Histologic Study of the Small Pulmonary Arteries in 38 Patients With Pulmonary Atresia and Intact Ventricular Septum

Takashi Tanaka, M.D., Shigeo Yamaki, M.D.*
and Hideyuki Kakizawa, M.D.

The structure of the small pulmonary arteries was studied during autopsies performed on 38 patients with pulmonary atresia with intact ventricular septum. The thicknesses of the media of these small pulmonary arteries measured using a quantitative morphometric method varied widely. However, there was a notable tendency toward thinning of the media, especially in neonates. In cases in which the patient had undergone prostaglandin E₁ treatment, the media was thinner, which suggests that the longer the treatment, the thinner the media. Intimal lesions were observed in 18 of the 38 patients (47%), including 12 of the 22 neonates (55%). Intimal lesions were also found in the patients with thinner media. Based on these results, we propose that organized thrombus formation and intimal proliferation are more likely to develop in patients with reduced pulmonary blood flow, such as in those with pulmonary atresia and intact ventricular septum. In prostaglandin-treated patients, an imbalance between the markedly thinner median muscle and the relatively higher pulmonary blood flow and pressure may contribute to fibrous intimal proliferation. Small pulmonary arteries with a strikingly thinner media may be vulnerable to higher pressure, predisposing the patient to the development of intimal lesions.

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Pulmonary atresia with intact ventricular septum is characterized by complex anomalies of the right ventricle and volume overload of the left ventricle. In most cases, severe cyanosis and heart failure appear in the early days of life. For those patients who have a hypoplastic right ventricle without an infundibular portion, or with sinusoidal communication, surgical management in the neonatal period consists only of a shunt operation. Following the shunt operation, the Fontan procedure is applied to some patients with suitable pulmonary vascular conditions.

Therefore, the analysis of pulmonary vasculature in this disease is as important as the study of the right and left ventricular anatomy. In this study, the pulmonary arterial changes in the patients with pulmonary atresia and intact ventricular septum were analyzed morphometrically and compared with those of normal controls. Since most of the patients in this study were neonates, we can speculate about the condition of the pulmonary vasculature prior to birth. In addition, since some patients were treated with prostaglandin E₁ (PGE₁), we can also discuss the pulmonary vasculature modifications caused by prostaglandin E₁.

Key words:
Pulmonary atresia with intact ventricular septum
Small pulmonary artery
Medial thickness
Thrombosis
Prostaglandin E₁

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The Departments of Pediatrics and Thoracic and Cardiovascular Surgery, Tohoku University School of Medicine, Sendai, Japan
Mailing address: Takashi Tanaka, M.D., Tohoku University School of Medicine, Department of Pediatrics, 1-1 Seiryo-machi, Aoba-ku, Sendai 980, Japan

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TABLE I CLINICAL CHARACTERISTICS OF THE PATIENTS (N=38)

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>PA IVS</th>
<th>critical PS</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Age (months)</td>
<td>2.2±5.5</td>
<td>4.0±5.6</td>
</tr>
<tr>
<td>PGE1 treatment</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Surgery</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>BT shunt</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>AP shunt</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Valvotomy</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>RVOTR</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>RVOTR + BT shunt</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

AP shunt: aorto-pulmonary shunt, BT shunt: Blalock-Taussig shunt, PA IVS: pulmonary atresia with intact ventricular septum, PGE1: prostaglandin E1, PS: pulmonary stenosis, RVOTR: right ventricular outflow tract reconstruction.

METHODS

Patients
Samples of lung tissue obtained at autopsy from 38 patients with pulmonary atresia and intact ventricular septum (including 11 patients with critical pulmonary stenosis) were studied morphometrically. These patients ranged in age from 0 to 30 months (mean age: 2.8±5.7 months). Twenty-four of the patients underwent 1 or 2 surgeries (Table I), but only 3 patients survived longer than 1 week postoperatively. Six of the patients received prostaglandin E1 treatment for 1 to 24 days (mean: 12.5±9.6 days). For control purposes, the medial thicknesses of the small pulmonary arteries were measured in tissue samples obtained at autopsy from 20 normal individuals without cardiac disease.

Measurements
Histologic sections stained with hematoxylin-eosin and according to the Elastica-Goldner method, obtained from at least 3 blocks of various lung lobes, were used for the measurements. The thickness of the media of small pulmonary arteries with a radius of 100 μm was measured using a previously reported method in which the internal elastic lamina is presumed to be completely stretched.1,2 The arteries were selected based on the absence of significant intimal fibrosis, since severe intimal fibrosis may produce secondary atrophy of the media. Approximately 20 pulmonary arteries were measured, and the thickness of the media (D) and the radius (R) of each artery were plotted on a logarithmic coordinate system. For comparative analysis, we used D that was calculated as at a radius of 100 μm (D_{R=100 μm}) for the regression equation. Prior to performing the measurements, we attempted to determine if D differed among the lung lobes in each patient. Two patients were chosen randomly, one with prostaglandin E1 treatment and the other without treatment, in each of whom 5 lobes were studied and compared statistically. We found that the thickness of the media of the small pulmonary arteries in these 2 patients did not significantly differ among the 5 lobes (Table II). Therefore, 3 or more blocks of the various lung lobes we studied were considered to represent whole lungs.

Intimal Lesions
Our study of the intimal lesions of small pulmonary arteries included an evaluation of thrombotic lesions and intimal proliferation.

Statistical Analysis
All averaged values are expressed as the mean±SD. Differences between the means were analyzed using the Mann-Whitney U test. A p value of less than 0.05 was considered significant.

TABLE II PILOT STUDY: THE THICKNESS OF THE MEDIA OF THE SMALL PULMONARY ARTERIES (N=2)

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>D_{R=100 μm}</th>
<th>Patient 2</th>
<th>D_{R=100 μm}</th>
</tr>
</thead>
<tbody>
<tr>
<td>lobe: right upper</td>
<td>10.54</td>
<td>lobe: right upper</td>
<td>6.71</td>
</tr>
<tr>
<td>right middle</td>
<td>10.47</td>
<td>right middle</td>
<td>6.67</td>
</tr>
<tr>
<td>right lower</td>
<td>10.23</td>
<td>right lower</td>
<td>6.34</td>
</tr>
<tr>
<td>left upper</td>
<td>10.14</td>
<td>left upper</td>
<td>7.13</td>
</tr>
<tr>
<td>left lower</td>
<td>10.40</td>
<td>left lower</td>
<td>6.90</td>
</tr>
<tr>
<td>mean</td>
<td>10.36</td>
<td>mean</td>
<td>6.75</td>
</tr>
</tbody>
</table>

D_{R=100 μm}: Thickness of the media (μm) calculated at a radius of 100 μm. PGE1: prostaglandin E1.
RESULTS

**Thickness of the Media of Small Pulmonary Arteries**

In the controls, the media of the small pulmonary arteries demonstrated thinning following birth, which gradually progressed for 5 months. After approximately 5 months, the medial thickness stabilized at 5–7 μm (Fig 1-a).

In patients with pulmonary atresia and intact ventricular septum, the medial thickness varied widely, but demonstrated a notable tendency toward thinning, especially during the neonatal period (Fig 1-b). A comparative analysis of medial thicknesses between the controls and patients revealed a significant difference in the neonatal period (Table III). The thickness of the media of the small arteries (D_R=100 μm) in the controls ranged from 9.4 μm to 9.9 μm (mean 9.5 ± 0.4 μm). On the other hand, the medial thickness ranged from 5.3 μm to 10.9 μm (mean 7.6 ± 1.5 μm) in patients without PGE1 treatment, and from 4.0 to 9.3 μm (mean 5.7 ± 2.3 μm) with PGE1 treatment.

The media appeared thicker than normal in shunted patients, in whom more than 2 weeks had passed since the operation. One was autopsied 5 months after placement of an aortico-pulmonary shunt; the medial thickness (D_R=100 μm) in this patient was 9.6 μm. The other patient was autopsied 1 year after right ventricular outflow reconstruction and Blalock-Taussig shunt surgery. The medial thickness (D_R=100 μm) in this patient was 6.9 μm at 30 months. In both cases, the thickness of the media was above the normal range for the corresponding age group (Fig 1-a).

The media appeared thinner in patients treated with prostaglandin E1 than in untreated patients. In fact, those with treatment (range: 4.0 μm to 9.3 μm; mean: 5.7 ± 2.3 μm) tended to show thinner media than those without treatment (range: 5.3 μm to 11.0 μm; mean: 7.6 ± 1.5 μm, p=0.08) dur-

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**TABLE III THICKNESS OF THE MEDIA OF THE SMALL PULMONARY ARTERIES IN NEONATES**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=6)</th>
<th>Patients (n=23)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (days)</td>
<td>13.7±12.7</td>
<td>9.7±10.9</td>
<td>0.45</td>
</tr>
<tr>
<td>D_R=100 μm</td>
<td>9.0±1.3</td>
<td>7.1±1.8</td>
<td>0.03</td>
</tr>
</tbody>
</table>

D_R=100 μm: Thickness of the media (μm) calculated at a radius of 100 μm.
ing the neonatal period. Thinner media seemed to be associated with longer treatment (Fig 1-b).

**Intimal Lesions of Small Pulmonary Arteries**

Thrombotic lesions were observed in 18 of the 38 patients (47%), including 12 of 22 neonates (55%).

Patients with thrombotic lesions manifested thinner media in their small pulmonary arteries (Fig 2-a). In neonates, the thickness of the media in those with thrombotic lesions ranged from 4.0 μm to 7.7 μm (mean: 6.0 ± 1.4 μm); on the other hand, it ranged from 6.6 μm to 11.0 μm (mean: 8.5 ± 1.5 μm) in those without thrombotic lesions. A significant difference was demonstrated between these groups (p < 0.05).

In 11 of the 18 cases of thrombosis (61%), only recent thrombi were found; in the other 7 cases (39%), organized thrombi with or without recent thrombi were found. Among all of the patients with thrombotic lesions, the media appeared to be thinner in those with organized thrombi (Fig 2-b). In neonates, the thickness of the media in those with recent thrombi ranged from 4.0 μm to 7.7 μm (mean: 6.5 ± 1.4 μm). On the other hand, it ranged from 4.0 μm to 6.6 μm (mean: 5.3 ± 1.1 μm) in those with organized thrombi (p = 0.13).

Intimal proliferation was usually observed with thrombotic lesions. Recanalization (Fig 3) and fibrous septa (Fig 4) were sometimes observed in these regions of intimal proliferation. Therefore, it is probable that intimal proliferation is based on the organization of a thrombus, which is different from that observed in cases of pulmonary hypertensive diseases.

Intimal lesions were observed in 5 of the 6 patients with prostaglandin E1 treatment (83%). Only one had recent thrombi, and the others had organized thrombi and intimal fibrous proliferation. Intimal fibrous proliferation in these cases was concentric and easily distinguishable from thrombi (Fig 5).

**DISCUSSION**

There have been many reports on the thickness of the media of the small pulmonary arteries in patients with congenital heart diseases with increased pulmonary blood flow. However, there are only a few reports in cases of decreased pulmonary blood flow, especially in cases of pulmonary atresia. Furthermore, our present study is unique in allowing for the assessment of the medial thickness for hypothetically distended arteries, thus eliminating the effects of collapse or contraction of arteries. Using this method, we found that the medial thickness of small pulmonary arteries was strikingly thin in some patients with pulmonary atresia and intact ventricular septum. It is interest-
Fig 3. Pulmonary muscular artery with organized and recanalized thrombus in a 25-day-old patient (Elastica-Goldner, ×200).

Fig 4. Pulmonary muscular artery with intravascular fibrous septa in a 25-day-old patient (Elastica-Goldner, ×200).

ing that this tendency is more apparent during the neonatal period. Thinning of the media has been demonstrated in neonates as early as 0 or 1 day after birth. Our present results confirm those in a previous study which suggested that the media of small pulmonary arteries is underdeveloped prior to birth in some patients with pulmonary atresia.4,6

Thrombotic lesions are common in tetralogy of Fallot and in other cyanotic diseases of older patients. It has been suggested that such thrombosis results from increased viscosity due to secondary polycythemia, a reduction in blood flow, or an abnormality of the coagulation system.7-11 In this study, we observed various types of thrombotic lesions which were similar to those reported by Best and Heath in their study of patients with cyanotic congenital heart disease without pulmonary hypertension? Similar lesions were found within only a few days of birth in patients with pulmonary atresia and intact ventricular septum. Organized thrombi were
Fig 5. Pulmonary muscular artery in a 30-day-old patient who underwent prostaglandin E₁ treatment for 24 days. Note the concentric intimal fibrous proliferation (Elastica-Goldner, ×200).

Fig 6. Pulmonary muscular artery in a 0-day-old patient. The media is extremely thin, and the vessel is totally occluded by an organized thrombus (Elastica-Goldner, ×200).

observed at the time of death in a patient 0 days old (Fig 6). In this case, many small arteries less than 100 μm in diameter revealed organized thrombi. Since it is unlikely that such organized thrombi would develop in just a few hours, it may be assumed that the organized thrombi were formed prior to birth. Another patient who died at the age of 24 days demonstrated extensive intravascular thrombosis which sometimes contained regions of recanalization (Fig 3).

In our study, thrombotic lesions were found in patients whose small pulmonary arteries demonstrated thinner media; this tendency was marked in patients with organized thrombi. We propose that an organized thrombus is likely to develop in a patient whose pulmonary blood flow is continuously reduced, while the media is likely to underdevelop. However, despite the possibility of larger pulmonary blood flow through ductus and the antiplatelet actions of prostaglandin,
prostaglandin E₁-treated patients showed thinner media and more frequent intimal lesions (5 of 6 patients).

Our data indicate that a longer treatment with prostaglandin E₁ is associated with a thinner media in small pulmonary arteries. Thus, our findings are consistent with those previously reported by Haworth et al.² Their reported cases consisted of 8 patients who had received prostaglandin E₁ from 30 h to 12 days, and who had no intimal lesions. However, in our cases, intimal lesions were found in patients treated with prostaglandin E₁ for 6 to 24 days. In 1 patient (24 days) concentric intimal proliferations and severe fibrotic changes were observed after 23 days of prostaglandin E₁ treatment (Fig 5). In this case, the medial thickness was strikingly thin (DR = 100 μm; 4.01). It has been suggested that medial hypertrophy protects pulmonary arteries from the development of vascular disease due to pulmonary hypertension.13 In prostaglandin-treated cases, an imbalance between the markedly thinner median muscle and the relatively higher pulmonary blood flow and pressure may contribute to the formation of the intimal lesions; i.e., prostaglandin might interrupt the muscle-protection mechanism. These small pulmonary arteries, with strikingly thinner media, may be vulnerable to higher pressures, and may easily develop intimal lesions.

Only a few, but relatively severe, cases of intimal lesions were found in our 38 patients, including the prostaglandin E₁-treated patients. However, it remains unclear whether these lesions impaired the natural course or operative outcome. Further study is needed to investigate this hypothesis.

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REFERENCES