CLINICOPATHOLOGIC CORRELATIONS

Hypertensive Pulmonary Vascular Disease
Associated with Patent Ductus Arteriosus
Primary or Secondary?

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SUMMARY
In an infant with patent ductus arteriosus and pulmonary hypertension, elevated pulmonary vascular resistance persisted following ligation of the ductus. Histologic examination of a pulmonary biopsy at two years of age and tissue obtained at autopsy at three years of age showed obstructive pulmonary vascular disease. The question as to whether the organic pulmonary vascular lesions are secondary to the effects of the patent ductus or part of primary pulmonary hypertension cannot be resolved. The age of the patient favors a primary etiology.

Additional Indexing Words:
Hypertensive pulmonary vascular disease
Primary pulmonary hypertension

OBSTRUCTIVE PULMONARY VASCULAR DISEASE is recognized as a potential complication of the altered dynamics in various communications between the two circulations such as atrial or ventricular septal defects and patent ductus arteriosus (hereinafter called septal defects). Yet, the structural characteristics of the pulmonary vascular bed late in this process are shared by the findings in late stages of primary pulmonary hypertension.

Because of the histological similarities, distinguishing the source of obstructive pulmonary vascular disease depends upon the gross characteristics of the central circulation. When a septal defect is present, existing obstructive pulmonary vascular disease is usually designated as a complication of the identified septal defect. If no gross communication between the two circulations is present, the histologic findings in the lungs are considered a part of the late stage of primary pulmonary hypertension.

There are situations, however, wherein one cannot be certain that the pulmonary vascular disease is, in fact, secondary to an existing defect, since it is possible for primary pulmonary hypertension to be present in an individual with a septal defect without that condition being the contributing cause of pulmonary vascular disease. Such a question arises particularly in infants and young children, since among patients with various septal defects, complicating obstructive pulmonary vascular disease is exceedingly uncommon in patients under the age of three years. In the present case with patent ductus arteriosus it is impossible to establish, with certainty, the basis for obstructive lesions in the pulmonary vascular bed.

A male infant was first examined at the age of four months because of pulmonary "congestion." Physical examination showed a grade II/VI, "to-and-fro" murmur at the upper left sternal border. The hepatic edge lay 4 cm below the right costal margin. Blood pressures taken simultaneously were equal in the right arm and right leg. Thoracic roentgenograms revealed cardiomegaly and increased pulmonary vascularity. The electrocardiogram showed a northwest quadrant axis (+220°), with right ventricular hypertrophy and bialtrial enlargement (fig. 1). The clinical diagnosis was total anomalous pulmonary venous connection. On right-sided cardiac catheterization, levels of oxygen saturations suggested a left-to-right shunt at the
pulmonary artery level. This was confirmed and established as a patent ductus arteriosus by a left ventriculogram. The pulmonary arterial pressures were at systemic levels, while the pulmonary arterial wedge pressure was normal (table 1). Following these tests, the patent ductus arteriosus was ligated and the immediate recovery was uneventful. However, the patient experienced recurrent respiratory symptoms postoperatively for which he was observed on several occasions until the time of his death at the age of three years.

At the age of eight months, cardiac catheterization was repeated to rule out associated anomalies because of continued difficulty with tachypnea and symptoms of congestive cardiac failure. Blood in the left-sided chambers was fully saturated with oxygen. The pulmonary arterial wedge pressure was normal. The pulmonary arterial pressure was found to be elevated although not to the point that it had been at the age of four months. Based on assumed oxygen consumption, the cardiac index was normal. The total pulmonary vascular resistance was markedly elevated (table 1).

Cardiac catheterization at two years of age again failed to demonstrate left-to-right shunt. There was some desaturation of blood in the left atrium (85%) suggesting a transatrial, right-to-left shunt. The pulmonary arterial pressure had risen from a level of 90/50 mm Hg at eight months to 120/55 mm Hg, while the cardiac index was within normal limits. Total pulmonary resistance was calculated to be 3000 DSC. A biopsy of the lung was performed on this admission. The interpretation was that of grade III hypertensive pulmonary vascular disease (Heath-Edwards classification).

At two-and-a-half years of age, results of a xenon pulmonary scan were interpreted as normal, as were measurements of alveolar-capillary pO2 and pCO2 gradients.

At the age of three years, the patient presented features of a deteriorating course from pulmonary hypertension. The symptoms were those of decreased exercise tolerance and upper respiratory infections; additionally, the skin showed chronic duskeness. One episode of acute respiratory distress with increased cyanosis was reported. The physical examination revealed a chronically ill child with a right ventricular heave and a markedly accentuated pulmonary component of the second cardiac sound. A grade II/VI, systolic, ejection murmur was heard at the upper left sternal border. Additionally, a new murmur of grade II/VI with a holosystolic quality was present at the mid-left sternal border. The latter was felt to represent tricuspid insufficiency. A thoracic roentgenogram showed massive cardiomegaly and marked increase in the caliber of the proximal pulmonary arterial segments. Shortly after returning home, the child experienced sudden cardiorespiratory arrest and expired.

Pathologic examination showed an hypertrophied heart with dilatation of the right ventricle and atrium. The thickness of the right ventricular wall measured 1.0 cm (fig. 2a). A valvular competent foramen ovale was present and the ventricular septum was intact. The ductus arteriosus was found to have been surgically closed. The cardiac valves were normal, as were the left-sided chambers (fig. 2b).

Histologic examination of the pulmonary biopsy

**Table 1**

<table>
<thead>
<tr>
<th>Site</th>
<th>4 mo</th>
<th>8 mo</th>
<th>2 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary artery</td>
<td>130/70</td>
<td>90/50</td>
<td>120/55</td>
</tr>
<tr>
<td>Pulmonary artery (mean)</td>
<td>90/0</td>
<td>70/0</td>
<td>75/0</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>130/0</td>
<td>90/0</td>
<td>120/0</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>120/0</td>
<td>115/0</td>
<td>100/0</td>
</tr>
<tr>
<td>Pulmonary artery wedge (mean)</td>
<td>4/0</td>
<td>7/0</td>
<td>10/0</td>
</tr>
<tr>
<td>Output and Resistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>—</td>
<td>1.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Cardiac index (L/min/M2)</td>
<td>—</td>
<td>3.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (DSC)</td>
<td>—</td>
<td>3500</td>
<td>3000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oxygen Saturation (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior vena cava</td>
</tr>
<tr>
<td>Right atrium</td>
</tr>
<tr>
<td>Right ventricle</td>
</tr>
<tr>
<td>Pulmonary artery</td>
</tr>
<tr>
<td>Descending aorta</td>
</tr>
<tr>
<td>Right atrium</td>
</tr>
</tbody>
</table>

*Figure 1*

Electrocardiogram at four months of age.
specimen obtained at the age of two years was compared with tissues obtained at autopsy. The biopsy specimen showed one large muscular artery. Its media was hypertrophied and the lumen was almost obliterated by marked nonspecific fibrous intimal proliferation (fig. 3). No plexiform lesions were found.

The picture was that of hypertensive pulmonary vascular disease, grade III (Heath-Edwards).

The pulmonary tissue obtained at autopsy showed more extensive pulmonary vascular disease (fig. 4). Medial hypertrophy was clearly evident in the large and some small muscular arteries. Many small muscular arteries showed luminal obstruction by plexiform lesions beyond which the arterial walls were thin. An occasional focus showed a collection of dilated small muscular arteries, a picture resembling the so-called “dilatation lesions.” One large muscular artery showed replacement of its wall with fibrous tissue, indicating a healed stage of necrotizing arteritis. The lumen of this vessel was occluded by an organized thrombus.

In view of the evidence for arteritis and the presence of plexiform and dilatation lesions, the hypertensive pulmonary vascular disease was categorized as grade VI (Heath-Edwards).

Comment

In the child whose case is described, severe hypertensive pulmonary vascular disease was associated with a patent ductus arteriosus. The structural changes observed in the pulmonary arterial system conform to complicating lesions that may oc-
cur in association with septal defects, including patent ductus arteriosus (fig. 5). The changes are also compatible with late changes of primary pulmonary hypertension (fig. 6). When attempting to determine whether the basis for these changes was secondary to the patent ductus or primary pulmonary hypertension, it is “safer” to consider them as part of a given disease state such as the patent ductus arteriosus. While such a conclusion cannot be entirely refuted in the case presented, it is unusual for severe pulmonary vascular disease to complicate septal defects in patients under three years of age.

Blount and associates\(^2\) indicated that a patent ductus arteriosus may have more marked effect on the pulmonary circulation than a ventricular septal defect and that irreversible pulmonary vascular changes may occur under two years of age. Hemodynamic and pathologic evidence of this, however, was not presented. These researchers stated that they had seen one case with fixed pulmonary vascular changes at two-and-a-half months of age. No other data were presented. Rudolph and Nadas\(^3\) briefly described a

![Figure 5](image-url)

**Figure 5**
Photomicrographs of pulmonary arteries from adults with patent ductus arteriosus and hypertensive pulmonary vascular disease. a) A large muscular artery shows medial hypertrophy and nonspecific intimal proliferation. A branch shows a plexiform lesion (P). Elastic tissue stain; \(\times\) 78. b) A large muscular artery (upper portion of illustration) shows medial hypertrophy and occlusion of the lumen by an organized thrombus. A branch shows a plexiform lesion (P). Beyond this, the arteries (right side of illustration) show dilatation. Elastic tissue stain; \(\times\) 34.

![Figure 6](image-url)

**Figure 6**
Photomicrographs of pulmonary arteries from an adult with primary pulmonary hypertension. a) A large muscular artery shows medial hypertrophy and nonspecific intimal proliferation. A branch shows a plexiform lesion (P). Elastic tissue stain; \(\times\) 86. b) A large muscular artery shows arteritis. There is necrosis of the wall with leukocytic infiltration and a thrombus present in the lumen. H & E; \(\times\) 77.
case of a patient with patent ductus arteriosus with irreversible pulmonary vascular changes who was operated on at one year of age and died a year later of right-sided cardiac failure. No pathological evidence is presented in this case. In 1967, Wagenvoort and associates* did histologic studies upon biopsies of the lung of 44 patients with ventricular septal defect, the patients ranging in age from four months to 30 years (average, 9.1 years). Plexiform lesions were found in two patients, aged three and seven years, respectively. In the same study, 74 cases of isolated patent ductus arteriosus were studied (age range, five months to 43 years; average, 8.6 years). In none were plexiform lesions observed.

In an earlier study, Wagenvoort and associates6 studied the lungs obtained at autopsy from 50 subjects with ventricular septal defect, ranging in age from fetal life to 12 years. Plexiform lesions were not found under two and a half years of age. In our case with patent ductus arteriosus, obstructive pulmonary vascular disease was confirmed at the age of two years by biopsy of the lung and abnormally high levels of pulmonary vascular resistance identified even as early as eight months of age. In a six-month-old infant with total anomalous pulmonary venous connection to the right atrium, Levy and associates6 observed severe obstructive pulmonary vascular processes, including plexiform lesions.

Based upon the age at which pulmonary hypertensive vascular disease was found in the case described, we favor the view that a primary pulmonary vascular condition was present. While definitive proof cannot be given, we were led to our conclusion by the following findings. At the age of four months the pulmonary and systemic systolic pressures were equivalent and only a left-to-right shunt was present. These features are compatible with those of a wide "hypertensive" patent ductus without organic obstructive pulmonary vascular disease; however, four months following ligation of the ductus, the pulmonary arterial pressure had fallen only slightly. It was below systemic levels but remained at an abnormally high level in the presence of a normal cardiac output. The high levels of underlying pulmonary vascular resistance were probably, in part at least, governed by organic vascular lesions already present. Such lesions were later demonstrated by biopsy at the age of two years.

Regardless of the basis for the pulmonary vascular disease, the degree of vascular change had markedly increased from the time of biopsy at two years to the time of death at three years. While progression of vascular disease is a reasonable assumption, the diagnostic accuracy of a pulmonary biopsy is not uniform. For example, Wagenvoort and associates6 found that while plexiform lesions might be absent, in biopsied subjects who died shortly after the time of biopsy, autopsy might reveal numerous plexiform lesions.

The transatrial right-to-left shunt identified at two years of age is explained by the valvular competent foramen ovale identified at autopsy.

References
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_Circulation_. 1975;52:157-161  
doi: 10.1161/01.CIR.52.1.157

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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