Extremely Thickened Media of Small Pulmonary Arteries in Fatal Pulmonary Hypertension With Congenital Heart Disease — A Morphometric and Clinicopathological Study

Kiyoshi Nagumo, MD; Shigeo Yamaki, MD*; Tohru Takahashi, MD**

There are patients with congenital heart disease and fatal pulmonary hypertension in whom the medial hypertrophy of the small pulmonary arteries is quite beyond the extent of ordinary cases of hypertension, a condition described as pulmonary hypertension with extremely thickened media of small pulmonary arteries (PH/ETM). Lungs from 6 infants, all younger than 2 years of age, who had congenital heart disease and fatal pulmonary hypertension, were analyzed by accurately measuring the media using Suwa’s method. In PH/ETM, the media of the small pulmonary arteries was shown to be not only unusually thick, but extending toward the periphery, whereas the intimal changes were unexpectedly mild. In the PH/ETM group, the wall thickness at a diameter of 50 μm (%Tw(50)), determined from regression analysis, was 23.2±1.3%, which was significantly higher than in either the control (10.3±1.2%) or ventricular septal defect group (18.9±1.6%). In persistent pulmonary hypertension of the newborn (PPHN), it was 22.3±1.8%, not significantly different from PH/ETM. The striking medial hypertrophy in PH/ETM and PPHN was apparently confined to small pulmonary arteries and in both conditions is likely to be the result of maldevelopment of these arteries. Surgical intervention may trigger a critical elevation of the pulmonary arterial resistance. (Jpn Circ J 2000; 64: 909-914)

Key Words: Congenital heart disease; Persistent pulmonary hypertension of the newborn (PPHN); Pulmonary hypertension with extremely thickened media of small pulmonary arteries (PH/ETM)

In congenital heart diseases, such as ventricular septal defect (VSD), with a much increased flow of the pulmonary arteries, pulmonary hypertension develops from mechanical stretching of the arterial wall! In the early stage of such diseases, the morphological changes are characterized by mild hypertrophy of the media and its extension towards the arterial periphery! which usually does not evoke critical pulmonary hypertension. In the late advanced stage, however, irreversible intimal changes develop in the small pulmonary arteries and is considered to be responsible for the fatally increased pulmonary arterial resistance.

Occasionally, however, there are patients in whom medial hypertrophy alone appears to be creating severe pulmonary hypertension, in the absence of such intimal changes! and we propose that this condition be known as pulmonary hypertension with extremely thickened media of small pulmonary arteries (PH/ETM). The pathology of the arteries is similar to that seen in patients with persistent pulmonary hypertension of the newborn (PPHN), in whom the pulmonary arterial pressure is elevated during the neonatal period in the absence of congenital cardiac disease. The similarity is intriguing because if there are some aspects in common, morphologically, between PH/ETM and PPHN, it assumes a similar pathogenesis. With this in mind we undertook morphometry of the small pulmonary arteries in lungs of PH/ETM patients in order to accurately evaluate the vascular changes, compare the results with cases of PPHN and those of ordinary cardiac anomalies, and correlate the results with the clinical course of the patients and hemodynamic data.

Methods

The basic study material was lung specimens from 6 patients with PH/ETM who all had congenital heart disease and severe pulmonary hypertension, and on microscopic examination of lung, proved to have an extremely thickened medial smooth muscle layer of the small pulmonary arteries (Table 1). The specimens were obtained at autopsy in 3 of the 6 patients, by intrasurgical biopsy in 2, and by open biopsy in 1. For comparative analysis, biopsy specimens from 3 patients who had VSD with pulmonary hypertension, but not a fatal clinical course, lungs from 3 autopsy cases of PPHN and autopsy specimens from 4 cases without signs of abnormal cardiovascular function (Table 2) were also examined.

In each patient, the specimens were usually taken from the upper lobe of the right lung, fixed in 10% formaldehyde for 3 days and embedded in ordinary paraffin. The size of the lung biopsy specimen was about 15×6 mm. From each paraffin block, 30 semi-serial sections were prepared at an interval of 50 μm, with each section being 3 μm thick. The sections were stained with Goldner’s stain together with Weigert’s stain for elastic fibers, a combination which
Table 1 Clinical, Hemodynamic and Histological Findings of the Patients With PH/ETM

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age</th>
<th>Clinical diagnosis</th>
<th>Cardiac catheterization</th>
<th>Surgical procedure (age)</th>
<th>Histological findings</th>
<th>Clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7 mo</td>
<td>AS, CoA, PDA, Turner syndrome</td>
<td>Pp/Ps: 0.89</td>
<td>Aortic valvotomy, EAAA (7 mo)</td>
<td>HE: 1.0 IPVD: 1.0</td>
<td>Residual PH</td>
</tr>
<tr>
<td>2</td>
<td>6 mo</td>
<td>VSD, CoA, PDA</td>
<td>Rp: 13.3</td>
<td>EAAA, PAB (41 days)</td>
<td>HE: 1.3 IPVD: 1.3</td>
<td>No ICR</td>
</tr>
<tr>
<td>3</td>
<td>6 mo</td>
<td>Muscular VSD, large ASD</td>
<td>Qp/Qs: 1.1</td>
<td>ICR (2 mo)</td>
<td>HE: 1.3 IPVD: 1.3</td>
<td>Residual PH</td>
</tr>
<tr>
<td>4</td>
<td>4 mo</td>
<td>VSD, ASD</td>
<td>Qp/Qs: 1.5**</td>
<td>ICR (4 mo)</td>
<td>HE: 1.4 IPVD: 1.4</td>
<td>Perioperative death</td>
</tr>
<tr>
<td>5</td>
<td>22 mo</td>
<td>VSD, PDA, Down syndrome</td>
<td>Rp: 5.5</td>
<td>PDA ligation, PAB (18 mo)</td>
<td>HE: 1.1 IPVD: 1.1</td>
<td>Perioperative death</td>
</tr>
<tr>
<td>6</td>
<td>10 mo</td>
<td>ASD, PDA</td>
<td>Rp: 35</td>
<td>ICR (10 mo)</td>
<td>HE: 1.5 IPVD: 1.5</td>
<td>Perioperative death</td>
</tr>
</tbody>
</table>

*Reclosure of VSD, **data obtained during mechanical ventilation, Qp/Qs, ratio of pulmonary to systemic flow; Pp/Ps, ratio of pulmonary to systemic pressure; Rp, pulmonary arteriolar resistance (units/m²); AS, aortic stenosis; CoA, coarctation of the aorta; PDA, patent ductus arteriosus; VSD, ventricular septal defect; ASD, atrial septal defect; HE, Heath–Edwards classification; IPVD, index of pulmonary vascular disease; EAAA, extended aortic arch anastomosis; PAB, pulmonary artery banding; ICR, intracardiac repair; PH, pulmonary hypertension; mo, months.

Table 2 Patients With PPHN or VSD, and Normal Controls

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Clinical diagnosis</th>
<th>Age</th>
<th>Hemodynamics</th>
<th>Histological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPHN</td>
<td></td>
<td></td>
<td>Pp/Ps</td>
<td>Rp</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>0 day</td>
<td>0.7</td>
<td>1.6</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0 day</td>
<td>0.9</td>
<td>3.3</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>4 days</td>
<td>1.0</td>
<td>3.05</td>
</tr>
<tr>
<td>VSD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>4 mo</td>
<td>0.9</td>
<td>1.6</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>8 mo</td>
<td>0.9</td>
<td>3.3</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>10 mo</td>
<td>1.0</td>
<td>3.05</td>
</tr>
<tr>
<td>Normal controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Intussusception</td>
<td>5 mo</td>
<td>0.9</td>
<td>1.6</td>
</tr>
<tr>
<td>2</td>
<td>VAHS</td>
<td>8 mo</td>
<td>0.9</td>
<td>3.3</td>
</tr>
<tr>
<td>3</td>
<td>Neuroblastoma</td>
<td>15 mo</td>
<td>1.0</td>
<td>3.05</td>
</tr>
<tr>
<td>4</td>
<td>AML</td>
<td>19 mo</td>
<td>1.0</td>
<td>3.05</td>
</tr>
</tbody>
</table>

Qp/Qs, ratio of pulmonary to systemic flow; Pp/Ps, ratio of pulmonary to systemic pressure; Rp, pulmonary arteriolar resistance (units/m²); HE, Heath–Edwards classification; IPVD, index of pulmonary vascular disease; PPHN, persistent pulmonary hypertension of the newborn; VSD, ventricular septal defect; VAHS, virus-associated hemophagocytic syndrome; AML, acute myeloblastic leukemia; mo, months.

ensured the best discrimination among the media, intima and adventitia of the small pulmonary arteries.

First, the sections were observed microscopically so as to define the advancement of pulmonary arteriopathy using both the Index of Pulmonary Vascular Disease (IPVD) and the Heath–Edwards classification (HE). Both classification systems represent the severity of the intimal change, and if the IPVD value is less than 2.2, we recommend intracardiac repair.

The medial thickness of the arteries was measured using the modified method of Suwa and Takahashi (Fig 1). Using a projector (Visopan, Reichert), the microscopic slice of a lung tissue section was projected onto a sheet of tracing paper at a magnification ranging from ×200 to ×400. Of the pulmonary arteries contained in the section, those approximately cross-sectioned were sampled without discriminating the dimension, and the profiles of the internal and external elastic laminae were faithfully delineated. The tracing was thus subjected to measurement using a digital image analyzer (series 9000, model 216, Hewlett-Packard); the sheet was placed upon a digitizer, and the profiles of the elastic laminae were input into a computer by tracing with a cursor. Next, the perimeter length (L) of the more or less meandering internal elastic lamina and the cross-sectional area (S) of the media were computed. With L and S given, we could define the external diameter (De) and the medial thickness (Tm) that the artery would take when it is reduced to a standardized size on the cross-section, the internal elastic lamina is stretched to a circle without changing L, and the media is transformed into a belt of uniform breadth (Tm), with S also remaining unchanged (Fig 1):

\[ L = 2\pi (De/2 - Tm) \]
\[ S = \pi (De/2)^2 - \pi (De/2 - Tm)^2 \]

and therefore

\[ Tm = (\sqrt{L^2 + 4\pi S} - L)/2\pi \]
\[ De = \sqrt{L^2 + 4\pi S} \]

and therefore

To compare the grade of medial hypertrophy among different arteries, we introduced another index, the %wall thickness (%Tw), which gives the ratio of medial thickness to the arterial external diameter:

\[ %Tw = (Tm/De) \times 100 \]

In each case of PH/ETM, the average number of arteries sampled for all the serial sections was approximately 50.
In order to facilitate comparison among the subjects, and also among the case groups, the %Tw was further modified to express the average % wall thickness at 2 diameter levels: D_e = 50 and 200 μm. The values of the average %Tw at these diameters, %Tw(50) and %Tw(200), were calculated from the regression equation between %Tw and D_e (Fig 3).

To compare the degree of extension toward the periphery among the groups, the smallest external diameter of all the muscularized pulmonary arteries sampled was expressed as D_e(min).

Statistical treatment of the quantified data was performed using Student’s t-test. The between-groups difference was defined as being significant when the p-value was less than 0.05.

Of the clinical information, the hemodynamics data obtained in the VSD group by cardiac catheterization was checked and related to the morphometry results.

Results

Table 1 lists the PH/ETM cases and the type of cardiac anomaly, hemodynamic data, clinical course and the grade of vascular changes as evaluated by the HE and IPVD classifications. Cases 2 and 4 were premature births and Case 2 also had a Group B streptococcal infection during the neonatal period. Although all the PH/ETM patients had poor bodyweight gain or oxygen desaturation, apparently a result of pulmonary hypertension during the clinical course, these findings did not always start from the early neonatal period. None of the PH/ETM patients had an episode of asphyxia, meconium aspiration or diaphragmatic herniation, or an apparent maternal abnormality, which causes PPHN. In 5 of the 6 patients, intracardiac repair was performed, but not in Case 2 in which severe medial hypertrophy of small pulmonary arteries was confirmed on lung biopsy. In

Cases 4, 5 and 6, severe pulmonary hypertension caused death shortly after operation. In Cases 1 and 3, pulmonary hypertension continued to exist even after intracardiac repair. Cardiac catheterization was performed in 4 patients, disclosing severe elevation of pulmonary arteriolar resistance (Rp) in 3. In Case 4, in whom cardiac catheterization was performed with mechanical ventilation respiratory support, the resistance was not markedly elevated but the patient died from a perioperative crisis of pulmonary hypertension. Thus, patients with PH/ETM usually have an unfavorable clinical course and if subjected to cardiac repair, a hypertensive crisis very often occurs.

There were mild intimal changes of small pulmonary arteries and arterioles in the PH/ETM lungs, as shown by the IPVD rating, which ranged from 1.0 to 1.5 (Fig 2), and the HE grade, which was as low as 1–2. This grade of intimal change was similar to the range in the VSD group, although in the latter group, the IPVD values were slightly higher (Table 2). Thus, in both the PH/ETM and VSD group, the

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**Fig 1.** Morphometric determination of the external diameter ($D_e$) and the medial thickness ($T_m$) and the % wall thickness ($%T_w$) in small pulmonary arteries. The medial cross sectional areas ($S$) and the perimeter length of the internal elastic lamina ($L$) are transformed to a hypothetical state, in which the internal elastic lamina was stretched to make a perfect circle and the media was replaced by a layer of uniform thickness with an area equal to $S$.

**Fig 2.** Intracircular small pulmonary arteries (Top) and preacinar small pulmonary arteries (Bottom) in PH/ETM (A), PPHN (B), and VSD (C).
intimal change in the pulmonary arteries was only mild. However, the medial smooth muscles in cases of PH/ETM seemed unusually thickened, mainly involving the small arteries located in the intra-acinar alveolar areas (Fig 2). In addition to this extreme hypertrophy, the medial coat was apparently extending toward the periphery of the pulmonary arterial tree. D(min) was 25.9±4.4 μm in the PH/ETM group, 30.7±0.5 μm in the VSD group and 27.5±5.2 μm in PPHN group, against the much higher value in the control group of 46.7±8.6 μm. Thus, in PH/ETM, the medial smooth muscles were not only unusually thick, but extend abnormally toward the periphery. Statistically, D(min) in PH/ETM was significantly lower than in the control group, but the difference from VSD as well as PPHN was not significant.

To what degree the media in small arteries is hypertrophic is clearly understood if the %Tw values are compared among the groups. In each of the cases in the all groups, there was a close negative correlation between %Tw and D(min) (Fig 3), showing that the more peripheral the arteries, the more hypertrophic their media. Based on this, %Tw(50) was calculated from the regression equation and, as shown in Table 3, was 23.2±1.3% and 22.3±1.8 in the PH/ETM and PPHN groups, respectively, showing that medial hypertrophy in the smallest arteries had advanced to essentially the same degree. In the VSD group, the %Tw(50) was 18.9±1.6%, of which was much higher than in the control group (10.3±1.2%) yet significantly lower than the PH/ETM value. Thus, in both PH/ETM and PPHN, the peripheral pulmonary arteries have an extraordinarily hypertrophic media. On the other hand, %Tw(200) was 10.0±4.4% in the PH/ETM group, a value not significantly different from the 8.6±1.7% and 8.8±1.0% of the VSD and PPHN groups, respectively. The extremely thickened media in PH/ETM as well as in PPHN is confined to the intra-acinar peripheral segments of the pulmonary arteries.

**Discussion**

Yamaki et al. noticed that there are a small number of patients, mostly young infants, with congenital heart disease in whom the small pulmonary arteries have an unusually thickened media smooth muscle layer and who are doomed to have an unfavorable clinical course. They regarded this

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**Table 3** Percentage Wall Thickness (%Tw) Calculated by Regression Analysis

<table>
<thead>
<tr>
<th></th>
<th>%Tw(50)</th>
<th>%Tw(200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH/ETM</td>
<td>23.2±1.3</td>
<td>10.0±4.4</td>
</tr>
<tr>
<td>PPHN</td>
<td>22.3±1.8</td>
<td>8.6±1.7</td>
</tr>
<tr>
<td>VSD</td>
<td>18.9±1.6</td>
<td>5.2±0.5</td>
</tr>
</tbody>
</table>

NS, not significantly different. PH/ETM, pulmonary hypertension with extremely thickened media of small pulmonary arteries; PPHN, persistent pulmonary hypertension of the newborn; VSD, ventricular septal defect; %Tw(50), % wall thickness at a diameter of 50 μm; %Tw(200), % wall thickness at a diameter of 200 μm.

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(Nagumo K et al.)
as a special type of pulmonary hypertension, but as yet this condition has not been accurately defined on the basis of quantitative treatment of arterial changes. The present study used morphometry to quantitatively analyze whether or not the medial changes in this condition differ essentially from those in the usual cases of pulmonary hypertension with cardiac anomalies.

We demonstrated that in the PH/ETM group, %TW(50) was significantly increased from the VSD group, which justifies its separate designation. Yamaki has undertaken a preliminary measurement of the PH/ETM lung using an eyepiece and has shown that when the number of small arteries with such enormously thickened media exceeds 10% of the total segments, surgical intervention becomes a critical risk? Because in PH/ETM, as in PPHN, the intimal changes are minimal, if any, the overly hypertrophic media itself is the likely cause of the elevated pulmonary vascular resistance.

Chronic hypoxia is a cause of medial hypertrophy of the pulmonary arteries! but there none of the PH/ETM patients had had such an episode. Maternal hypoxia during pregnancy can also result in medial hypertrophy of the pulmonary arteries of the fetus! but again none of the patients had any record of such episodes.

In patients with congenital heart disease with a much increased pulmonary blood flow, such as VSD, it is well known that in the early stage, the media in the small pulmonary arteries demonstrates not only marked thickening but also extension to the vascular periphery where smooth muscles normally do not exist.

In the late advanced stage, irreversible intimal changes develop in the small pulmonary arteries and these are considered to be responsible for the fatally increased pulmonary arterial resistance. In the present series, 5 of the 6 PH/ETM patients had greatly elevated pulmonary arterial resistance before intracardiac repair was performed, but the intimal changes of the small pulmonary arteries and arterioles were only mild, which implies that the arterial change seen with PH/ETM does not develop as in simple VSD. Yamaki et al studied how and to what degree the abnormally thickened media changes after pulmonary arterial banding (PAB) in another series of patients, corresponding to PH/ETM! They confirmed no difference between the lung biopsy at PAB and that taken when intracardiac repair was performed at a certain period after PAB, which suggests that the extremely thickened media in PH/ETM develops not as a result of the increased amount of pulmonary blood flow, and that the high vascular resistance may be attributable not so much to the left to right shunt as to the abnormalities of the pulmonary vessels themselves. Seeing that there are little if any intimal changes in the pulmonary arterial system, there is no apparent cause for the elevated resistance other than the extreme medial hypertrophy. Possibly, a small pulmonary artery with abnormally thickened smooth muscles can create luminal stenosis not only by overreacting to contractile stimuli, but also by intruding into the lumen.

One patient in the present series (Case 4), the youngest one, did not have elevated pulmonary arterial resistance at the preoperative cardiac catheterization, although it was performed under mechanical ventilation respiratory support. In this patient, the medial hypertrophy of the small pulmonary arteries, though already present at the time of cardiac catheterization, did not seem so severe as to cause the elevated resistance to pulmonary blood flow. However, the arterial media, which must have been more or less hypertrophic, is likely to have triggered the pulmonary hypertensive crisis.

There are neonates who have no cardiac anomaly, but who succumb to severe pulmonary hypertension (ie, PPHN). Microscopic changes of the lung vessels in PPHN resemble those seen in PH/ETM: medial thickening of intra-acinar pulmonary arteries combined with extension of media to the periphery. This is considered to result from one or more of 3 factors: (1) underdevelopment of the lung and its vascular bed, as in the case of diaphragmatic herniation, (2) maldevelopment of the pulmonary vascular bed caused by an unknown mechanism or maternal ingestion of some drugs; and (3) persistent vasoconstriction of fetal and neonatal pulmonary arteries not sufficiently adapted to perinatal stress! Even if some of these factors are implicated in the development of PPHN, it seems quite possible that the hypertension in PPHN is closely associated with the marked medial thickening found in the small pulmonary arteries of such patients.

None of the PH/ETM patients had the severe pulmonary hypertension in their neonatal period as PPHN, when judged from the patient's symptoms and clinical course. In addition, none of the PH/ETM patients had the apparent pre- or perinatal episode that causes PPHN after birth. However, with regard to the microscopic changes of the lung vessels, there was no difference not only in terms of routine quantitative microscopy, but in the results of morphometry. We strongly suspect that in both PH/ETM and PPHN, the same mechanism, particularly maldevelopment of small pulmonary arteries, evokes the elevated vascular resistance of the lung. More studies and other methods of research will clarify in more detail the pathogenesis and pathophysiology of this complicated disease.

Five of the 6 PH/ETM patients underwent cardiac repair and more than half died perioperatively from pulmonary hypertensive crisis. In the 2 other patients who did not experience such a crisis, pulmonary hypertension persisted for at least a few years. All this makes it crucially important to search the pre- or intrasurgical lung biopsy for unusually hypertrophic media in small pulmonary arteries. If it is found, it is essential to prepare for possible perioperative events, such as a critical elevation of pulmonary arterial resistance.

References

9. Meyrick B, Reid L: Ultrastructural findings in lung biopsy material