Congenital Heart Disease and Pulmonary Artery Hypertension. I. Pulmonary Vasoreactivity to 15% Oxygen Before and After Surgery

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Pulmonary vasoreactivity at sea level was studied in 22 children before and in 15 children after corrective cardiac surgery for congenital heart disease and pulmonary artery hypertension; 8 children were studied both before and after cardiac surgery. During cardiac catheterization in 28 children, pulmonary and systemic hemodynamics were determined in room air and during breathing of 15% oxygen, which corresponds to a maximal hypoxic level commonly encountered during airplane travel.

Before surgery, 19 of 22 children tolerated 15% oxygen (O2), which caused the following hemodynamic changes from room air status: the ratio of pulmonary to systemic arterial pressure increased from 0.70 to 0.78 (p < 0.05), the ratio of pulmonary to systemic flow decreased from 2.2 to 2.0 (p > 0.05) and the ratio of pulmonary to systemic vascular resistance increased from 0.33 to 0.40 (p < 0.02). In two children, severe pulmonary vasoconstriction developed within 5 minutes of 15% oxygen administration, requiring immediate discontinuation of hypoxia; neither patient had lasting deleterious effects. There was no evidence of increased pulmonary vasoreactivity in children with Down's syndrome compared with genetically normal children. After corrective surgery in 15 children (including both of the hyperreactors), no significant pulmonary vascular response to 15% oxygen was found.

It is concluded that, in a small number of children with unrepaired congenital heart disease and pulmonary artery hypertension, pulmonary vascular hyperreactivity can be induced by breathing 15% oxygen; this reaction is life-threatening but reversible with the administration of 100% oxygen. Air travel without supplemental oxygen may be dangerous in these patients. It is our policy to repair the heart defect on an urgent basis when pulmonary hyperreactivity is found. One year after early surgery, pulmonary vascular status appears to be normal even in the hyperreactors.

Methods

Study patients. Twenty-two children were studied before surgery (Table 1). Twelve had perimembranous ventricular septal defect, six had a complete atrioventricular (AV) canal defect (three with additional patent ductus arteriosus), three had large patent ductus arteriosus and one had tetralogy of Fallot with pulmonary atresia and a Potts anastomosis. Median age at study was 13 months (mean 29 months, range 6 months to 19 years). Eleven of the 22 children had trisomy 21. Subsequently, all children underwent corrective surgery; one (Case 15) died postoperatively.

Fifteen children had postoperative studies (eight of whom were also evaluated before surgery) (Table 2). In 12 patients, there was no significant residual heart disease. One child (Case 19) had severe mitral regurgitation after repair of complete AV canal defect, one child (Case 26) had a small leak in the intraatrial baffle after repair of complex transposition of the great arteries and one (Case 28) had pul-
monary vascular obstructive disease. Median age at surgery was 22 months, and the average length of time between surgery and postoperative catheterization was 18 months (median 17, range 4 to 33).

Protocol. The sedative regimen included intramuscular administration of Innovar (0.02 cc/kg) (droperidol [2.5 mg/cc] and fentanyl [50 µg/cc]) 30 minutes before the study and ketamine hydrochloride (4 to 5 mg/kg) at entrance to the catheterization laboratory. Acquisition of hemodynamic data generally commenced 30 to 45 minutes after the ketamine hydrochloride injection. Pressures were measured with fluid-filled catheters; zero reference was determined by radiographic technique (4). Before surgery, the left atrium was entered in 18 of 22 patients. In nine patients with a flap-competent foramen ovale, a fully saturated left atrial sample in room air was considered representative of pulmonary venous effluent; a direct pulmonary vein sample was obtained in those with atrioventricular canal or atrial septal defect. In the four with intact interatrial septum, sampling at the mitral orifice was considered representative of pulmonary venous blood. Superior vena cava blood was used for a mixed venous sample. Informed consent was obtained from one or both parents in all patients and the protocol was first approved by the Institutional Review Board on January 25, 1979.

After study in room air (20.84% oxygen), 14.95% oxygen in nitrogen (hypoxia) was administered via a head hood. After 5 minutes of hypoxia, a systemic arterial blood sample was taken to assess blood gas status. Hemodynamic evaluation was commenced after 10 minutes of spontaneous respiration of the hypoxic atmosphere. Fourteen of the 22 children were also tested in 100% oxygen; the order was hypoxia-hyperoxia in 7 and hyperoxia-hypoxia in 7. Between the two oxygen concentrations, the patient breathed room air for 5 minutes.

Calculations. Preoperative calculations employed the Fick principle using an assumed oxygen consumption (VO₂) based on the data of La Farge and Miettinen (5) in those over 3 years of age; in those younger than 3 years, the following formula was used: VO₂ (oxygen consumption) = [(weight in kg × 5.49] + 12.68)/body surface area (m²) (Muster AJ, MD, personal communication). Calculations

### Table 1. Clinical and Hemodynamic Data in 22 Children Before Surgery

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Down's</th>
<th>Age at Study</th>
<th>PAP/SAP: Oxygen</th>
<th>Qp/Qs: Oxygen</th>
<th>Rp: Oxygen</th>
<th>Rp/Rs: Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 VSD</td>
<td>+ 6mo</td>
<td>0.73</td>
<td>0.85</td>
<td>2.9</td>
<td>2.0</td>
<td>6.7</td>
<td>10.6</td>
</tr>
<tr>
<td>2 VSD</td>
<td>+ 7mo</td>
<td>0.63</td>
<td>0.54</td>
<td>2.0</td>
<td>1.5</td>
<td>4.1</td>
<td>5.3</td>
</tr>
<tr>
<td>3 VSD</td>
<td>+ 9mo</td>
<td>0.68</td>
<td>1.00</td>
<td>1.6</td>
<td>2.1</td>
<td>4.0</td>
<td>8.0</td>
</tr>
<tr>
<td>4 VSD</td>
<td>+ 11mo</td>
<td>0.84</td>
<td>0.79</td>
<td>1.8</td>
<td>1.0</td>
<td>9.8</td>
<td>17.1</td>
</tr>
<tr>
<td>5 VSD</td>
<td>+ 1yr4mo</td>
<td>0.37</td>
<td>0.49</td>
<td>2.2</td>
<td>2.6</td>
<td>1.8</td>
<td>3.7</td>
</tr>
<tr>
<td>6 VSD</td>
<td>+ 1yr5mo</td>
<td>0.73</td>
<td>0.85</td>
<td>1.5</td>
<td>1.6</td>
<td>6.9</td>
<td>5.6</td>
</tr>
<tr>
<td>7 VSD</td>
<td>- 5mo</td>
<td>0.47</td>
<td>0.60</td>
<td>2.9</td>
<td>2.1</td>
<td>8.5</td>
<td>3.4</td>
</tr>
<tr>
<td>8 VSD</td>
<td>- 10mo</td>
<td>0.50</td>
<td>0.58</td>
<td>3.1</td>
<td>3.5</td>
<td>1.7</td>
<td>2.4</td>
</tr>
<tr>
<td>9 VSD</td>
<td>- 2yr1mo</td>
<td>0.48</td>
<td>0.39</td>
<td>2.3</td>
<td>2.1</td>
<td>1.9</td>
<td>2.6</td>
</tr>
<tr>
<td>10 VSD</td>
<td>- 2yr4mo</td>
<td>0.45</td>
<td>0.62</td>
<td>2.2</td>
<td>2.1</td>
<td>2.5</td>
<td>4.5</td>
</tr>
<tr>
<td>11AVC</td>
<td>- 1yr1mo</td>
<td>0.42</td>
<td>0.58</td>
<td>4.1</td>
<td>3.2</td>
<td>3.3</td>
<td>5.2</td>
</tr>
<tr>
<td>12AVC</td>
<td>+ 1yr3mo</td>
<td>0.88</td>
<td>1.00</td>
<td>2.2</td>
<td>2.3</td>
<td>5.6</td>
<td>7.9</td>
</tr>
<tr>
<td>13AVC, PDA</td>
<td>+ 7mo</td>
<td>0.95</td>
<td>1.00</td>
<td>1.8</td>
<td>1.8</td>
<td>7.2</td>
<td>9.5</td>
</tr>
<tr>
<td>14AVC, PDA</td>
<td>+ 8mo</td>
<td>0.82</td>
<td>1.00</td>
<td>2.2</td>
<td>1.3</td>
<td>6.4</td>
<td>15.7</td>
</tr>
<tr>
<td>15AVC, PDA</td>
<td>+ 9mo</td>
<td>0.84</td>
<td>1.00</td>
<td>1.6</td>
<td>2.0</td>
<td>9.0</td>
<td>20.8</td>
</tr>
<tr>
<td>16PDA</td>
<td>+ 6mo</td>
<td>0.87</td>
<td>0.97</td>
<td>2.5</td>
<td>2.2</td>
<td>7.6</td>
<td>11.7</td>
</tr>
<tr>
<td>17PDA</td>
<td>- 19yr</td>
<td>0.96</td>
<td>0.99</td>
<td>2.4</td>
<td>3.1</td>
<td>12.4</td>
<td>8.7</td>
</tr>
<tr>
<td>18PDA, ASD</td>
<td>+ 8yr4mo</td>
<td>0.95</td>
<td>0.92</td>
<td>1.0</td>
<td>1.0</td>
<td>13.5</td>
<td>20.8</td>
</tr>
<tr>
<td>19AVS, small VSD, PDA</td>
<td>+ 1yr2mo</td>
<td>0.88</td>
<td>0.91</td>
<td>1.6</td>
<td>1.2</td>
<td>9.5</td>
<td>22.2</td>
</tr>
<tr>
<td>20ToF, PA; Potts</td>
<td>- 7yr2mo</td>
<td>0.47</td>
<td>0.60</td>
<td>2.2</td>
<td>2.2</td>
<td>4.3</td>
<td>4.7</td>
</tr>
<tr>
<td>21VSD</td>
<td>- 8mo</td>
<td>0.66</td>
<td>1.12</td>
<td>1.5</td>
<td>—</td>
<td>9.1</td>
<td>—</td>
</tr>
<tr>
<td>22AVC</td>
<td>+ 6mo</td>
<td>0.90</td>
<td>1.16</td>
<td>1.1</td>
<td>—</td>
<td>8.8</td>
<td>—</td>
</tr>
<tr>
<td>Mean</td>
<td>2yr5mo</td>
<td>0.70</td>
<td>0.78</td>
<td>2.2</td>
<td>2.0</td>
<td>6.5</td>
<td>9.5</td>
</tr>
<tr>
<td>SD</td>
<td>4yr3mo</td>
<td>0.20</td>
<td>0.21</td>
<td>0.7</td>
<td>0.7</td>
<td>3.4</td>
<td>6.5</td>
</tr>
</tbody>
</table>

ASD = atrial septal defect, secundum type; AVC = (complete) atrioventricular canal defect; mo = months; PAP/SAP = ratio of pulmonary to systemic mean arterial pressure; PDA = patent ductus arteriosus; Potts = descending aorta to left pulmonary artery anastomosis. Qp/Qs = ratio of pulmonary to systemic blood flow. Rp/Rs = ratio of pulmonary to systemic vascular resistance; SD = standard deviation; TGA = transposition of the great arteries. ToF, PA = tetralogy of Fallot with pulmonary atresia; VSD = ventricular septal defect; yr = years. 21, 15 and 100/o/c refer to inhaled oxygen percentage.
Table 2. Clinical and Hemodynamic Data in 15 Children After Surgery

<table>
<thead>
<tr>
<th>Cardiac Defect Repaired</th>
<th>Residual Defect(s)</th>
<th>Down's Age at Postop Study</th>
<th>PAP/SAP</th>
<th>Rp</th>
<th>Rp/Rs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>21%</td>
<td>15%</td>
<td>21%</td>
</tr>
<tr>
<td>VSD, ASD</td>
<td>+</td>
<td>1yr2mo 2yr</td>
<td>0.31</td>
<td>0.39</td>
<td>4.0</td>
</tr>
<tr>
<td>VSD</td>
<td>+</td>
<td>1yr2mo 2yr7mo</td>
<td>0.28</td>
<td>0.28</td>
<td>3.2</td>
</tr>
<tr>
<td>VSD</td>
<td>+</td>
<td>1yr1mo 2yr2mo</td>
<td>0.32</td>
<td>0.35</td>
<td>5.7</td>
</tr>
<tr>
<td>VSD</td>
<td>+</td>
<td>1yr6mo 3yr4mo</td>
<td>0.15</td>
<td>0.14</td>
<td>1.9</td>
</tr>
<tr>
<td>VSD</td>
<td></td>
<td>2yr5mo 5yr2mo</td>
<td>0.26</td>
<td>0.27</td>
<td>1.8</td>
</tr>
<tr>
<td>AVC</td>
<td></td>
<td>1yr3mo 3yr5mo</td>
<td>0.25</td>
<td>0.27</td>
<td>2.4</td>
</tr>
<tr>
<td>VSD</td>
<td></td>
<td>10mo 1yr4mo</td>
<td>0.25</td>
<td>0.37</td>
<td>3.6</td>
</tr>
<tr>
<td>AVC, Resid MR</td>
<td></td>
<td>7mo 2yr4mo</td>
<td>0.70</td>
<td>0.58</td>
<td>7.2</td>
</tr>
<tr>
<td>DORV, PS</td>
<td></td>
<td>10mo 1yr2mo</td>
<td>0.28</td>
<td>0.32</td>
<td>3.9</td>
</tr>
<tr>
<td>VSD</td>
<td></td>
<td>10mo 3yr5mo</td>
<td>0.25</td>
<td>0.29</td>
<td>2.4</td>
</tr>
<tr>
<td>VSD</td>
<td></td>
<td>3yr3mo</td>
<td>0.24</td>
<td>0.27</td>
<td>3.4</td>
</tr>
<tr>
<td>TGA, VSD, Atrial baffle leak</td>
<td></td>
<td>1yr5mo 2yr4mo</td>
<td>0.23</td>
<td>0.20</td>
<td>1.6</td>
</tr>
<tr>
<td>VSD</td>
<td></td>
<td>2yr8mo 4yr7mo</td>
<td>0.16</td>
<td>0.17</td>
<td>1.4</td>
</tr>
<tr>
<td>AVC, PS, PVOD</td>
<td></td>
<td>9yr4mo 10yr3mo</td>
<td>0.83</td>
<td>0.71</td>
<td>17.2</td>
</tr>
<tr>
<td>AVC</td>
<td>+</td>
<td>7mo 2yr2mo</td>
<td>0.24</td>
<td>0.33</td>
<td>5.2</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>1yr10mo 3yr4mo</td>
<td>0.31</td>
<td>0.33</td>
<td>4.3</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>1yr4mo 2yr4mo</td>
<td>0.19</td>
<td>0.15</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Patients 23 to 29 not tested preoperatively. DORV = double outlet right ventricle; Postop = postoperative; PS = pulmonary stenosis; PVOD = pulmonary vascular obstructive disease; Resid MR = residual mitral regurgitation; other abbreviations as in Table 1.

were performed utilizing oxygen content. Postoperatively, cardiac output was measured by thermodilution technique in 12 of the 15 patients.

Statistical analysis. Analysis of statistics was based on the two-tailed paired t test; significance was considered at the less than 0.05 level. For preoperative evaluation, the effect of hypoxia was primarily assessed by changes in the pulmonary to systemic resistance (Rp/Rs) ratio because 1) a free communication existed between the pulmonary and systemic circuits; 2) there is no method available to measure VO₂ during 15% oxygen breathing in patients with an intracardiac shunt; and 3) the Rp/Rs ratio is independent of the VO₂. For postoperative assessment, 13 of the 15 children had no residual shunt and because the two circuits were separate, absolute pulmonary resistance (measured using thermodilution cardiac output) more accurately reflected pulmonary vascular status than the Rp/Rs ratio.

Results

Preoperative findings in 20 mild reactors (Table 1). In Patients 1 to 20, the average pulmonary venous partial pressure of oxygen (P₀₂) in room air was 85.4 ± 12.3 mm Hg (range 60 to 110) in room air and 45.4 ± 9.6 mm Hg (range 38 to 55) during hypoxia (Fig. 1). The change in P₀₂ was highly significant (probability [p] < 0.001). There was no change in mean arterial partial pressure of carbon dioxide (PₐC₀₂) from room air (41.25 ± 3.62) to 15% oxygen (41.25 ± 4.53).

Average systolic and mean pulmonary artery pressures were 74.2 ± 17.09 and 45.5 ± 14.7 mm Hg, respectively.

Figure 1. Effect of breathing 15% O₂ on the pulmonary venous P₀₂ in 22 children with congenital heart disease and pulmonary artery hypertension. A decrease is seen in each patient when the ambient atmosphere is changed from 21% O₂ (sea level; room air) to 15% O₂. Mean P₀₂ (O) decreased from 85 mm Hg in room air to 45 mm Hg during hypoxia. Arrows indicate the two hyperreactors.
Figure 2. Effect of 15% O₂ on the ratio of pulmonary to systemic mean arterial pressure (PAP/SAP) before and after surgical correction of congenital heart disease. **Left panel,** Before surgery in 18 of the 22 children, 15% O₂ caused the PAP/SAP ratio to increase. The arrows indicate the two hyperreactors (see text). **Right panel,** After surgery, most of the 15 children had a normal PAP/SAP ratio in room air. The two with persistent elevation of PAP/SAP had residual mitral regurgitation and pulmonary vascular disease, respectively. In most children, 15% O₂ caused a small but not significant increase in the PAP/SAP ratio. Arrows again indicate the two hyperreactors, both of whom tolerated 15% O₂ after surgery.

in room air; hypoxia caused a significant increase in both of these measurements. Although the hypoxic effect on systolic systemic arterial pressure was not significant, there was a significant increase in mean systemic arterial pressure. A significant (p < 0.001) increase was found in the ratio of pulmonary to systemic mean pressure (PAP/SAP) from room air to 15% oxygen (Fig. 2). The net left to right shunt (Qp/Qs) decreased during hypoxia but the change was not significant.

Both pulmonary and systemic vascular resistance increased significantly during hypoxia (p < 0.01 and p < 0.05, respectively) (Fig. 3). The magnitude of increase in pulmonary vascular resistance was greater than the increase in systemic vascular resistance resulting in a net significant elevation of the Rp/Rs ratio induced by hypoxia.

Pulmonary vascular response to 15% oxygen in children with Down’s syndrome was compared with the response in genetically normal children with congenital heart disease, both in the total preoperative group (Down’s 14, normal 8) and those with ventricular septal defect (Down’s 6, normal 4). Comparing average age, PAP/SAP, Qp/Qs and Rp/Rs, no significant differences were found between patients with Down’s syndrome and the remainder of the group.

One hundred percent oxygen (hyperoxia) was administered in 13 of the 20 patients. Hyperoxia caused a small but significant decrease in pulmonary to systemic artery mean pressure ratio and a large increase in the left to right shunt. In 100% oxygen, the ratio of pulmonary to systemic vascular resistance (Rp/Rs) decreased from 0.33 ± 0.07 to 0.11 ± 0.06 (p < 0.005).

Preoperative findings in two hyperreactors (Table 1). Both patients (Cases 21 and 22) had moderate relative pulmonary artery hypertension (PAP/SAP 0.66 and 0.90) (Fig. 2) with a small net left to right shunt; one had Down’s syndrome. Hypoxia induced suprasystemic pulmonary arterial pressure within 2 to 4 minutes. As the pulmonary diastolic pressure increased (Fig. 4), both systemic and pulmonary systolic pressures began to decrease and the patient was immediately placed on 100% oxygen. At the time of suprasystemic pulmonary pressure, profound left atrial hypoxemia was noted with Po₂ values of 20 and 24 mm Hg, respectively (Fig. 1). Shunt calculations were not possible due to the urgent termination of hypoxia, but the Rp/Rs in each patient of necessity was greater than 1.00 (Fig. 3).

Postoperative findings in 15 children (Table 2). Eight of the 15 children were studied both preoperatively and postoperatively. Thirteen children had no residual intracardiac shunt; in these children, the systemic arterial blood sample was considered representative of pulmonary venous blood. Hypoxia decreased the Po₂ from 86.7 ± 10.8 mm Hg in room air to 50.4 ± 7.2 mm Hg. The change in Po₂ induced by hypoxia postoperatively was not significantly different from the change noted before surgery (t = 1.660). One child (Case 26) had a small intraatrial baffle leak with a Qp/Qs ratio in room air of 0.9. Patient 28 had pulmonary vascular obstructive disease and a right to left ventricular shunt (Qp/Qs ratio = 0.6). Flow and resistance calculations during hypoxia were not made in these two patients.

Most of the 15 children had normal pulmonary artery pressure in room air: 13 had a mean pressure less than 23 mm Hg; 12 had a PAP/SAP ratio less than 0.30. Although hypoxia increased mean pulmonary artery pressure in 12 patients, the change was not significant (t = 1.079). The following measurements were not significantly affected by hypoxia: mean systemic arterial pressure, ratio of pulmonary to systemic mean pressures (Fig. 2), absolute pulmonary vascular resistance (Fig. 3) and ratio of pulmonary to systemic vascular resistance. Both of the preoperative hyperreactors (Cases 21 and 22) were studied postoperatively; each tolerated 15% oxygen without difficulty.
Figure 3. Effect of breathing 15% O₂ on pulmonary (Rp) and systemic (Rs) vascular resistance before and after surgical correction of congenital heart disease. Arrows indicate the two hyperreactors. **Upper left panel.** Before surgery, pulmonary vascular resistance increases in most children during hypoxia (p < 0.01). Quantification of the increased pulmonary vascular resistance during hypoxia in the two hyperreactors is not possible (question marks). **Lower left panel.** Before surgery, pulmonary and systemic vascular resistance both increased during hypoxia; however, the effect on Rp was greater, resulting in a significant increase in the Rp/Rs during hypoxia (p < 0.02). The two hyperreactors developed Rp/Rs > 1.00. **Upper right panel.** After surgery, most children had normal pulmonary vascular resistance in both room air and hypoxia. Hypoxia had no significant effect on Rp in these children, including the two hyperreactors.

**Discussion**

**Previously reported data.** Limited data are available on the pulmonary vascular effects of acute hypoxia in children with congenital heart disease. Most prior work has dealt with the effects of chronic hypoxia, that is, in patients residing in Denver, Colorado. Blount (6) suggested that the endemic hypoxia of high altitude living causes increased medial musculature in the pulmonary resistance vessels. Vogel, McNamara and Blount (7,8) compared infants with ventricular septal defect living in Denver with similar infants living at sea level (Houston); the higher altitude group had higher pulmonary vascular resistance that was more responsive to tolazoline. Willerson et al. (9) reported on one child with ventricular septal defect who had pulmonary artery hypertension while in Denver but normal pressure when in Boston. It is clear that the chronic hypoxia of the Denver atmosphere provides a stimulus to increased pulmonary vascular tone that plays a clinically significant role in children with unrepaired congenital heart disease (10).

Postoperative hemodynamic studies of the pulmonary vascular system have been reported from near sea level (Rochester, Minnesota) as well as Denver. DuShane et al. (11) at the Mayo Clinic, found normal pulmonary vascular resistance more than 5 years after surgical repair of ventricular septal defect when the operation was performed in children under 2 years of age; 7 of the 25 children studied
were given 12% oxygen to breathe and each had three or four units (m^2) of pulmonary vascular resistance. Vogel et al. (10) in Denver, also found that the Eisenmenger reaction was rare under 2 years of age. Late postoperative studies with hypoxic challenge have been reported by Lueker et al. (12) from Denver. At cardiac catheterization in 72 patients over 5 years after repair of atrial septal defect, ventricular septal defect or patent ductus arteriosus, hemodynamic measurements were made in room air and after 4 minutes of 10% oxygen. Abnormal pulmonary vasoreactivity was found in many patients, even those with normal hemodynamic values at rest. It was suggested that the excessive medial musculature persisted in these patients as a result of the chronic hypoxic stimulus of altitude residence. We are unaware of any studies of pulmonary vasoreactivity at sea level before and after repair of congenital heart disease associated with pulmonary artery hypertension.

**Hemodynamics at sea level: reactors and hyperreactors.** Our preoperative patients had pulmonary hypertension at rest that can be presumed to be secondary to arterial constriction in response to both volume and pressure overload of the pulmonary circuit. Demonstration of increase in pulmonary blood flow during hypoxemia suggests that the arterial narrowing was an active muscular phenomenon rather than fixed obstruction as might be found with scattered pulmonary emboli or irreversible pulmonary vascular disease. Hypoxia caused a mild increase in pulmonary pressure and resistance in the majority of children before surgery. The degree of change in pulmonary vascular tone was not related to the level of pulmonary artery hypertension found in room air.

A striking feature was the exaggerated response to hypoxia found in two preoperative patients (Cases 21 and 22) called hyperreactors: pulmonary resistance became suprasystemic, pulmonary blood flow acutely decreased and intracardiac right to left shunting increased; coupled with a decrease in pulmonary venous return, this resulted in extreme hypoxemia. It was clear to the physician performing the catheterization that the two hyperreactors would have died if hypoxia had been continued.

The development of suprasystemic pulmonary pressure is confusing because both children had an interventricular communication that appeared on angiography to be unrestrictive; that is, a defect at least equal in size to the aortic anulus and pressure equalization across the interventricular septum. Yet, during hypoxia, each developed suprasystemic pulmonary pressure, a hemodynamic non sequitur. We conjecture that the acute clinical deterioration resulted in a nonsteady state that transiently allowed a hemodynamic inconsistency.

The two hyperreactors were both under 1 year of age, and both had moderately to severely increased pulmonary artery pressure and resistance with a small net left to right shunt in room air; one of the two had trisomy 21. The clinical and hemodynamic characteristics of the hyperreactors were similar to those of many of the mild reactors, making it impossible to predict which patient would be likely to experience pulmonary vascular hyperreaction.

**Patients with Down’s syndrome.** Down’s syndrome may predispose to early pulmonary vascular disease. In separate clinical studies, both Chi (13) and Soudan (14) and their co-workers concluded that the presence of Down’s syndrome predisposed children with congenital heart disease to elevated pulmonary vascular resistance. A different conclusion was reached by Wilson et al. (15) in a review of pathologic specimens. They concluded that patients with Down’s
syndrome had no propensity for early or severe hypertensive pulmonary vascular disease. In our preoperative series, half of the children had Down’s syndrome as did one of the two hyperreactors. No evidence was found for excessive pulmonary vasoreactivity when those with trisomy 21 were compared with genetically normal children.

Air travel and pulmonary hypertension. The level of hypoxia (15% O₂) was chosen to correspond to the maximal hypoxic condition a sea level dweller is likely to encounter, that is, commercial airplane travel. When a standard airplane is flying at 11,000 to 12,000 meters the cabin altitude is approximately 2,400 meters (16), which is comparable with breathing 15% O₂ at sea level. It is understood that conditions in the catheterization laboratory are not completely physiologic (fasting patient who is supine and anesthetized) and that the hypoxic challenge lasted only 10 to 15 minutes. Also, there are no reported cases of cardiovascular collapse during flying in patients with congenital heart disease and pulmonary artery hypertension. However, we consider it prudent to recommend avoidance of air travel before surgery in these patients and, if such travel is necessary, to advise the use of supplemental oxygen.

Surgery and its effects. Prompt corrective surgery may be warranted in children demonstrating pulmonary vascular hyperreactivity: the hypoxia-induced phenomenon seen in the catheterization laboratory may occur under other circumstances and has been reported in the immediate postoperative period (17). Furthermore, early surgery appears more likely to result in normal pulmonary vascular status. In Boston, Rabinovitch et al. (2) developed a morphometric quantification of pulmonary vascular changes associated with congenital heart disease. In patients operated on at or less than 9 months of age with the most severe (grade C) pulmonary vascular changes, Rabinovitch et al. (personal communication) found normal postoperative hemodynamics in both room air and 15% O₂. This suggests reversibility of pulmonary vascular changes if early operation is performed.

Our postoperative data support the efficacy of early corrective surgery. Of importance is the lack of hyperreaction after surgery in the two patients who developed life-threatening hypoxic pulmonary vasoconstriction before surgery. The disparity between our results (normal postoperative pulmonary vasoreactivity) and those of Lueker et al. (12) (frequent excessive pulmonary vascular reactivity) is probably related to differences in patient population and study conditions. Comparing our experience with that of Lueker et al.: 1) average age at surgery was 1.8 versus 10.7 years, respectively; 2) average time from surgery to study was 1.5 versus 4.6 years; 3) a residual left to right shunt was present in 33% versus none; 4) altitude of residence was 5,000 versus sea level; and 5) hypoxic challenge was 10% oxygen for 4 minutes versus 15% oxygen for 10 minutes.

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References