.

Symptoms and physical findings. The frequency of symp-
toms at diagnosis (initial catheterization) was dyspnea in 94%,
synecope or near syncope in 61% and chest pain in 5.5%.
Effort-related palpitations and cyanosis were present in 50% and
33%, respectively. Leg edema was reported by 11% of the
patients, and in 2 (11%) of the 18 patients, generalized seizures
were part of the presenting symptoms. None of the patients
reported symptoms of Raynaud's phenomena. Mean time from
onset of the first symptom to diagnosis of primary pulmonary
hypertension was 2.06 ± 1.93 years (range 0 to 8.2). At
diagnosis 5.5% of the patients were in New York Heart
Association functional class I, 33.3% in class II, 38.8% in class
III and 22.2% in class IV.

Physical findings in the patients with primary pulmonary hypertension were those usually found in any patient with
pulmonary hypertension. An increase in the pulmonary com-
ponent of the second heart sound (P2) was reported in all
patients. A soft systolic pulmonary murmur was found in 33%
of patients, tricuspid regurgitation in 28%, pulmonic insuf-
ciency in 11%, cyanosis in 33% and peripheral edema in 16.5%.

Laboratory findings. The chest roentgenogram showed the
typical changes associated with pulmonary hypertension,
namely prominence of the main pulmonary artery in all patients and enlarged hilar vessels in most. Mean diameter of the
right main pulmonary artery at the parsinterlobaris was
14.2 ± 2.48 mm (normal <16 mm), and the mean pulmonary
lobe diameter/maximal transverse diameter of the thorax index
was 42 ± 12.3 (normal <38) (3.25,26). Mean cardiothoracic
index of the group was 55 ± 7 and was >0.5 in 66.6% of the
patients. The electrocardiogram showed sinus rhythm and evidence of right ventricular hypertrophy in all patients. Signs
of right ventricular strain (i.e., T wave inversion with or
without ST segment depression in the right precordial leads)
were present in 78% of patients (3.27). The echocardiogram
confirmed right ventricular hypertrophy and showed variable
degrees of right ventricular enlargement (3). A lung perfusion
scan was obtained in 13 patients and findings were considered
completely normal in 8 (61.5%). In three patients (23%), the
lung perfusion scan findings were characterized as abnormal
and were described as a diffuse bilateral patchy pattern (21). In
the remaining two patients (15.4%), the distinction between a
normal and an abnormal patchy pattern was not possible;
however, in none of the studies there was evidence for lobar
or single segmental defect. Results of an antinuclear antibody test
were negative in all patients. Mean hemoglobin level of the
group was 15.3 ± 1.5 g, and total platelet count was normal.

Pulmonary function. Pulmonary function tests could be
performed in 11 patients (mean age 11 ± 2.7 years). Mean
values of selected variables are presented in Table 1. Mild
pulmonary restriction as assessed by the decrease in both vital
capacity and total lung capacity was present in 33% of patients.
There was no evidence for airway obstruction. Mild to
critical hypoxemia was present in 40% of patients, and hypocap-
nia with normal pH was present in all. Normal values for
Mexico City are arterial oxygen tension 67.5 ± 2.5 mm Hg and
arterial carbon dioxide tension 35 ± 2.5 mm Hg (28). The
arterial oxygen tension correlated significantly with the mixed
venous oxygen tension (r = 0.58, p < 0.05). Dead space as well
as total shunt were only slightly increased in most of the
patients. Diffusing capacity for carbon monoxide was not
measured.

Hemodynamic findings. In Table 1 selected hemodynamic
variables in children with primary pulmonary hypertension at
the time of initial diagnostic catheterization are summarized
and compared with those in the adult group. Children with
primary pulmonary hypertension had severe pulmonary arte-
rerial hypertension, with a threefold increase in mean pulmonary
pressure (66 ± 15 mm Hg, range 36 to 89), a mild elevation in
eight atrial pressure (5.4 ± 2 mm Hg, range 1 to 9.5) and right
ventricular end-diastolic pressure (7.6 ± 4 mm Hg, range 1 to
15.6), a normal pulmonary capillary wedge pressure and a
mildly reduced to normal cardiac index (4.1 ± 1.5 liters/min
per m², range 1.9 to 8.37). Calculated pulmonary vascular
resistance index was 18.4 ± 7 U/m². Mean pulmonary/systemic
vascular resistance ratio for the whole group was 0.91 ± 0.21.

Patients with more severe symptoms (functional class III or
IV) had a higher right ventricular end-diastolic pressure than
did their less symptomatic counterparts (functional class I or
II) (9.1 ± 3.9 vs. 5.45 ± 3.8 mm Hg, respectively, p < 0.05).
There was no correlation between the hemodynamic values
and duration of symptoms before diagnosis. As noted in Table
1, except for mean pulmonary artery pressure and pulmonary/
systemic vascular resistance ratio, hemodynamic variables in
children with primary pulmonary hypertension were signifi-
cantly different from those in the adult group, and the children
had significantly lower right atrial pressure and right ventricular end-
diastolic pressures and a higher cardiac index than their
counterparts in the adult group. Pulmonary vascular resistance
index was not modified by oxygen breathing in the group as a
whole (22.6 ± 2.76 U/m² before vs. 22.87 ± 2.53 U/m² after,
p = NS).

Immediate hemodynamic response to vasodilator drugs.
The hemodynamic response to the short-term administration
of vasodilators could be assessed in 17 of the patients (Table
2). Seven of the 17 patients did not respond to vasodilator
therapy (nonresponders). In these patients, neither pulmonary
artery pressure nor pulmonary vascular resistance index were
decreased by administration of the drug. Nonresponder chil-
don's had a significantly higher baseline pulmonary artery
pressure than did their counterpart responder children (74.3 ±
15 vs. 57.9 ± 13.3 mm Hg, respectively). There were no
differences in cardiac index and right atrial pressure. Of the
responders (n = 10), seven patients (Patients 4, 18, 21, 42, 45,
56 and 57) had an immediate and significant decrease (>20%)
Table 1. Pulmonary Function Variables and Hemodynamic Findings at Study Entry

<table>
<thead>
<tr>
<th>Pulmonary function</th>
<th>Children</th>
<th>Adults</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC (% of predicted)</td>
<td>98 ± 23</td>
<td>92 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>FVC (% of predicted)</td>
<td>89.9 ± 30.7</td>
<td>85.4 ± 7.7</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1 (% of predicted)</td>
<td>103.5 ± 24.1</td>
<td>85 ± 18</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>FEF25-75 (% of predicted)</td>
<td>59.8 ± 30.3</td>
<td>89 ± 25</td>
<td>NS</td>
</tr>
<tr>
<td>PaO2 (mm Hg)*</td>
<td>65.4 ± 5.0</td>
<td>62.3 ± 8.0</td>
<td>NS</td>
</tr>
<tr>
<td>PacO2 (mm Hg)†</td>
<td>26.8 ± 3.6</td>
<td>27.1 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial pH§</td>
<td>7.42 ± 0.04</td>
<td>7.44 ± 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Vd/Vt (%)</td>
<td>0.42 ± 0.08</td>
<td>0.42 ± 0.09</td>
<td>NS</td>
</tr>
<tr>
<td>Qs/Qt (%)</td>
<td>7.7 ± 2.3</td>
<td>8.9 ± 3.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemodynamic variables</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>98 ± 16</td>
<td>81 ± 14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>5.4 ± 2</td>
<td>7.7 ± 4.9</td>
<td>0.01</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td>7.6 ± 4.0</td>
<td>11.2 ± 6.0</td>
<td>0.03</td>
</tr>
<tr>
<td>PAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>94 ± 20</td>
<td>97 ± 28</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>46 ± 11</td>
<td>47 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (mm Hg)</td>
<td>66 ± 15</td>
<td>65 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>5.7 ± 4.4</td>
<td>9 ± 5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>77 ± 10</td>
<td>83 ± 17</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>CI (liters/min per m²)</td>
<td>4.1 ± 1.52</td>
<td>2.75 ± 0.97</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>PVO2 (mm Hg)</td>
<td>34 ± 4</td>
<td>32 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>PVRI (U/m²)</td>
<td>16.4 ± 7.06</td>
<td>25.9 ± 12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Rp/Rs</td>
<td>0.9 ± 0.21</td>
<td>0.79 ± 0.29</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Normal values for Mexico City 67.5 ± 2.5 mm Hg (28). †Normal values for Mexico City 7.33 ± 2.5 mm Hg (28). §Normal values for Mexico City 7.33 to 7.43 (28). Data presented are mean value ±SD or number of patients. CI = cardiac index; FEF25-75 = maximal midexpiratory flow; FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity; HR = heart rate; PacO2 = arterial carbon dioxide pressure; Pao2 = arterial oxygen pressure; PAP (SAP) = pulmonary artery (systemic arterial) pressure; PCWP = pulmonary capillary wedge pressure; PVO2 = mixed venous oxygen pressure; PVRI = pulmonary vascular resistance index; Qs/Qt = intrapulmonary shunt; RAP = right atrial pressure; Rp/Rs = pulmonary/systemic resistance ratio; RVEDP = right ventricular end-diastolic pressure; TLC = total lung capacity; Vd/Vt = physiologic dead space.

in both pulmonary artery pressure and pulmonary vascular resistance index after administration of the drug. The proportion of patients with this response was higher in children (7 [58%] of 12) than in adults (8 [25%] of 31) with primary pulmonary hypertension. In the remaining three patients (Patients 15, 24 and 46), the response was characterized by a significant decrease in pulmonary vascular resistance index only (i.e., increase in cardiac index, but no change in pulmonary artery pressure). We found no significant correlation between age and the immediate response to the vasodilator, as assessed by change in pulmonary artery pressure (r = -0.25, p = NS) or change in pulmonary vascular resistance index (r = -0.26, p = NS), or both, but the decrease in both pulmonary artery pressure and pulmonary vascular resistance index in response to the vasodilator was more frequent (40%) in children <10 years old than in those >10 years old (28.5%).

Treatment with vasodilator drugs. On the basis of the results of the short-term vasodilator trial, patients with a beneficial hemodynamic response (n = 10) received long-term vasodilator treatment (nifedipine in 9, hydralazine in 1). Eight of the 18 patients had no vasodilator treatment. This group includes the seven nonresponder patients and one patient who did not undergo a short-term vasodilator trial. Among the patients with treatment, four died, and one was lost to follow-up. At present, four (80%) of the five remaining treated patients receive nifedipine (mean daily dose 40 mg), and one patient still receives hydralazine (after 13 years). The long-term hemodynamic status of patients with vasodilator treatment was assessed by repeated catheterization, and these results are also shown in Table 2. Only patients with a significant decrease in pulmonary artery pressure and pulmonary vascular resistance index in the short-term trial (Patients 4, 18, 21 and 56) did these variables remain lower than originally calculated (at baseline).

Survival. By September 1992, 5 of the 18 patients with primary pulmonary hypertension had died, and none of these 5 survived >5 years (mean survival time 29.2 months). Right heart failure either alone or combined with other events (discontinuation of treatment in n = 1, cardiac catheterization in n = 2) was the cause of death in all patients. Postmortem findings were available in two of these patients. Both had marked enlargement and hypertrophy of the right side of the heart, and there was great dilation of the pulmonary artery and its branches in the lungs, together with lipid deposits. Microscopic examination of pulmonary arterioles showed medial hypertrophy and well marked intimal proliferation that...
Table 2. Baseline Values and Immediate and Late Effects of Vasodilator Therapy on Mean Hemodynamic Variables in Patients With Primary Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Pt No./ Gender</th>
<th>Age (yr)</th>
<th>PAP (mm Hg)</th>
<th>CI (lites/min per m²)</th>
<th>PVRI (U/m')</th>
<th>PAP (mm Hg)</th>
<th>CI (lites/min per m²)</th>
<th>PVRI (U/m')</th>
<th>Time (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/M</td>
<td>15</td>
<td>48</td>
<td>4.4</td>
<td>11</td>
<td>17</td>
<td>4.0</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>16/M</td>
<td>15</td>
<td>46</td>
<td>7.8</td>
<td>11</td>
<td>34</td>
<td>4.5</td>
<td>7.6</td>
<td>54</td>
</tr>
<tr>
<td>18/F</td>
<td>9</td>
<td>57</td>
<td>2.2</td>
<td>26</td>
<td>31</td>
<td>2.2</td>
<td>14</td>
<td>54</td>
</tr>
<tr>
<td>21/F</td>
<td>10</td>
<td>62</td>
<td>5.3</td>
<td>12</td>
<td>40</td>
<td>6.4</td>
<td>6</td>
<td>53</td>
</tr>
<tr>
<td>46/M</td>
<td>15</td>
<td>80</td>
<td>1.2</td>
<td>25</td>
<td>81</td>
<td>4.7</td>
<td>17</td>
<td>71</td>
</tr>
<tr>
<td>56/F</td>
<td>8</td>
<td>72</td>
<td>2.8</td>
<td>25</td>
<td>35</td>
<td>4.0</td>
<td>9</td>
<td>45</td>
</tr>
<tr>
<td>24/F</td>
<td>10</td>
<td>42</td>
<td>4.7</td>
<td>9</td>
<td>37</td>
<td>5.9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>42/F</td>
<td>8</td>
<td>57.5</td>
<td>3.2</td>
<td>18</td>
<td>46</td>
<td>4.9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>45/F</td>
<td>7</td>
<td>67</td>
<td>5.6</td>
<td>12</td>
<td>53</td>
<td>6.0</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>57/F</td>
<td>11</td>
<td>57.5</td>
<td>2.5</td>
<td>23</td>
<td>29</td>
<td>3.5</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R-LT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>±SD</td>
</tr>
<tr>
<td>R.1</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>±SD</td>
</tr>
<tr>
<td>NR</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>±SD</td>
</tr>
</tbody>
</table>

*p < 0.05 different from baseline values by paired t test; tp < 0.05 different from responders by unpaired t test. F = female; M = male; NR = nonresponders; Pt = patient; R-I = responders, immediate response; R-LT = responders, long-term response; other abbreviations as in Table 1.

significantly narrowed the vessel lumen. No plexiform lesions were identified, and no thromboemboli were found in the large or small pulmonary arteries on careful examination. The main pulmonary artery showed fewer, shorter and more irregular elastic fibers than the aorta, indicating that pulmonary hypertension was acquired after birth.

Summary statistics on survival and length of follow-up for the 18 evaluable patients are shown in Figure 1. Two (11%) of the 18 patients were followed up <1 year, 16 (88.8%) for at least 1 year, 12 (66.6%) for at least 2 years, 11 (61.1%) for at least 3 years, 11 (61.1%) for at least 4 years and 7 (38.8%) for at least 5 years. Four patients were lost to follow-up at different times. Median survival for the children with primary pulmonary hypertension was 4.12 years (range 4 months to 14.6 years, 95% confidence interval [CI] 0.75 to 8.66), not statistically different from the 3.12-year median survival for adults with primary pulmonary hypertension (range 1 month to 15.2 years, 95% CI 0.5 to 13.25, chi-square log-rank 0.81, p = NS) (Fig. 1).

As previously mentioned, 10 patients (55.5%) had long-term vasodilator therapy after discharge. We compared survival times for patients receiving vasodilator drug therapy at discharge with those of patients not receiving such therapy. Median survival time was 4.41 years (range 0.33 to 8.66, 95% CI 0.75 to 7.33) for those without vasodilator treatment at discharge and 4.04 years (range 1.33 to 14.66, 95% CI 1.33 to 8.41) for those with vasodilator treatment (chi-square log-rank 0.39, p = NS).

Seven (38.8%) of the 18 patients survived >5 years (mean survival 94.8 ± 36.9 months), and 5 (27.7%) died (mean survival 29.2 ± 16.4 months). There were significant differences (p < 0.05, respectively, in baseline right ventricular end-diastolic pressure (6.25 ± 3.52 vs. 11.8 ± 3.03 mm Hg), cardiac index (5.40 ± 1.3 vs. 3.04 ± 0.55 liter/min per m²), mixed venous oxygen tension (35.2 ± 2.0 vs. 30.5 ± 4.5 mm Hg), pulmonary vascular resistance index (12.5 ± 4.3 vs. 21 ± 4.4 U/m'), and stroke volume index (52.9 ± 7.58 vs. 34.8 ± 10.6 ml/beat per m²) between the two groups.
Factors associated with survival in univariate and multivariate analysis. Univariate analysis of the relation between mortality and variables measured at entry (initial catheterization) are shown in Table 3. Mortality was not associated with age at diagnosis, family history of primary pulmonary hypertension, Raynaud’s phenomenon or syncope or with the apparent duration of symptoms before diagnosis. Likewise, pulmonary function tests were not predictive of survival. However, functional class III or IV (rate ratio 2.3) and clinical evidence of systemic venous congestion (rate ratio 3.0), favorable hemodynamic response to vasodilators (rate ratio 0.34) and decreased mixed venous oxygen tension (rate ratio 7.62) all were associated with a poor survival, whereas female gender (rate ratio 0.44) had a protective effect against such a risk.

Of the hemodynamic variables at diagnosis, mean systemic and mean pulmonary artery pressures and the pulmonary/systemic vascular resistance ratio did not affect survival. However, increased right atrial pressure (rate ratio 8.41), increased right ventricular end-diastolic pressure (rate ratio 5.10), decreased cardiac index (rate ratio 3.35) and decreased mixed venous oxygen tension (rate ratio 7.62) all were associated with an increased risk of death. Likewise, variables derived from these measured hemodynamic variables, such as increased pulmonary vascular resistance index and decreased stroke volume index, were also associated with mortality. Even though all of these variables were associated with a poor survival, right atrial pressure was the only statistically significant predictor of mortality. For illustration, the Kaplan-Meier survival curve for patients with primary pulmonary hypertension according to right atrial pressure (<7.5 mm Hg and >7.5 mm Hg) is shown in Figure 2.

After completion of univariate analysis, any variable that was p < 0.25 (Table 3) was considered a candidate for the multivariate model because the use of a more traditional p value (e.g., p = 0.05) often fails to identify variables known to be important (23,24). When each of these variables was adjusted for age and gender, only decreased stroke volume index (rate ratio 32.9, 95% CI 1.02 to 1058, p < 0.04) and increased right atrial pressure (rate ratio 10.2, 95% CI 0.96 to 108.2, p < 0.053) were associated with an increased risk of death. Compared with the variable of vasodilator treatment, these two hemodynamic variables were still associated with mortality; however, the 95% confidence intervals go up to 1.0 (p = NS) (Table 4).

Discussion

Primary pulmonary hypertension is widely recognized as a disease of young people (3,29,30), with certain features of the disease differing before and after puberty (31). However, very little information exists regarding clinical characterization, natural history, response to treatment and survival in the pediatric population (32-36). This relative lack of knowledge is partly due to the fact that primary pulmonary hypertension is itself a relatively uncommon disease and has its highest frequency beyond the pediatric age (3,4,7,8,13,29,35).

The 18 patients discussed here represent a dynamic cohort of children with primary pulmonary hypertension in whom the diagnostic and therapeutic criteria, as well as the follow-up approach, were applied in all patients by the same group of investigators. In contrast to other clinical studies of primary pulmonary hypertension in children (33,34), the age range in our study was limited to the pediatric and puberty periods only.

Table 3. Univariate Analysis Relating Survival Time With Selected Baseline Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic and historical data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.09 (0.78–1.53)</td>
<td>0.30</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.30 (0.44–2.09)</td>
<td>0.21</td>
</tr>
<tr>
<td>NYHA functional class III or IV</td>
<td>2.30 (0.21–24.4)</td>
<td>0.46</td>
</tr>
<tr>
<td>Systemic venous congestion</td>
<td>3.84 (0.55–26.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>Acute response to vasodilator</td>
<td>0.34 (0.03–3.75)</td>
<td>0.36</td>
</tr>
<tr>
<td>Vasodilator treatment</td>
<td>0.32 (0.03–3.47)</td>
<td>0.33</td>
</tr>
<tr>
<td>Pulmonary function tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>0.94 (0.04–22.5)</td>
<td>0.95</td>
</tr>
<tr>
<td>FEV1</td>
<td>1.46 (16–16)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hemodynamic variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (&gt;87 beats/min)</td>
<td>0.41 (0.06–3.10)</td>
<td>0.39</td>
</tr>
<tr>
<td>RAP (&gt;7.4 mm Hg)</td>
<td>5.41 (0.99–71.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>RVEDP (&gt;10.4 mm Hg)</td>
<td>5.10 (0.73–35.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>PAP (&gt;65.8 mm Hg)</td>
<td>1.28 (0.18–8.84)</td>
<td>0.78</td>
</tr>
<tr>
<td>SAP (&lt;80 mm Hg)</td>
<td>0.88 (0.10–7.67)</td>
<td>0.90</td>
</tr>
<tr>
<td>CI (&lt;3 liters/min per m²)</td>
<td>3.35 (0.47–23.9)</td>
<td>0.21</td>
</tr>
<tr>
<td>PVRI (&gt;24.3 U/m²)</td>
<td>2.17 (0.30–15.6)</td>
<td>0.41</td>
</tr>
<tr>
<td>SVRI (&gt;29.7 U/m²)</td>
<td>2.30 (0.19–27.7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Rvi/Rs (&gt;0.89)</td>
<td>1.65 (0.23–11.6)</td>
<td>0.59</td>
</tr>
<tr>
<td>SV1 (&lt;37.5 ml/beat per m²)</td>
<td>0.80 (0.59–97.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>Gas exchange</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2 (&lt;55 mm Hg)</td>
<td>1.35 (0.11–16.5)</td>
<td>0.79</td>
</tr>
<tr>
<td>PaCO2 (&lt;31.4 mm Hg)</td>
<td>7.62 (0.84–68.5)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

CI = confidence interval; NYHA = New York Heart Association; SVRI = systemic vascular resistance index; other abbreviations as in Table 1.
Data from patients with persistent pulmonary hypertension of the newborn (17) and those from young adults with primary pulmonary hypertension were excluded. The present study was performed at an altitude of 2,240 m and included both patients who were born and raised at this altitude as well as those from lower altitudes or even sea level. Accordingly, the separate effect of relative acute and chronic altitude hypoxia on pulmonary hemodynamic variables has to be considered. The lack of hemodynamic response to oxygen breathing that we observed tends to support the idea that relative alveolar hypoxia at this altitude does not make our patients clinically different from those who have the disease elsewhere (13,18). Moreover, in the National Institutes of Health Registry on primary pulmonary hypertension (6), neither survival rate nor clinical variables nor hemodynamic variables in patients with primary pulmonary hypertension were affected by the altitude of the reporting center. For these reasons and for its prospective nature, we believe that the present study adds pertinent information to the clinical characterization and natural history of children affected with primary pulmonary hypertension.

**Clinical characterization.** As in previous studies (2,32,35), we found that the gender distribution in primary pulmonary hypertension is more uniform in children (female/male ratio 1.6:1) than in adults (female/male ratio 4.25:1). This female preponderance after puberty has led to speculation that hormonal influences contribute to the pathogenesis of the disease (30–32).

With regard to the clinical presentation of childhood primary pulmonary hypertension there are similarities as well as some differences compared with that in adults, and our results are in general agreement with previous reports (35). As in adults with primary pulmonary hypertension (4,35), dyspnea is the most common symptom at diagnosis in children with the disease, and syncope, with or without generalized seizures, is a more frequent presenting symptom in young children than in adults with the disease. By contrast, angina is an uncommon symptom in children, which may be related to the difficulty of assessing typical angina correctly in this age group. Likewise, edema as a reflection of right ventricular failure is somewhat less frequent in children (10%) than in adults with primary pulmonary hypertension (20%). However, unlike other investigators (35), we found that edema is likely to occur even in children <10 years old in the presence of severe right ventricular dysfunction. In our study, the two children with edema at diagnosis had a right ventricular end-diastolic pressure of 14.5 and 15.5 mm Hg respectively. Finally, Raynaud’s phenomenon does not occur in childhood primary pulmonary hypertension.

With regard to hemodynamic function, despite an earlier age, these children already had severe pulmonary hypertension with pulmonary artery pressure not significantly different from that in the adult group (Table 1). This finding is in agreement with the current concept that once the patient with primary pulmonary hypertension becomes symptomatic enough to be diagnosed, the pulmonary artery pressure is already high and remains elevated without further elevation with increasing age (3,4). Baseline cardiac index was higher in the children, probably due to higher oxygen consumption in this age group. As a result of a higher cardiac index, the calculated pulmonary vascular resistance index was significantly lower in the children, and right ventricular function as assessed by right atrial pressure and cardiac index appears to be better in children than in adults with primary pulmonary hypertension (Table 1). Both of these findings suggest an earlier stage of the disease in the study children (3,30,35). It is also likely that patients with primary pulmonary hypertension who present at a younger age are better able to compensate for right ventricular hypertrophy than their adult counterparts.

**Response to vasodilator drugs.** As in adults (3,18,34,37), not all children with primary pulmonary hypertension respond to vasodilator therapy. However, the present study confirms and extends previous observations (34,35) that children with primary pulmonary hypertension generally respond better to vasodilator therapy than their adult counterparts. In our experience, when the significant decrease in both mean pulmonary artery pressure and pulmonary vascular resistance index is considered a positive response, the proportion of children who respond is higher (41%) than that for adults (25%). Previous histopathologic studies (30,32) in children and adults with primary pulmonary hypertension support this observation because greater pulmonary vascular medial hypertrophy and less intimal fibrosis and fewer plexiform lesions were found in children than in adults: in whom irreversible changes associated with intimal fibrosis have developed, suggesting a more vasoreactive pulmonary vascular bed in chil-
resistance index, seems to be the appropriate physiologic and physical property of the pulmonary vascular bed. In the study of Barst et al. (33), both infants and young adults (9 months to 23 years old) were included. In our group of children with primary pulmonary hypertension, which may be a result of the limiting the study to the pediatric and puberty period (4 to 15 years of age), whereas Barst (34) included both infants and young adults (9 months to 23 years old). In fact, when correlations from that study were repeated using the data for Patients 3 to 7 (the same age range as our patients), most correlations were not statistically significant.

Natural history. A major objective of the present study was to determine whether survival in children with primary pulmonary hypertension is better than that in adults with the disease if the diagnosis is made earlier in life. Our results show that childhood primary pulmonary hypertension is a disease with a poor prognosis and a survival expectancy not statistically different from that in the adult disease (Fig. 1). To some extent this finding is unexpected because of 1) the younger age, 2) the relatively better baseline hemodynamic profile, and 3) the better hemodynamic response to vasodilator therapy observed in children in the present study. We do not have a clear explanation for the finding of similar survival expectancy in children and adults with primary pulmonary hypertension, and, except for the study of Barst et al. (33), there is very little published information in this regard. In a group of patients with primary pulmonary hypertension (9 months to 23 years old), Barst et al. (33) found that age at diagnosis and immediate prostaglandin I₂ vasodilator response were significant predictors of survival. They concluded that children with primary pulmonary hypertension diagnosed early in life who receive long-term vasodilator therapy on the basis of a positive response to short-term prostaglandin I₂ testing, have an increased life expectancy. As shown in the present study and as discussed later, neither age at diagnosis nor response to vasodilator therapy was associated with survival according to univariate and multivariate analysis. However, an important difference between the two studies is the age range of the patients studied. In the study of Barst et al. (33), both infants and young adults were included, making the significance of their results difficult to interpret. Another difference is that we did not use prostacyclin as the testing agent.

Although discontinuation of treatment (one patient) and repeated (follow-up) right heart catheterization (two patients) might be implicated, right heart failure either alone or combined with these events was the leading cause of death in our patients. Accordingly, our patients with primary pulmonary hypertension appear to have evolved, as have most of their counterparts in the adult group, to right heart failure and death. This observation is supported by previous investigators (32), who also found that early right ventricular failure and death may occur in children with primary pulmonary hypertension even in the absence of advanced vascular lesions.

Factors associated with survival. In contrast to previous experience (35) but similar to other multiple studies on primary pulmonary hypertension in the general population (3,6,13-16), survival in childhood primary pulmonary hypertension in our study also appears to be related to the hemodynamic profile of the patients at diagnosis; once right ventricular failure develops, the prognosis is extremely poor. In our study patients with primary pulmonary hypertension who died had a worse and significantly different hemodynamic profile at diagnosis than those who survived >5 years. Furthermore, although not statistically significant by multivariate analysis (perhaps because of sample size), both elevated right atrial pressure and decreased stroke volume index are the variables most strongly associated with increased risk of death in this group of children with primary pulmonary hypertension (Fig. 2). Taken together these abnormalities are a reflection of right ventricular failure. It then appears that the prognosis of children with primary pulmonary hypertension depends on the functional status of the right ventricle, as is the case for the general population with this disease (3,6,13-16), and could thus be predictable. In support of this statement is the close correlation between actual survival and survival as predicted by the prognostic equation recently proposed by the National Institutes of Health Registry on primary pulmonary hypertension (6,13) (Fig. 3). As mentioned earlier, other variables reported to be important determinants of survival in children with primary pulmonary hypertension, such as age at diagnosis and beneficial hemodynamic response to vasodilator treatment (33,35), were not associated with survival in our study, which

![Survival Curve](image-url)
might be explained by the more strictly limited pediatric age included in our study.

We are indebted to Eulo Lupi-Herrera, MD and Fause Attie, MD for their thoughtful comments and criticisms in the review of the manuscript. We thank M. Luzardo Guerrero, MD for assistance with the statistical analysis and Sonia Meza, MD and Efren Santos, MD and the nurses of the cardiopulmonary department for their assistance in the care of the study patients.

References