Early Onset of Pulmonary Vascular Obstruction in Patients with Aortopulmonary Transposition and Intact Ventricular Septum

By Jeffrey B. Lakier, M.D., Paul Stanger, M.D., Michael A. Heymann, M.D., Julien I.E. Hoffman, M.D., and Abraham M. Rudolph, M.D.

SUMMARY
Of 29 patients with aortopulmonary transposition with intact ventricular septum who underwent cardiac catheterization as neonates, five subsequently developed increased pulmonary vascular resistance at an early age (7 months to 2½ years). The resistance was high in two patients (11.0 and 12.9 units (U)/m²), moderate in one (5.5 U/m²) and mild in two (3.6 and 4.6 U/m²). The two patients with the highest resistances died as a result of the pulmonary vascular obstruction and it was probably a contributing factor in the death of a third patient. The finding of pulmonary vascular obstruction at an early age in five of 29 patients with transposition of the great arteries with intact septa is noteworthy. It assumes even greater significance as the measurement methods tend to underestimate pulmonary vascular resistance. The possible errors in assessing pulmonary vascular resistance and factors possibly contributing to early development of pulmonary vascular obstruction are discussed.

Additional Indexing Words: Aortopulmonary transposition Patent ductus and/or vascular obstruction
Cardiac catheterization Pulmonary blood flow Pulmonary vascular resistance

Patients with Aortopulmonary Transposition and a ventricular septal defect (VSD) and/or patent ductus arteriosus (PDA) commonly develop severe pulmonary vascular obstruction at an early age. This association has been demonstrated at cardiac catheterization, lung biopsies and in necropsy series. Similar but less severe pulmonary vascular obstructive changes have been found infrequently at necropsy in infants with aortopulmonary transposition and only an atrial septal defect (ASD) and documented rarely at cardiac catheterization. In a group of 29 patients with aortopulmonary transposition and ASD, 27 of whom we have recatheterized, five children aged 7 months to 2½ years demonstrated early development of pulmonary vascular obstruction. In two of these patients the obstruction was severe and led to early deaths, and in a third patient, probably contributed to a postoperative death. Possible factors contributing to the early development of pulmonary vascular obstruction in these patients are discussed as are the problems inherent in the determination of pulmonary vascular resistance in patients with aortopulmonary transposition.

Materials and Methods
During the period July 1966 to June 1974, 86 infants with simple aortopulmonary transposition (i.e., without associated single ventricle or atroventricular valve abnormalities) underwent cardiac catheterization at the University of California Medical Center, San Francisco. Twenty-nine of these patients had an intact ventricular septum and either a minute patent ductus arteriosus (17 patients) or a closed ductus (12 patients) at the initial catheterization. A small PDA was still present at recatheterization in only one patient. Patients with a moderate size or large PDA or associated abnormalities such as total anomalous pulmonary venous connection at the initial catheterization were excluded from the study group as were patients who had pulmonary outflow gradients greater than 30 mm Hg or peripheral pulmonic stenosis at repeat catheterization. Anatomic diagnoses were made by biplane cineangiograms in the right ventricle, left ventricle, and aorta.
All 29 patients were first studied within seven weeks after birth and 27 were recatheterized at ages 2½ months to 4½ years. The initial cardiac catheterization was performed through direct exposure of the femoral vessels in all 29 infants and a Rashkind balloon atrial septotomy was performed in all. The second procedure was performed by direct exposure of the femoral vessels or by percutaneous technique.
Ten neonates were studied while breathing oxygen and the remainder while breathing room air. Repeat cardiac catheterizations were all performed with the patient breathing room air. Infants under four months of age received no premedication; those over four months of age were premedicated with meperidine (1 mg/kg) and hydroxyzine hydrochloride (1 mg/kg) intramuscularly and often required additional amounts of meperidine (0.25 mg/kg) intravenously for sedation during the procedure.

Prior to the use of Swan-Ganz catheters, our efforts to enter the pulmonary artery were brief if left ventricular systolic pressure was below 45 mm Hg. At the initial catheterization, pulmonary arterial pressures were recorded in five infants, all under one week of age. At recatheterization, the pulmonary artery was entered in 14 of 27 patients, mainly with Swan-Ganz catheters. Pressures were recorded on an Electronics for Medicine DR-8 recorder with Statham P23 Db pressure transducers positioned at mid-chest level.

Pulmonary and systemic flows were measured by the Fick technique using assumed oxygen consumption. The equations used for oxygen consumption in patients receiving no sedation was:

\[
V_O_2 \text{ ml/min} = -65.75 + 9.37 \text{ Weight} + 0.38 \text{ heart rate} + 19.17 \text{ age in years}
\]

For those receiving sedation the equation used was:

\[
V_O_2 \text{ ml/min} = -10.36 + 132 \text{ body surface area} - 8.2 + 0.263 \text{ heart rate}
\]

with subtraction of 20.6 if arterial saturation < 88%; and 8.2 if patient is female.

Oxygen contents were calculated using oxygen saturation values and a capacity based upon hemoglobin concentration as measured by the cyanmethemoglobin technique. Two methods of obtaining oxygen saturations for flow calculations were used during the study period. Prior to 1970, oxygen saturations were measured by oximetry only. Since 1970, we have measured oxygen saturation by oximetry and also have derived saturations from pH corrected PO\textsubscript{2} values using an oxyhemoglobin dissociation nomogram. The derived saturations were used for flow calculations in preference to oximeter values as oximetry is inaccurate above 94% and gets progressively more inaccurate below 70%. In contrast, blood oxygen tension measurements are quite accurate throughout the entire range of measurements.

Pulmonary vascular resistance was calculated using the formula:

\[
PVR = \frac{\text{mean PA pressure} - \text{mean PV pressure}}{\text{pulmonary flow}}
\]

where PA = pulmonary arterial and PV = pulmonary venous.

In patients in whom pulmonary vascular resistance could be calculated, it was considered to be normal if 3.0 units/m\textsuperscript{2} or less. All five patients with increased pulmonary vascular resistance were given pulmonary vasodilators in order to assess the reactivity of the pulmonary vascular bed. Each of the five was given an infusion of tolazoline (1 mg/kg) into the main pulmonary artery and two also received 100% oxygen by hood. Flows and pressures were measured before and after administration of the pulmonary vasodilators.

**Results**

Although complete anatomic data were usually obtained at the initial catheterizations, the physiologic data were frequently incomplete or unreliable. Patients were often catheterized while in acute distress and acidemic. Even in those in whom the pulmonary artery was entered, elevated pressures might have been the residue of the high fetal pulmonary vascular resistance in a neonate and/or vasoconstriction due to acidemia. Angiographic evidence of a small PDA was common at the initial catheterization when performed during the first week of life (17/23 patients); however, all but one were found closed at recatheterization. Patients #1, #2, #4 and #5 (table 1) had minute PDAs at their initial catheterizations only.

The pulmonary artery was entered in 14 of the 27 recatheterized patients. Of these 14 patients, two had markedly increased (greater than 10 U/m\textsuperscript{2}), one had moderately increased (5–10 U/m\textsuperscript{2}), and two had mildly increased (3–5 U/m\textsuperscript{2}) calculated pulmonary vascular resistance (table 1). Nine patients had normal calculated pulmonary vascular resistance (less than 3U/m\textsuperscript{2}). Of the 13 patients in whom the pulmonary artery was not entered, ten had left ventricular systolic pressures less than 45 mm Hg, and were considered to have normal pulmonary vascular resistance. The other three had left ventricular systolic pressures of 50 mm Hg, 50 mm Hg, and 65 mm Hg, respectively; however two of the three patients had cineangiographic evidence of left ventricular outflow obstruction and one had evidence of parenchymal lung disease at the time of the study. As pulmonary arterial pressures were not obtained, mildly increased pulmonary vascular resistance could not be excluded in these three patients and they are not included in the group of patients with pulmonary vascular obstruction. This may result as an underestimate of the incidence of this problem.

Branch pulmonary arterial and pulmonary venous stenosis were not sources of error in the assessment of pulmonary vascular resistance in the five patients with elevated resistance. Although both branch pulmonary arteries were not entered in each of the five cases, none had angiographic evidence of branch or peripheral pulmonic stenosis. One or more pulmonary veins were entered at recatheterization in four cases and there was no evidence of pulmonary vein stenosis. The fifth showed no pulmonary vein stenosis at necropsy. Pulmonary venous oxygen and carbon dioxide tensions were normal in four cases and were evidence against pulmonary disease and/or hypoventilation due to sedation as the cause of increased pulmonary vascular resistance. Arterial P\textsubscript{CO\textsubscript{2}} was normal in the fifth patient.

Table 1 summarizes the catheterization data in the five cases with increased pulmonary vascular resistance. Two patients (#1 and #2) had markedly in-
increased pulmonary vascular resistance with minimal responsiveness to oxygen and tolazoline. Both patients had moderately severe systemic arterial hypoxemia and pulmonary arterial hypertension. It is of particular interest that patient #2 was first restudied at age 14 months and was found to have normal pulmonary arterial pressures and a mildly elevated calculated pulmonary vascular resistance (3.8 units/m²). Patient #3 had moderate elevation of pulmonary vascular resistance and minimal responsiveness to tolazoline. Patients #4 and #5 had mild elevation of pulmonary vascular resistance and no responsiveness to oxygen and tolazoline.

Pressures were measured across the left ventricular outflow in 14 patients. There was no systolic pressure difference across the left ventricular outflow tract in the five patients with elevated pulmonary vascular resistance. In the nine patients with normal calculated pulmonary vascular resistance, a 4–28 mm Hg systolic pressure drop was recorded.

The two patients with markedly increased pulmonary vascular resistance died three weeks and two days after cardiac catheterization. Patient #1 died of progressive hypoxemia, patient #2 with a vagal episode associated with a venipuncture. The patient with moderate elevation of pulmonary vascular resistance (#3) underwent a Mustard procedure and died in the immediate postoperative period with low cardiac output and pulmonary complications. It was believed that her elevated pulmonary vascular resistance contributed to her death. Both patients with mild elevation of pulmonary vascular resistance underwent Mustard procedures. Patient #4 died of pulmonary complications. Patient #5 is doing well and at recatheterization six months postoperatively had normal pulmonary arterial pressures and a high normal pulmonary vascular resistance (2.8 U/m²).

Necropsies were performed on three patients (#2, #3, #4) and in each the anatomy was as defined at cardiac catheterization. Patients #2 and #3 showed grade 3 (Heath-Edwards) pulmonary vascular changes while patient #4 showed grade 2 changes.

Possible factors contributing to the early development of pulmonary vascular obstruction were statistically analyzed using the unpaired Student’s t-test. Patients with increased pulmonary vascular resistance did not have significantly different hemoglobin concentrations, hematocrits, pulmonary blood flows, pulmonary-systemic flow ratios, or effective pulmonary flows, compared to patients with normal pulmonary vascular resistance. Systemic arterial oxygen saturations were lower in the five patients with elevated pulmonary vascular resistance than in patients with normal pulmonary vascular resistance; however, it was not possible to determine whether the lower oxygen saturation values were the cause or the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Cardiac Catheterization Data in Five Patients with Aortopulmonary Transposition and Intact Ventricular Septum Who Had Elevated Pulmonary Vascular Resistance at Recatheterization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Age</td>
</tr>
<tr>
<td>---------</td>
<td>------</td>
</tr>
<tr>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
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<tr>
<td>3</td>
<td>55</td>
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<tr>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
</tr>
</tbody>
</table>

**Abbreviations:** b = hours; d = days; w = weeks; m = months; Hct = hematocrit; Qp = mean pressure; LV = left ventricle; PA = pulmonary arterial venous blood pressure; Qs = right ventricle; RA = systemic vascular resistance; RV = right ventricle; Tota = tobaline.

**Notes:**
- The data in Table 1 represent the average of two to six measurements in each patient.
- The metabolic studies were performed using a respiratory gas analyzer and a metabolic cart.
- The oxygen saturation values were measured using a pulse oximeter.
- The data were analyzed using the Student’s t-test.
result of the pulmonary vascular changes. None of the five patients lived at a high altitude.

Discussion

There is some disagreement as to the incidence of pulmonary vascular obstruction in patients with aortopulmonary transposition without a large communication at the ventricular or great artery level. Although it has not been considered to be a problem in infants, pulmonary vascular obstruction has not been uncommon in older children. Plauth and coworkers found increased pulmonary vascular resistance in ten of 22 patients age 2½ to 17 years. Newfeld and coworkers found grade 4 pulmonary vascular disease in four patients age 2, 2½, 3 and 14 years but also found grade 2 changes in seven of 60 infants (12%). Our own experience suggests that early vascular obstruction may not be rare and is another potential complication occurring in the first two years. If early corrective surgery is not recommended, repeat cardiac catheterization at 6 to 9 months of age is indicated in order to determine if surgery may be safely delayed. Clinical assessment alone is inadequate as deterioration due to increased pulmonary vascular resistance may not become evident until pulmonary vascular obstruction is severe. The two patients with severe pulmonary vascular obstruction were clinically stable until two to three weeks prior to the recatheterization, when increasing cyanosis, tachypnea, and lethargy became apparent. The three patients with mild or moderate elevation of pulmonary vascular resistance had shown no clinical changes but were among those patients who underwent recatheterization at ages 6 to 9 months because of our prior experience with the first two patients.

While it is not difficult to determine the presence of markedly elevated pulmonary vascular resistance in patients with aortopulmonary transposition at cardiac catheterization, there are problems associated with the calculation of pulmonary vascular resistance when it is marginally elevated. One major source of error is the inability to determine pulmonary blood flow accurately regardless of the technique of measurement. Two factors are responsible for the inaccuracy of this assessment using the Fick technique. First, the pulmonary arteriovenous oxygen difference in patients with aortopulmonary transposition is usually narrow so that even minor errors in oxygen concentrations will introduce major errors in the calculation of pulmonary blood flow. This is illustrated in Table 2. Assuming a pulmonary venous oxygen saturation of 95% and a pulmonary arterial oxygen saturation of 91%, a 1% error in measurement in each value could result in a three-fold range of calculated pulmonary blood flows. As oximetric values are inaccurate, it is preferable to derive saturations from blood gas measurements or to measure oxygen contents directly.

Second, as most of the bronchial flow enters the pulmonary circuit distal to the sampling site in the major pulmonary arteries, the contribution of bronchial flow to the oxygen saturation in the distal pulmonary arteries is not considered in the calculation of pulmonary blood flow. In aortopulmonary transposition, therefore, a sample obtained from a catheter in a major pulmonary artery would have a higher oxygen saturation than the true mixed pulmonary artery oxygen saturation (fig. 1). The measured pulmonary arteriovenous oxygen saturation difference would be falsely low and the calculated pulmonary flow greater than actual flow. Although it would seem that bronchial contribution to pulmonary flow is too small to produce a major discrepancy, figure 1 shows an example in which a bronchial contribution of only 10% results in a 40% overestimate of pulmonary flow. Consequently, calculated pulmonary vascular resistances are minimum values and marginally elevated resistance values assume even greater significance. Limited bronchial flow has been noted in patients with aortopulmonary transposition without severe pulmonary stenosis or pulmonary

Table 2

Example of Maximal Error that Could be Introduced into Calculation of Pulmonary Blood Flow by 1% Error in Each Determination of Oxygen Saturation
(Assuming O2 Capacity of 20.0 ml/100 ml and O2 Consumption of 150 ml/min, Pulmonary Arterial Saturation = 91% and Pulmonary Venous Saturation = 95%)

<table>
<thead>
<tr>
<th>Site</th>
<th>O2 Saturation</th>
<th>O2 Content</th>
<th>A-V O2 Difference</th>
<th>Pulmonary blood flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Then with a 1% error in oxygen saturation</td>
<td>Pulmonary artery</td>
<td>90</td>
<td>18.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Or</td>
<td>Pulmonary vein</td>
<td>96</td>
<td>19.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary artery</td>
<td>92</td>
<td>18.4</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Pulmonary vein</td>
<td>94</td>
<td>18.8</td>
<td></td>
</tr>
</tbody>
</table>

Range of Calculated Pulmonary Flow: 12.5 - 37.5 L/min
Actual Qp: 18.75

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arterial banding at the time of cardiopulmonary bypass as assessed by pulmonary venous return to the left atrium. However, measurement of pulmonary venous return to the left atrium would not take into account the unknown volume of blood passing from the pulmonary to the systemic venous system through the bronchial venous circulation. This may explain the discrepancy between the findings at surgery and those at necropsy. In fact, we have demonstrated angiographically increased bronchial arterial vessels in nine of our patients with pulmonary outflow gradients less than 28 mm Hg. Patients #1, #2, and #4 were among these nine patients.

Measurement of pulmonary blood flow by indicator dilution methods in aortopulmonary transposition also has its problems. The use of dyes as indicators is technically difficult as two venous catheters are required; there may be marked streaming inequities and the indicator dilution curves show early and very pronounced recirculation. The latter is less of a problem with thermodilution techniques and only one catheter is required; however, streaming may still introduce considerable error. With pulmonary arterial sampling, both dilution methods underestimate total pulmonary blood flow by a volume equal to the bronchial flow and, therefore, the error is considerably less than with the Fick technique. With pulmonary venous sampling, dye dilution curves would include bronchial flow.

Pulmonary flows derived from angiographic volume measurements show considerable variation among patients with aortopulmonary transposition with intact septum. The outputs have been shown to be comparable to outputs measured by thermodilution and both are generally smaller than Fick estimates. Angiographic volume measurements do not include bronchial contribution and the underestimate is equal to the bronchial contribution. Serial measurements (e.g., after oxygen and tolazoline) are not desirable because of the large volumes of contrast necessary.

In summary, the bronchial contribution to pulmonary flow introduces an error in the calculated pulmonary flow. For a given set of bronchial and pulmonary flows, the magnitude and direction of error depends upon the method of measurement.

There, a 10% bronchial contribution results in a 40% overestimate of pulmonary blood flow. Similarly, a 20% bronchial contribution results in an 80% overestimate. The amount of error in a given patient depends not only on the proportion of bronchial contribution to total pulmonary flow but on the pulmonary arterial and bronchial arterial saturations. The higher the pulmonary arterial saturation and the lower the bronchial arterial saturation, the greater will be the error.

Figure 1

Bronchial contribution to pulmonary flow in aortopulmonary transposition. Example of error in calculating pulmonary blood flow by the Fick technique in a patient with a 10% bronchial contribution to total pulmonary blood flow. O₂ capacity = 200 ml O₂/liter blood; O₂ consumption = 150 ml O₂/min-m².

A) Erroneous Qp calculation using pulmonary arterial saturation:

\[
Q_p = \frac{150}{(0.96 - 0.91)} \times 100 = 15.0 \text{ l/min-m²}
\]

B) Correct Qp calculation requires use of a mixed, precapillary saturation:

\[
Q_p = \frac{150}{(0.96 - 0.89)} \times 100 = 10.7 \text{ l/min-m²}
\]

Method of Measurement Error in Qp due to 10% Bronchial Flow
Fick technique Approximately 10%–50% overestimate
Angiographic volumes 10% underestimate
Thermodilution 10% underestimate
Dye dilution
LV → PA 10% underestimate
LV → PV Includes bronchial flow

Another obvious source of error is the use of assumed oxygen consumptions in the Fick method. Although we currently measure oxygen consumption by a hood collection technique, each of the five patients were studied prior to its use. The use of the predictive equations of Fixler and coworkers as compared with Cayler and coworkers resulted in only minor differences in the calculated pulmonary vascular resistances found at the last catheterization of the five patients with increased pulmonary vascular resistance (−4.7%, −1.3%, 0%, +10.7% and +15.7%, respectively). The data of Fixler and coworkers suggests that errors of greater than 30% were most unusual using their predictive equations.
The cause of early pulmonary vascular obstruction in these patients is unknown. Aortopulmonary transposition with intact ventricular septum is the only congenital cardiac lesion with a combination of initially normal pulmonary arterial pressures, increased calculated pulmonary blood flow, and a high hematocrit. Hematocrit levels above 50% result in a progressive increase in viscosity or resistance to pulmonary blood flow, an effect which is accentuated by increasing blood flow. The increased shear forces acting on the endothelial surface of the small pulmonary vessels may cause progressive intimal changes with eventual obliteration of the vessel lumen. Similar vascular changes occur in patients with atrial septal defects at a later age, and the earlier development of these changes in patients with aortopulmonary transposition and intact ventricular septum may be a reflection of differences in hematocrit levels between the two groups. Preferential blood flow to the right lung in patients with transposition has been documented and it has been suggested that such flow inequities might add to the early development of pulmonary vascular obstruction.

We do not know whether early surgical management will delay or halt progression of pulmonary vascular obstruction; the postoperative course in one of our patients (#5) suggests that it may. However, this patient had the lowest resistance and was the youngest of the five with a raised pulmonary vascular resistance, so that general conclusions from her course are not warranted. The development of marked pulmonary vascular obstruction following Mustard's procedure has been reported in three patients whose pulmonary artery pressures and pulmonary vascular resistance were normal prior to surgery.

References


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