Persistent pulmonary hypertension complicating diagnosis and treatment of total anomalous pulmonary venous return in the neonate

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Persistent fetal circulation (PFC) or persistent pulmonary hypertension of the newborn must be differentiated from cyanotic congenital heart disease as soon as possible after birth to provide appropriate therapy. Clinical and echocardiographic features of pulmonary hypertension with right-to-left shunting at atrial and/or ductal levels in the absence of obvious congenital heart disease may suggest PFC, but do not rule out cardiac causes of pulmonary hypertension, specifically total anomalous pulmonary venous return (TAPVR).

We report 4 cases of obstructed infradiaphragmatic TAPVR in newborn infants, each initially diagnosed as PFC. Severe pulmonary vasospasm was present in each case and was clinically responsive to mechanical hyperventilation before correction of TAPVR in 2 patients. This pulmonary vasospasm persisted and complicated the operative course and postoperative management.

From this clinical experience it is apparent that severe pulmonary vasospasm associated with obstructed TAPVR may obscure diagnosis of this lesion and increase the intraoperative and postoperative complications of such patients.

Case reports

Case 1. An 1870-g baby girl, twin B, product of a 37-week gestation, born to a 25-year-old gravida 1 (Table 1),
Table 1. Patient profiles

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (kg)</td>
<td>1.87</td>
<td>3.80</td>
<td>2.52</td>
<td>3.66</td>
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<tr>
<td>Gestation age (wk)</td>
<td>37</td>
<td>39</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>Apgar score 1 min/5 min</td>
<td>9/9</td>
<td>8/9</td>
<td>8/8</td>
<td>8/9</td>
</tr>
<tr>
<td>Age at admission (days)</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac size</td>
<td>Normal</td>
<td>Enlarged</td>
<td>Enlarged</td>
<td>Normal</td>
</tr>
<tr>
<td>Vascularity</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>RVH</td>
<td>RVH/RAD</td>
<td>RVH/RAD</td>
<td>RVH/RAD</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>0.5</td>
<td>...</td>
<td>0.64</td>
<td>0.67</td>
</tr>
<tr>
<td>(RVPEP/RVET)</td>
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RVH = right ventricular hypertrophy; RAD = right axis deviation; RVPEP/RVET = right ventricular pre-ejection period/right ventricular ejection time.

was delivered by cesarean section because of fetal bradycardia. Twin A weighed 2600 g with no medical problems. Twin B had Apgar scores of 7 and 9, and was well until 24 hours of age when she became tachypneic and cyanotic. A chest radiograph revealed minimally increased vascularity and normal cardiac size (Fig. 1). A capillary gas on room air had a PaO₂ of 30 torr, and on an FIO₂ of 0.9 remained between 27 and 40 torr. On the fourth day of life, the patient was transferred to a neonatal intensive care unit. On
admission, heart rate was 138 beats/min; respiration, 60/min; and blood pressure, 80/40 mm Hg in the upper and lower extremities. The infant had circumoral cyanosis in 100% oxygen and no grunting, flaring, or retractions. A grade II/VI systolic murmur was present at the left upper and mid-sternal border, with a soft third heart sound. The pulses were full and the liver was 1 cm below the right costal margin. The clinical, radiographic, and echocardiographic features are summarized in Table 1. The diagnosis was PFC and the patient was intubated and mechanically hyperventilated with 100% oxygen causing the \( \text{PaO}_2 \) to increase from 42 to 154 torr (Table 2). However, \( \text{PaO}_2 \) subsequently fluctuated between 60 and 90 torr. After another three days of hyperventilation and continuous tolazoline infusion (1 mg/kg/hr) the patient developed severe gastrointestinal bleeding and congestive heart failure and died. At autopsy, all four pulmonary veins drained into a single anomalous vein passing through the diaphragm closely associated with the esophagus. It was not possible to demonstrate the insertion of this vessel. Histology of the lungs showed congestion and some hyaline membranes.

**Case 2.** A 3800-g baby boy was born at 39 weeks gestation to a 19-year-old gravida I (Table 1). The labor was complicated by prolonged second stage and double nuchal cord at delivery. Apgar scores were 8 and 9 at one and five minutes, respectively. Shortly after birth, the infant was noted to be cyanotic, and a capillary \( \text{PaO}_2 \) of 25 torr on room air was noted. No increase in oxygenation occurred with an FIO\(_2\) of 1.0. Respirations were 80/min; pulse, 140/min; the infant was grunting, flaring, and retracting. The lungs were clear to auscultation. Cardiac examination showed a hyperdynamic impulse with no murmur. The pulses in all four extremities were normal. The chest radiograph, electrocardiogram, and echocardiogram are summarized in Table 1. Cardiac catheterization showed right-to-left shunting through a patent foramen ovale and ductus arteriosus. Suprasystemic pressures were recorded in the right ventricle and pulmonary artery. Pulmonary angiography in the levo-phase did not clearly demonstrate the venous return phase. No other cardiac defects were demonstrable. The condition was diagnosed as PFC and the patient was treated with tolazoline infusion (2 mg/kg/hr) and hyperventilation with 100% oxygen. Following this, the \( \text{PaO}_2 \) increased from only 23 to 39.8 torr (Table 2) with no clinical improvement. Acidosis developed and the infant died 48 hours later. At autopsy, the patient had TAPVR with a common vein draining to the liver. No gross connection to the portal vein, hepatic artery, or the hepatic vein was found. Examination of the lungs revealed prominent vascular congestion with evidence of pulmonary edema.

**Case 3.** A 2520-g baby girl was born after 39 weeks gestation to a 20-year-old gravida 2, primipara (Table 1). The infant was delivered by cesarean section for placenta previa. The infant was cyanotic at birth with Apgar scores of 8 and 8 at one and five minutes, respectively. A capillary blood gas in 50%
Fig. 2A. Case 3. Prehyperventilation angiogram demonstrates a dilated hypertrophied right ventricle with dilated main pulmonary artery. The descending artery is visualized via right-to-left shunting at the ductus level. Poor visualization of the distal pulmonary arteries suggests peripheral vasoconstriction and decreased total pulmonary blood flow.

B. Posthyperventilation. Note persistence of a right-to-left shunt at the ductus level, with a dilated main pulmonary artery. This represents a marked change from 2A in that the distal pulmonary arteries are much better visualized with what is clearly a change in pulmonary flow pattern through the right and left lung following hyperventilation.

Oxygen revealed a PaO₂ of 18 torr. On admission to this hospital at 20 hours of age, her temperature was 36°C; respirations, 80/min; pulse, 166/min; and blood pressure, 71/42 mm Hg. The patient was active and became cyanotic when stimulated. The lungs were clear, and cardiac examination showed a II–III/VI holosystolic murmur at the lower left sternal border. The liver was palpable 2 cm below the right costal margin. Brachial and femoral pulses were present, but diminished. An arterial blood gas on 100% oxygen revealed a PaO₂ of 29 torr (Table 2). The chest radiograph, electrocardiogram, and echocardiogram are summarized in Table 1. Coronary angiography revealed suprasystemic pressures in both the right ventricle and pulmonary artery, with right-to-left shunting across a patent ductus arteriosus and foramen ovale. Markedly reduced pulmonary blood flow was demonstrated angiographically (Fig. 2A), and no pulmonary venous return could be visualized (Fig. 3A and B). Tolazoline (1 mg/kg) was injected as a bolus directly into the pulmonary artery, but no increase in pulmonary blood flow, arterial oxygenation, or decrease in pulmonary artery pressure occurred. The diagnosis was PFC, and the patient was intubated and hyperventilated with 100% oxygen. Arterial oxygenation increased to a PaO₂ of 177 torr (Table 2). Hyperventilation was continued for six days, and although initially it was possible to decrease the FIO₂ to 0.6, increasing hypoxia developed, and by the seventh day of life, the infant had a PaO₂ of 45 torr on 100% oxygen. A second cardiac catheterization was performed and repeat pulmonary angiography showed a marked increase in pulmonary blood flow since the initial study (Fig. 2B). Pulmonary venous drainage consisted of a single anomalous pulmonary vein inserting into the inferior vena cava below the diaphragm (Fig. 4A and B). With the infant under deep hypothermia (cardioplegia) and cardiopulmonary bypass, the anomalous vein was ligated and a side-to-side anastomosis with the left atrium was created. The patent foramen ovale and ductus arteriosus were ligated. However, cardiac arrest occurred following discontinuation of cardiopulmonary bypass. Following maximal support with pharmacologic agents and direct manual cardiac compression, tolazoline (1 mg/kg) was administered causing an increase in partial pressure of oxygen from 40 to 164 torr (Table 2). Ligatures of the ductus arteriosus were removed to reduce the load on the right ventricle, but the heart was
Fig. 3. Case 3. Prehyperventilation AP view of the right ventricle, levophase. Pulmonary venous return is not visualized.

Fig. 4. Case 3. Total anomalous pulmonary venous return below the diaphragm following hyperventilation. Arrows indicate anomalous common pulmonary vein draining below the diaphragm. Note obstruction at the level of the diaphragm (4A). Pulmonary venous congestion is marked in both lungs (4B).

unble to maintain adequate perfusion and the child died.

At autopsy the previously described finding of TAPVR consisting of a common pulmonary vein originally emptying into the hepatic portal vein about 2 cm from the liver was confirmed. The left ventricle was small and the right atrium and ventricle were dilated. The heart was otherwise normal except for a secundum-type atrial septal defect. The lungs were grossly and microscopically normal.

Case 4. A 3660-g baby girl was born at full term to a 26-year-old gravida IV, para 3 who had had one abortion. The baby was delivered by cesarean section because of face presentation (Table 1). The infant was meconium-stained at birth. Apgar scores were 8 and 9 at one and five minutes, respectively. At three hours of age, the infant was cyanotic, crying, and tachypneic. The lungs were clear and cardiac examination revealed no murmur. The liver was not enlarged and the peripheral pulses were normal. The chest radiograph, electrocardiogram, and echocardiogram are summarized in Table 1. Arterial blood gases revealed a PaO2 of 34 torr in 40% oxygen, which was unchanged by inspiration of 100% oxygen (Table 2). The diagnosis was PFC, and the patient was intubated and mechanically hyperventilated with 100% oxygen. Tolazoline was infused (1 mg/kg/hr) for pulmonary vasodilation.
With these methods, however, the PaO_2 increased from only 34 to 64 torr (Table 2). During the following three days, congestive heart failure and gastrointestinal bleeding developed. On the fifth day of life, the patient underwent cardiac catheterization. The pulmonary artery pressures were suprasystemic, and right-to-left shunting was demonstrated through an atrial septal defect and a patent ductus arteriosus. Selective right and left pulmonary angiography demonstrated all four pulmonary veins draining into a common vertical vein passing below the diaphragm to the inferior vena cava. A Rashkind balloon septostomy was performed, but no increase in arterial oxygenation occurred. The patient was transferred to this hospital for surgical correction of TAPVR.

After induction of deep hypothermia (cardioplegia) on cardiopulmonary bypass, the anomalous common pulmonary vein was ligated and an anastomosis made to the left atrium. The atrial septal defect was closed but the ductus arteriosus was left open to decompress the right ventricle. The infant tolerated the surgery well, but shortly after weaning from bypass, blood pressure and perfusion decreased. A tolazoline bolus (1 mg/kg) was given resulting in a decrease in right atrial pressure and increases in both left atrial pressure and oxygenation. A simultaneous gas from above (60 torr) and below (20 torr) the ductus arteriosus indicated severe right-to-left shunting through the ductus. The patient was given continuous tolazoline drip (2 mg/kg/hr), and hyperventilated on 100% oxygen. Within two hours, the umbilical artery PaO_2 rose to 135 torr (Table 2). A tolazoline drip of 1 mg/kg/hr was continued for 18 hours. The FIO_2 was reduced to 0.75 by 24 hours postoperatively. However, at this time, the umbilical arterial oxygenation suddenly decreased from 120 to 70 torr. Nitroprusside, 1 μg/kg/min, was administered causing an increase in oxygenation to 200 torr. The nitroprusside drip was continued for 24 hours and the infant was slowly weaned from the ventilator. The patient was extubated on the sixth postoperative day and left the hospital 10 days after surgery. At five months of age, he is growing and developing normally.

Discussion

Total anomalous pulmonary venous return, which represents less than 3% of all congenital heart lesions, has a varied natural history depending on the insertion of the veins and the presence or absence of obstruction of pulmonary blood flow. When TAPVR is accompanied by obstruction and severe pulmonary venous congestion, death usually occurs within the first month of life. The differential diagnosis of TAPVR and persistent pulmonary hypertension of the newborn is at best difficult because of the lack of specific clinical findings in obstructed TAPVR. Recently, the difficulties of differential diagnosis of TAPVR and PFC were emphasized by a case of TAPVR with severe pulmonary vasospasm in which cardiac catheterization failed to demonstrate the anomalous pulmonary veins when pulmonary angiography was omitted. Several others have reported that even with pulmonary angiography, anomalous venous return may not be demonstrable. In each of these 4 patients the concurrent presence of severe pulmonary vasospasm obscured the diagnosis of TAPVR. Such pulmonary hypertension is always associated with obstructed infradiaphragmatic TAPVR. Pulmonary vasodilatation did result from hyperventilation, and repeat angiography visualized the anomalous venous return which previously could not be demonstrated in one case. Two patients with TAPVR had marked improvement in arterial oxygenation following hyperventilation. These transient responses supported the diagnosis of PFC and delayed diagnosis of TAPVR. It may,
therefore, be appropriate to catheterize infants with PFC if they fail to maintain oxygenation with vasodilators or hyperventilation. It may also be necessary to restudy, after hyperventilation, patients in whom initial pulmonary angiography does not demonstrate the route of pulmonary venous return.

The surgical mortality of infradiaphragmatic TAPVR with pulmonary venous obstruction may exceed 30%. Katz et al noted that the highest operative mortality occurred in infants with severe obstruction who were critically ill before correction. In 25 patients with TAPVR reported by Hammon et al, 4 of 5 infants who died had required preoperative ventilatory support, and all had angiographically documented pulmonary venous obstruction. All 5 patients had postoperative pulmonary insufficiency, and died either of right ventricular failure or low cardiac output. These authors concluded that preoperative pulmonary venous obstruction is the single factor predicting high risk of operative mortality. Lincoln et al have recently reported intraoperative use of tolazoline as a life-saving maneuver for patients with severe persistent pulmonary vasospasm following complete repair of TAPVR and other lesions. Also, postoperatively 2 patients with TAPVR developed acute pulmonary vasospasm and clinical deterioration, which responded to tolazoline infusion. Postoperative pulmonary hypertensive crisis has also been successfully treated with tolazoline following surgery for closure of ventricular septal defects.

Autopsy studies have shown that patients with TAPVR have abnormally increased pulmonary arterial muscularity. Pulmonary arterial vessel walls were thicker and muscular hypertrophy extended into more peripheral arteries than is usual in normal infants. These abnormalities were present by the eighth day of life. Arterial muscular hypertrophy may result from pulmonary hypertension in utero and predispose patients to pulmonary vasospasm.

In Case 3 reported here it appears that the fatal operative outcome resulted from persistent pulmonary vasospasm leading to acute right ventricular failure. This vasospasm was demonstrated by the intraoperative response to tolazoline. Based on our experience of the first 3 cases reported here, residual pulmonary arterial vasospasm was anticipated in the fourth patient and the surgical approach was modified leaving the ductus arteriosus patent with otherwise complete repair. Intraoperative and postoperative use of pulmonary vasodilators was clearly efficacious and necessary. Right-to-left shunting through the ductus arteriosus postoperatively demonstrated the value of leaving the ductus open as a conduit to decompress the right ventricle in the face of persistent pulmonary artery vasospasm. This shunt was corrected as pulmonary vascular resistance decreased with time and the patent ductus arteriosus closed physiologically.

Our experience with 4 infants with this extremely rare congenital lesion highlights the critical nature of TAPVR with severe pulmonary venous obstruction in newborns. The fact that 2 patients died before the diagnosis was made indicates that surgical mortality data do not completely reflect the mortality associated with this lesion. Even so, surgical correction of this lesion is associated with significant mortality. It appears that residual pulmonary vasospasm and acute right ventricular failure may represent the pathophysiology of the surgical mortality of some of these infants. Our experience, though limited, may indicate that modification of the
traditional repair of TAPVR of the obstructive type, by closing the atrial septal defect, leaving the ductus arteriosus patent, combined with intraoperative and postoperative employment of aggressive medical treatment of pulmonary vasospasm may lead to improved operative outcome for these infants.

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References


