Natural and Post-operative History of Pulmonary Vascular Obstruction Associated with Ventricular Septal Defect

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The natural history of pulmonary vascular obstruction in VSD associated with PH was studied by measuring PVR before and after injection of tolazoline 1 mg/kg. Organic pulmonary vascular obstruction (PVO) was minimal in infancy, but increased linearly progressively with advancing age, and average rate of increase in PVR after tolazoline was 1 unit·m²/year. The rate of increase in PVR after tolazoline in Eisenmenger complex was variable and ranged between 0.7 to 4 unit·m²/year in most cases. Analysis of 7 cases of post-operative late death due to PVO revealed that usually these cases were over 5 years of age at operation, and pre-operative PVR was more than 12 unit·m². Reduction of PVR was confirmed post-operatively in most of these cases whose pre-operative PVR before and after tolazoline were less than 8 unit·m² and 7 unit·m² respectively. Early surgical repair is indicated in VSD and PH to prevent progress of PVO.

THE natural history, indications for repair and post-operative course of ventricular septal defect (VSD) are influenced greatly by associated pulmonary hypertension (PH) and pulmonary vascular obstruction (PVO). Recently, considerable attention has been focused on the post-operative progression or regression of PVO. In the clinical evaluation of PVO associated with VSD, organic PVO and pulmonary vasoconstriction should be assessed separately as constituents of high pulmonary vascular resistance (RVR). This can be accomplished by studying the reduction of PVR following administration of pulmonary vascular dilating agents. During the last ten years tolazoline hydrochloride has been used routinely to evaluate PH and PVO in VSD in our catheterization laboratory. In this report data were analysed to elucidate the natural history and post-operative course of PVO associated with VSD.

MATERIALS AND METHODS

Catheterization data are summarized in Table I. All had pulmonary hypertension with systolic pulmonary arterial pressure more than 80 percent of systemic pressure. Age ranged from one month to 32 years. These patients were catheterized by standard methods and premedication with meperidine hydrochloride (1 to 2 mg/kg) and hydroxyzine (0.5 to 1 mg/kg). Room air was breathed and samples were taken to calculate PVR before and after injection of 1 mg/kg of tolazoline into the main pulmonary artery. Pulmonary artery was entered in all cases, but pulmonary vein or left atrium was entered in a third of preoperative cases, and usually was not enter-

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- Ventricular septal defect
- Pulmonary hypertension
- Pulmonary vascular obstruction
- Natural history
- Eisenmenger complex

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TABLE 1  PATIENT MATERIALS

<table>
<thead>
<tr>
<th>Procedure</th>
<th>N</th>
</tr>
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<tbody>
<tr>
<td>Pre-operative catheterization</td>
<td>148</td>
</tr>
<tr>
<td>Tolazoline test (+)</td>
<td>115</td>
</tr>
<tr>
<td>(Repeated)</td>
<td>9</td>
</tr>
<tr>
<td>(Eisenmenger complex - non-surgical)</td>
<td>17</td>
</tr>
<tr>
<td>(Post-op. fatal PVO)</td>
<td>2</td>
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<tr>
<td>(Post-op. catheterization (+)</td>
<td>13</td>
</tr>
<tr>
<td>(Post-op. tolazoline test (+)</td>
<td>8</td>
</tr>
<tr>
<td>(associated with ASD)</td>
<td>5</td>
</tr>
<tr>
<td>(associated with PDA)</td>
<td>14</td>
</tr>
<tr>
<td>(associated with mitral regurgitation)</td>
<td>6</td>
</tr>
<tr>
<td>Tolazoline test (-)</td>
<td>33</td>
</tr>
<tr>
<td>(Post-op. fatal PVO)</td>
<td>5</td>
</tr>
<tr>
<td>End-op. PAP Measurement</td>
<td>19</td>
</tr>
<tr>
<td>(Post-op. fatal PVO)</td>
<td>4</td>
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<tr>
<td>Post-operative catheterization</td>
<td>41</td>
</tr>
<tr>
<td>Pre-op. tolazoline test (+)</td>
<td>13</td>
</tr>
<tr>
<td>Post-op. tolazoline test (+)</td>
<td>8</td>
</tr>
<tr>
<td>Residual shunt (+)</td>
<td>16</td>
</tr>
<tr>
<td>Post-op. fatal PVO</td>
<td>4</td>
</tr>
<tr>
<td>(associated with ASD &amp; Prematurity)</td>
<td>1</td>
</tr>
<tr>
<td>(associated with ASD, PDA &amp; surgical AV Block)</td>
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ed in the post-operative cases. Dye-curves were recorded routinely to check the presence of right-to-left shunt in cases where the pulmonary vein was not entered. If the dye-curve showed no right-to-left shunt, aortic saturation was used in place of pulmonary vein saturation. In those cases with evidences of right-to-left shunt and whose pulmonary vein was not accessible, pulmonary vein saturation was assumed to be 96 percent. Oxygen consumption was assumed to be 160 ml/min/m² both before and after tolazoline. This assumption is based on the following: oxygen consumption was measured with open circuit method in 10 patients continuously from ten minutes before injection of tolazoline until ten minutes after injection and did not change after injection of tolazoline. In those cases whose left atrium was not entered, pulmonary artery wedge pressure or left ventricular end-diastolic pressure was used in calculation of PVR. Oxygen saturation was measured with the AO Oxyimeter II (American Optical Co.), oxygen content of the blood was calculated from hemoglobin content and oxygen saturation, and pulmonary blood flow was calculated by Fick principle.

RESULTS

Tolazoline test in those patients with VSD and PH under the age of two years revealed the presence of marked pulmonary vasoconstriction in this age group (Figure 1). In these patients, in response to tolazoline, pulmonary blood flow increased invariably, pulmonary artery mean pressure decreased more than 10 mmHg in 44

Fig.1. Tolazoline test in VSD and PH under the age of two years. PVR before tolazoline (closed circle) and after tolazoline (open circle) shows marked pulmonary vasoconstriction in this age group.

Fig. 2. Progress of PVO in VSD and PH are shown as PVR before tolazoline (closed circle) and PVR after tolazoline (open circle) in six age groups from infancy to adulthood.

Fig. 3. Progress of PVO in VSD and PH are shown by serial catheterization with tolazoline test in 9 patients. Regression of pulmonary vasoconstriction and progress of organic PVO were disclosed by tolazoline test.

percent of these cases. PVR decreased more than 50 percent in 56 percent of these cases. PVO was evaluated with tolazoline test in 115 patients with VSD and PH including 17 cases

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with Eisenmenger complex. Analysis of data according to six age-groups revealed that PVR before and after tolazoline increased in parallel with advancing age. The difference between these two PVR was largest in infancy. PVR after tolazoline was very close to the line $Y = X$ (Fig. 2).

Repeat catheterization and tolazoline test in 9 patients with VSD and PH without surgical intervention revealed gradual increase in PVR before and after tolazoline, with annual increasing rates of 0.84 and 0.95 unit·m$^2$ respectively (Fig. 3).
Tolazoline test in 17 cases with Eisenmenger complex revealed minimal or no significant reduction of PVR (Fig. 4). PVR decreased more than 20 percent in only 5 out of 17 cases (29 percent) following tolazoline injection. PVR after tolazoline in these fell in the area between two lines of $Y = 0.7X$ and $Y = 4X$ except two cases (Fig. 4). Assuming linear annual progress of PVO, rising rate of PVR in these 15 cases were 0.7 to 4 unit·m²/year.

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Seven patients with VSD and PH survived intracardiac repair but died one to six years after operation due to progressive PVO. In four of these both pre- and post-operative catheterization data were available and in the remaining only pre-operative data were available. Analysis of these data revealed that in 5 out of 7 cases the age of operation was later (over 6 years-old), and pre-operative PVR was high (more than 12 unit-m$^2$), but two exceptional cases were observed (Fig. 5).

Post-operative PH and PVO in VSD were analyzed as follows.

Pre- and post-operative PVR were compared in 41 patients with VSD and PH (Figure 6). In those with pre-operative PVR less than 7 unit-m$^2$, post-operative PVR decreased with one exception. In those with pre-operative PVR more than 8 unit-m$^2$, post-operative PVR either remained high or rose more, and three of these died.

Prognostic significance of systolic pulmonary arterial pressure at completion of intracardiac repair measured on the operating table was evaluated in 19 patients with VSD and PH whose pre- and post-operative catheterization data were available (Fig. 7). In those 11 patients with end-operative pulmonary pressure less than 50 mmHg, post-operative systolic pulmonary pressure was less than 70 mmHg with one exception (Fig. 7). In those 8 patients with end-operative pulmonary pressure over 50 mmHg, post-operative pulmonary pressure was higher than 70 mmHg, and three out of these eight died of PVO.

Prognostic significance of pre-operative tolazoline test was assessed in 13 patients with VSD and PH, who had post-operative catheterization, and in eight with tolazoline test. In 7 out of 8 cases, reduction of PVR following injection of tolazoline decreased post-operatively (Fig. 8). Post-operative increase in PVR or persistence of high PVR occurred in 5 out of 8 patients (62 per cent) whose pre-operative PVR was more than 8 unit-m$^2$, and in 5 out of 6 patients (83 percent) whose preoperative PVR after tolazoline injection was more than 7 unit-m$^2$.

**DISCUSSION**

Severe PVO is generally indicated by PVR of more than 10 unit-m$^2$. But as shown in the present study and by others, varying degrees of pulmonary vasoconstriction contribute to the high PVR, and in pre-operative evaluation of an individual patient, this problem should be clarified by studying PVR following inhalation of 100% oxygen or injection of tolazoline into the main pulmonary artery.

In the present study, pulmonary vasoconstriction was demonstrated in vast majority of infants with VSD and PH, and reactivity to tolazoline, or pulmonary vasoconstriction, decreased and PVR after tolazoline increased in parallel with advancing age. This is compatible with histologic findings of lung vasculature in VSD. High PVR after tolazoline is more significant evidence of PVO than simple measurement of high PVR, and the present data of tolazoline test in 115 patients with VSD and PH have clarified linear progress of PVO in VSD and PH by catheterization data for

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the first time.

Some patients have high PVR in infancy, and repeat catheterization at 2 to 5 years of age shows marked fall in PVR. This report includes three such cases, who had repeat catheterization study with tolazoline, and pulmonary vasoconstriction, prominent in infancy in all three, decreased or disappeared in one to five years. PVR apparently decreased, but PVR after tolazoline remained unchanged in all three. This supports the early assumption that the initial high PVR results from delayed resolution of fetal vascular pattern in the lung.

The rate of progress in PVO is the most crucial problem in Eisenmenger complex and differs markedly from one patient to the other. Because pulmonary vasoconstriction varies individually, PVR measured following pulmonary vasodilating agent provides more definite assessment of PVO than simple PVR. Repeat studies of non-operated patients who are initially about 2 years of age and have VSD and PH indicate that PH persists in most cases, and PVR increases in 25 to 50 percent of patients over succeeding 5 to 6 years. Present study provides further evidences of progressive nature of PVO. Repeat study with tolazoline test reveals that increase in PVR is generally accompanied with increase in PVR after tolazoline, thus indicating progress in PVO, and progress in PVO may be disclosed after tolazoline even in those cases whose PVR before tolazoline remains at the same level.

Repair of VSD and other malformations accompanied by severe PH should generally be done before the patient has reached 2 years of age, when changes in the pulmonary vasculature are mild and may be reversed after closure of the defect. This is generally right, but as we experienced in a few cases, exceptionally early progress of PVO may occur in cases with VSD and PH associated with ASD or PDA.

Surgical indications may be difficult to determine in some cases with VSD and moderate to severe PVO. Operation is generally not recommended if PVR is higher than 10 unit-m⁻², or pulmonary to systemic flow ratio is less than 1.2 to 1.4 in older children or adults. The younger the age of the patients, the more probable is post-operative regression of PVO and the present study provides an explanation of the hemodynamic mechanism of this phenomenon, proving the existence of potent pulmonary vasoconstriction as a contributing factor to high PVR in infants with VSD and PH. A few exceptional cases were observed who developed post-operative progressive PVO even though intracardiac repair was performed at the age of one or two years. Reactivity to pulmonary vasodilator such as inhalation of 100 percent oxygen or infusion of tolazoline should be tested pre-operatively in all these patients, and present data show that post-operative progress of PVO would be very probable if PVR remains higher than 7 unit-m⁻² after injection of tolazoline in pre-operative catheterization study. On the other hand, the present study shows that post-operative prognosis is good in respect to PVO if pre-operative PVR is less than 8 unit-m⁻² or pre-operative PVR falls to less than 7 unit-m⁻² after injection of tolazoline in these patients with VSD and PH.

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