Progressive Pulmonary Vascular Disease after Surgery in a Case of Patent Ductus Arteriosus with Pulmonary Hypertension

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YAMAKI, S., ISHIDOYA, T., OSUGA, Y. and ARAI, S. Progressive Pulmonary Vascular Disease after Surgery in a Case of Patent Ductus Arteriosus with Pulmonary Hypertension. Tohoku J. exp. Med., 1983, 140 (3), 279-288 — In a 15-month-old girl with patent ductus arteriosus (PDA) with pulmonary hypertension, division of the PDA was undertaken, but she died of heart failure 7 months postoperatively. Morphometric study of biopsy and autopsy lungs showed that medial hypertrophy and pulmonary intimal lesions developed markedly after surgery. Severe pulmonary hypertension and hypoxemia were present preoperatively. The pulmonary hypertension remaining postoperatively and aggravated pulmonary hypoxemia are thought to have caused postoperative constriction of the pulmonary vessels and to bring about unusual medial hypertrophy. Since it is known that marked hypertrophy of the media can easily cause vasospasms, it is thought that, in the present case, the smooth muscle cells of the media became necrotic, which brought about damage to endothelial cells. Such damage, in turn, led to the development of occlusive pulmonary vascular disease.

Late death due to progressive pulmonary vascular disease (PVD) following total correction in cases of congenital heart disease with pulmonary hypertension is known to occur in cases not only of complete transposition of the great arteries (TGA), but also of ventricular septal defect (VSD). However, late death is extremely rare in patent ductus arteriosus (PDA). Recently we had an infant case of PDA in which late death followed the development of PVD postoperatively.

Here we report the morphometric study of the pre- and postoperative PVD in this case and discuss the mechanism of progressive PVD after surgery.

CASE REPORT

The patient, a 15-month-old girl, was hospitalized for examination of a suspected congenital heart disease. The chief complaints were underdevelopment and
frequent respiratory infections. She weighed 2,980 g after a full term normal delivery. On admission she was 74.2 cm tall and weighed 8.2 kg, indicating growth retardation. Blood pressure was 85/40 mmHg and pulse rate was regular at 110/min. When crying, cyanosis was evident in the lips and extremities. Accentuated pulmonic sounds and a systolic murmur (Levine II) at the left sternal border near the 2nd rib were audible. The liver was palpable 1 cm below the right costal margin. Red blood cell count was 534 × 10⁴/mm³, hemoglobin 13.6 g/100 ml, and hematocrit 40.5%. Chest X-ray showed a cardiothoracic ratio of 46%, distended arteries of the pulmonary hilus, and an enlarged pulmonary knob. The axis in ECG was +163° and there was marked right ventricular hypertrophy.

Cardiac catheterization (Table 1) gave a pulmonary arterial pressure of 88/45 (70) mmHg, pulmonary-systemic pressure ratio of 1.04, pulmonary-systemic flow ratio of 0.46 and pulmonary-systemic resistance ratio of 1.95. Pulmonary vascular resistance was 17.7 units/m², indicating severe pulmonary hypertension. The oxygen saturation of pulmonary veins, pulmonary arteries and aorta was 80%, 52% and 62%, respectively, indicating severe hypoxemia. Cineangiography allowed a diagnosis of PDA with patent foramen ovale and surgery to divide the PDA was planned.

The operative procedure included a left-sided posterolateral incision of the thorax at the 4th intercostal space. The left lung was found to be divided into 4 lobes and pulmonary emphysema was apparent. Temporary occlusion of the 9 mm PDA using tape was performed, resulting in a decrease in pulmonary arterial pressure from 90/45 mmHg to 60/30 mmHg while blood pressure increased from 90/50 mmHg to 110/75 mmHg. Since no abnormality of heart rate was observed, it was concluded that occlusion of the PDA would be effective and then PDA division was performed. Lung biopsy from the left lingula was also done during the operation.

Twenty-four hours postoperatively, measurement of pulmonary arterial pressure using a Swan-Gantz catheter showed 80/50 mmHg against systemic blood pressure of 110/70 mmHg, indicating the continuation of severe pulmonary hypertension. She was moved to the pediatrics ward and discharged after 2 weeks. However, due to right heart failure, the liver became 6 cm palpable and she was admitted and discharged from hospital a total of 4 times postoperatively. Seven months following the operation, she died of right heart failure.

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<th>Pressure (mmHg)</th>
<th>Oxygen saturation (%)</th>
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<tbody>
<tr>
<td>PA</td>
<td>88/45 (70)</td>
<td>52</td>
</tr>
<tr>
<td>RV</td>
<td>100/2</td>
<td>48</td>
</tr>
<tr>
<td>RA</td>
<td>(3)</td>
<td>46</td>
</tr>
<tr>
<td>MVC</td>
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<td>49</td>
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<tr>
<td>PV</td>
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<td>80</td>
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<tr>
<td>LA</td>
<td>(13)</td>
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<tr>
<td>Ao</td>
<td>85/40 (66)</td>
<td>62</td>
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Progressive Pulmonary Vascular Disease

AUTOPSY FINDINGS

Autopsy showed the right ventricular wall to be 8 mm thick, the left ventricular wall to be 7 mm thick, indicating hypertrophy of the right ventricle. The mitral, aortic and pulmonary valves were normal. However, dilatation of the tricuspid valve suggested the presence of regurgitation. Patent foramen ovale was closed and no other congenital heart diseases such as VSD were observed. The right lung and lower lobe of the left lung showed normal branching, but the upper left lobe had branched into 3 separate lobes. Hypertrophy of the liver (275 g) was evident, but other organs were normal.

MORPHOMETRIC RESULTS

In order to detect the small pulmonary arterial lesions in the biopsy lung tissue, the sample was fixed in 10% formalin and step sections of 200 µm were made throughout the entire block. A total of 50 histologic sections were prepared and examined. In the autopsy lung, 3 samples were taken from each lung lobe, giving a total of 21 samples. Elastica-Masson staining was performed.

The severity of the pulmonary vascular lesions was evaluated using the method of index of pulmonary vascular disease (IPVD) (Table 2) (Yamaki and Tezuka 1976; Yamaki and Wagenvoort 1981a). A total of 230 pulmonary arterial branches were examined in the biopsy lung. As shown in Fig. 1a, 144 small pulmonary arteries showed only medial hypertrophy without endothelial proliferation; 68 such arteries showed cellular intimal proliferation and 18 showed fibroelastic proliferation. One of the transverse sections of small pulmonary arteries showed severe intimal lesion with destruction of the media (Fig. 1b). Although intimal fibroelastic proliferation, which is an irreversible lesion, was found among the biopsy tissue, the IPVD score was 1.5, indicating relatively mild PVD. In contrast, in the autopsy lung, a marked medial hypertrophy was

| Table 2. The severity of pulmonary vascular lesions in biopsy and autopsy lungs |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Pulmonary arterial branches     | No intimal reaction ($n_1$) | Cellular intimal reaction ($n_2$) | Fibrous proliferation of intima ($n_3$) | Destruction of media ($n_4$) |
| Biopsy lung                     | 144             | 68              | 18              | 1               | 1.5             |
| Autopsy lung (total)            | 227             | 8               | 291             | 112             | 1.5             |
| Right upper lobe                | 33              | 6               | 57              | 18              | 2.5             |
| Right middle lobe               | 34              | 0               | 34              | 16              | 2.4             |
| Right lower lobe                | 24              | 2               | 32              | 10              | 2.4             |
| Left upper lobe (I)             | 38              | 0               | 36              | 24              | 2.5             |
| Left upper lobe (II)            | 36              | 0               | 50              | 12              | 2.4             |
| Left upper lobe (III)           | 32              | 0               | 40              | 14              | 2.4             |
| Left lower lobe                 | 30              | 0               | 42              | 18              | 2.5             |

* IPVD was defined by the formula: IPVD = \( \frac{(1 \times n_1) + (2 \times n_2) + (3 \times n_3) + (4 \times n_4)}{n_1 + n_2 + n_3 + n_4} \)
observed (Fig. 2a) and IPVD scores for each of the lung lobes were similar among all lobes and the mean score of 638 small pulmonary arterial branches was 2.5. This score indicated severe occlusive PVD (Fig. 2b). Although fibrinoid necrosis of the media was a characteristic pulmonary arterial lesion, the terminal stage of the plexogenic pulmonary arteriopathy such as the secondary atrophy and dilatation lesions was not observed in autopsy lung.

The medial thickness of small pulmonary arteries in both lungs of biopsy and autopsy was determined using Suwa’s method (Suwa and Takahashi 1971; Yamaki et al. 1980a; Yamaki and Wagenvoort 1981b). That is, the radius ($R$), the distance from the center of the lumen to the middle point of the muscular

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Fig. 1. Transverse sections of small pulmonary arteries in biopsy lung specimen.
a: Hypertrophy of the media is observed.
b: Destruction of the media is observed.
layer, and the medial thickness ($D$) were measured in small pulmonary arteries of various sizes, and plotted on a logarithmic coordinate system. A significant correlation was found between $R$ and $D$ in both biopsy and autopsy samples. Although medial hypertrophy was found even in the biopsy lung, the hypertrophy was further developed in the autopsy lung (Fig. 3).

Other histologic findings of the lung tissue found in both samples included dilatation of the alveolar septum and severe emphysema with discontinuity of the alveolar septum (Fig. 4). In autopsy tissue, cellular proliferation of the alveolar septum was seen and findings of septitis were also obtained (Fig. 5).
DISCUSSION

A number of cases of developed occlusive PVD after total correction of TGA and VSD have recently been reported in the literature (Rosengart et al. 1975; Momma et al. 1981). DuShane and Kirklin (1973) have noted that in VSD the more severe the preoperative pulmonary vascular resistance or the older the child, the greater is the likelihood that the PVD will increase postoperatively. Indeed, all of the VSD cases of pulmonary vascular lesions developing postoperatively which have been reported in the literature are children over 2 years of age (Walker et al. 1965; Hoffman and Rudolph 1965; Lillihei et al. 1968; Birks and Reidemeister 1971; Friedli et al. 1974; Momma et al. 1981).

Fig. 3. Morphometric results of the radius \( R \) and medial thickness \( (D) \) of small pulmonary arteries in biopsy and autopsy lungs plotted as linear regression. The elevation of the equation for biopsy lung was distinctly lower \( (p<0.001) \) than that for autopsy lung.

Fig. 4. Alveolar septum of biopsy lung. The findings of the pulmonary emphysema such as the dilatation and discontinuity of the alveolar septum are observed.
In contrast, pulmonary vascular lesions may be found to develop in children less than 2 years old since there is a pressure load directly on the pulmonary circulation in PDA. In fact, Blount and Vogel (1968) have reported a case of irreversible PVD in a child of 2.5 months old and Linden (1924) and Hufner and McNicol (1958) have reported similar cases in children of 11 months old. However, the report of late death cases due to progressive PVD after surgery is extremely rare in PDA with pulmonary hypertension. Prior to our case there have been only 2 cases of late death following PDA division of infants who showed progressive PVD postoperatively (Rudolph and Nadas 1962; Bessinger et al. 1975). The case of Rudolph and Nadas (1962) was a 1-year-old infant who died 1 year later and that of Bessinger et al. (1975) was a 4-month-old infant who died 2 years later. Since lung biopsy was not performed in either case, it is not possible to judge whether or not irreversible occlusive PVD had already developed prior to surgery.

In our case, severe pulmonary hypertension was found preoperatively. But test occlusion of the PDA produced a decrease in pulmonary pressure and an increase in systemic blood pressure. Therefore, the patient was judged operable and division of the PDA was undertaken. Although pulmonary vascular bed of the biopsy lung showed some irreversible intimal changes, the IPVD score was relatively low, 1.5; indicating that the case was within the critical limit for surgical correction (Yamaki et al. 1980b). Nonetheless, immediately after the operation pulmonary pressure rose again, heart failure increased and she died 7 months postoperatively. The media of small pulmonary arteries in autopsy samples was found to be extremely thicker than that in the preoperative samples and it was apparent that the late death was caused by further development of the occlusive PVD. Here we would like to discuss possible causes for the postoperative development of medial hypertrophy and intimal lesions.
In a 17-year-old male case of VSD in which closure of VSD was followed by progressive PVD and late death, Yoshizawa et al. (1975) reported that the cause of death was the remain of pulmonary hypertension together with strenuous exercise. In our case, although pulmonary hypertension remained postoperatively, she led a quiet life without excessive activity, suggesting that exercise load was not a factor leading to death. We have previously reported a TGA case which died at age of 30 months due to progressive PVD postoperatively (Yamaki et al. 1979). As to the cause of death in that case, we have hypothesized that there was indication of postoperative hypoxemia of pulmonary blood, in addition to irreversible PVD present prior to surgery. It is well known that hypoxemia of the pulmonary arteries can cause vasoconstriction and subsequent medial hypertrophy (Wagenvoort and Wagenvoort 1973; Yamaki et al. 1980c). Since total correction of TGA produces a relative hypoxemia of pulmonary arteries, it could result in small pulmonary arterial vasoconstriction, medial hypertrophy and ultimately obliterative PVD. We have since made morphometric studies of TGA cases with pulmonary hypertension which ended in late postoperative death (Yamaki and Horiuchi 1979). In all such cases, we have demonstrated that the media had become more hypertrophied postoperatively which was caused by a relative hypoxemia of pulmonary arteries.

Although the oxygen content of pulmonary artery in PDA or VSD is not so high as that found in TGA, relative hypoxemia of pulmonary arterial blood due to disappearance of left to right shunt does occur postoperatively and may be a cause of further medial hypertrophy. Since in many cases the surgical correction results in a decrease in pulmonary arterial pressure, the medial hypertrophy may gradually disappear if the patient survives the immediate postoperative period.

Since our patient showed abnormal hypoxemia due to pulmonary emphysema preoperatively, as indicated by oxygen saturation of pulmonary arterial blood of only 52%, it is thought that severe vasoconstriction had been present prior to the operation, resulting in accelerated pulmonary hypertension. Subsequent to PDA division, the disappearance of left to right shunt and septitis exacerbated the pulmonary arterial hypoxemia. The presence of irreversible intimal changes is also thought to have had an effect on maintaining pulmonary arterial systolic pressure at 80 mmHg, which is likely to have caused further vasoconstriction. As a result the media became extremely hypertrophied, and only slight stimulation would lead to frequent vasospasm, which would cause fibrinoid necrosis of the media. Damage to endothelial cells is thought to have then led to the development of occlusive pulmonary arterial intimal changes, with a fatal outcome.

References


