Different Grades of Medial Hypertrophy and Intimal Changes in Small Pulmonary Arteries among Various Types of Congenital Heart Disease with Pulmonary Hypertension

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YAMAKI, S., ENDO, M. and TAKAHASHI, T. *Different Grades of Medial Hypertrophy and Intimal Changes in Small Pulmonary Arteries among Various Types of Congenital Heart Disease with Pulmonary Hypertension*. Tohoku J. Exp. Med., 1997, **182** (1), 83–91 — Morphometric analysis of small pulmonary arterial changes was performed in three patients with different congenital heart disease with pulmonary hypertension: congenital mitral stenosis (MS), ventricular septal defect (VSD) and transposition of the great arteries (TGA). The material was biopsy or autopsy lung specimens, all having the same degree of elevated pulmonary arterial pressure. Medial thickness was determined by the method of Suwa and Takahashi, and the degree of intimal changes was quantified using the index of pulmonary vascular disease (IPVD) by Yamaki and Tezuka. It was demonstrated that the medial thickening of the small pulmonary arteries was the strongest in the patient with congenital MS, moderate in VSD, and the weakest in TGA, with statistically significant differences between each pair of these three conditions. Interestingly, the order of severity for intimal changes was reversed: it was the severest in TGA and the mildest in congenital MS. We surmise that in patients with TGA, medial hypertrophy is suppressed by sustained vasodilation resulting from the high oxygen saturation of pulmonary arterial blood, while in congenital MS, the media undergoes the severest hypertrophy because of the low oxygen saturation. We also conclude that in TGA intimal changes readily develop in the presence of attenuated media, while in congenital MS, the thickened media seems to prevent intimal changes. From a clinical viewpoint, these results urge us to recommend early surgical intervention in TGA and VSD where severe intimal changes can develop in the absence of extreme medial thickening. It may not be appropriate to extend operation on patients with congenital MS, since strongly thickened media can trigger vasospasms and medial necrosis. —

Received October 14, 1996; revision accepted for publication March 30, 1997.

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pulmonary vascular disease; congenital heart disease; medial thickness; intimal changes; morphometry

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In various cardiac disorders, hypertrophy of the small pulmonary arteries is a common occurrence as a consequence of pulmonary hypertension. We have previously shown that medial hypertrophy can differ markedly among congenital heart diseases such as transposition of the great arteries (TGA) and ventricular septal defect (VSD) even when they show the same level of pulmonary arterial pressure, with the former showing thinner media than the latter (Yamaki and Tezuka 1976). In the present study, we have compared thickness of the media among patients with TGA, VSD and congenital mitral stenosis (congenital MS) having similar levels of pulmonary arterial pressure. We have also compared the intimal changes of small pulmonary arteries among representative patients from these three types of congenital heart disease.

PATIENTS AND METHODS

Each one case of TGA, VSD and MS, with the same level of pulmonary arterial pressure, was selected. Comparisons were made of small pulmonary arteries following morphometric analysis of medial thickness and severity of the intimal changes. The clinical findings of these three cases are listed in Table 1.

In the case of TGA and that of VSD, the lungs were obtained at autopsy, and in the case of congenital MS, by surgical biopsy. The specimens were non-infusion fixed in 10% formalin and embedded in ordinary paraffin. Specimens were taken from each lobe in autopsy cases. In the biopsy case, thirty semi-serial sections were prepared from the block. The sections were stained by Elastica-Goldner staining.

Histometrical measurement of medial thickness in small pulmonary arteries

Because the medial thickness of small pulmonary arteries fluctuates with the post mortem arterial contraction which can be quite variable, the arteries examined were standardized by the following procedure (Suwa and Takahashi

TABLE 1. *Clinical findings of the three patients*

Case	Age (years)	Cardiac disease	PAP (mmHg)	PaSaO ₂ (%)
1	2	TGA	100/60 (80)	87
2	14	VSD	100/48 (72)	76
3	7	Congenital MS	112/63 (87)	66

PAP, pulmonary arterial pressure; PaSaO₂, Oxygen saturation of the pulmonary artery.

1971; Yamaki and Tezuka 1976; Yamaki and Wagenvoort 1981). Cross-sections of arteries and arterioles were selected in histological slides of lung and projected onto a sheet of tracing paper at a magnification of $\times 100$. Arterial sections with severe arterial changes were discarded because secondary atrophy of the muscular coat might affect the histometrical result. The external and internal elastic membranes were exactly followed and delineated. The contours were inputted into a computer by digitization, and the surface area (S) of the medial cross section and the perimeter length (L) of the internal elastic membrane were computed. The arterial section was then transformed to a state in which the internal elastic membrane was stretched to make an exact circle, and the cross-section of the muscular coat was replaced by a belt of uniform thickness, with L and S unchanged throughout this transformation. In this standardized state, the anatomical radius R and the medial thickness D were defined by:

$$R = S / (\sqrt{L^2 + 4\pi S} - L), \quad D = (\sqrt{L^2 + 4\pi S} - L) / 2\pi$$

The principles of this quantification are illustrated in Fig. 1.

In each case, the radius R and medial thickness D were obtained for a number of cross-sectioned muscular arteries of various dimensions. These measurements, when plotted together, revealed a linear regression between R and D on a logarithmic coordinate system.

Regression lines were obtained with the least-squares method with the aid of a microcomputer. Analysis of variance was used to determine the significance for the difference among the cases in the regression slopes and in the hights.

Grading of intimal changes in small pulmonary arteries

Microscopically, hypertensive arterial changes appear as variable pictures. However, all changes may begin with intramural plasmal invasion, and arteries

Fig. 1. Morphometrical determination of the radius R and medial thickness D in small pulmonary arteries. The artery in postmortem constriction is replaced to a hypothetical state of stretched internal elastic membrane.

with various stages of advancement are found in a lung section, ranging from cellular intimal reaction to medial destruction. To express the grade of advancement in a semi-quantitative way, a score from 1 to 4 was given for the following histological findings:

- 1: No intimal reaction
- 2: Cellular intimal reaction
- 3: Fibrous or fibroelastic proliferation of intima
- 4: Partial or total destruction of media.

An index of pulmonary vascular disease (IPVD) was then defined by:

$$\text{IPVD} = \frac{(1 \times n_1) + (2 \times n_2) + (3 \times n_3) + (4 \times n_4)}{(n_1 + n_2 + n_3 + n_4)}$$

where n_1 , n_2 , n_3 and n_4 are the numbers of arteries bearing scores of 1, 2, 3 and 4, respectively. This index expresses the mean grade of of intimal changes in each case and ranges from 1 to 4 (Yamaki and Tezuka 1976; Yamaki et al. 1980).

RESULTS

Medial thickness in small pulmonary arteries

A significant linear log-log correlation was found between R , the radius, and D , the medial thickness, in all of the three patients having either congenital MS, VSD or TGA (Fig. 2). The regression equations in the three patients were:

Congenital MS: $\log D = 0.630 \log R + 0.089$

VSD: $\log D = 0.629 \log R - 0.009$

TGA: $\log D = 0.505 \log R + 0.238$

Fig. 2. Results of morphometry of radius R and medial thickness D in three patients, plotted as linear regressions on a logarithmic coordinate system. The medial thickness D is always the highest in congenital MS ($\circ$, —), followed by VSD ($\bullet$, ----) and then by TGA ($\triangle$, —) over the whole range of R .

Notable is the fact that in the case of congenital MS, the regression line was running along a significantly higher level of log D, followed by VSD, and then, by TGA ($p < 0.05$). This means that, over the whole range of R, the medial thickness D of the small pulmonary arteries is always the largest in the patient with congenital MS, which is followed by the patient with VSD, while in that of and TGA, D remains the lowest.

For comparison, a small pulmonary artery about $100\ \mu\text{m}$ in diameter was selected in each case and shown in Fig. 3.

Severity of the intimal changes

In the patient with congenital MS, the numbers of small pulmonary arteries given IPVD scores of 1, 2, 3 and 4 were 70, 0, 51 and 5, respectively. Necrosis of the media was observed in several small pulmonary arteries in the patient with congenital MS (Fig. 4). The cause of medial necrosis has been considered to be vasospasms which usually occur in small pulmonary arteries with an extremely hypertrophied media. In the case of VSD, IPVD scores of 1, 2, 3 and 4 were given to 98, 6, 90 and 0 arteries, respectively. In the patient of TGA, the arterial numbers were 27, 0, 60 and 12. Plexiform lesions, which were not found in the patient with congenital MS, were observed in the patient with TGA. The IPVD values in the congenital MS, VSD and TGA cases were 1.8, 2.0 and 2.4, respectively, showing the highest value in the TGA patient, an order quite the reverse of that in the grade of medial hypertrophy.

DISCUSSION

It is well known that, in congenital heart diseases with pulmonary hypertension, obstructive pulmonary vascular disease can develop, but the progression differs depending upon the type of cardiac anomalies. In general, it is said that the vascular disease develops and progresses earlier and more severely when cardiac disease is complicated by Down syndrome than not (Wilson et al. 1979). We have found that the cause of this difference is explainable from the hypoplasia of smooth muscle cells of the pulmonary arteries which is unique to Down syndrome (Yamaki et al. 1983a). Moreover, it has been reported that obstructive pulmonary vascular disease develops from an early stage in complete atrio-ventricular canal defect (CAVC), especially cases with Down syndrome (Newfeld et al. 1977). We have observed that even in the absence of Down syndrome, CAVC patients develop intimal changes which progress in response to increased pulmonary arterial pressure but several months after birth their progression is accelerated, while the medial hypertrophy is markedly retarded compared with the elevated pressure. Particularly when associated with Down syndrome, this tendency is unmistakable, with the obstructive pulmonary vascular disease developing from an unusually early stage (Yamaki et al. 1993).

It is well known that in TGA, obstructive pulmonary vascular disease

Fig. 4. Necrosis of the media of small pulmonary arteries in congenital MS indicated by arrow heads.

progresses in a stage much earlier than in VSD (Viles et al. 1969). In 1976, we undertook a comparative study between 40 patients of TGA and 22 patients of VSD with regard to medial thickness (Yamaki and Tezuka 1976). There was a significant correlation between the pulmonary arterial pressure and the medial thickness in both of the cardiac anomalies. Also it was found that, under the same level of pulmonary arterial pressure, the media in TGA is significantly thinner than in VSD. We concluded that the less strengthened vascular wall in TGA is subjected to a greater physical stress and, as a consequence, allows the intimal lesions to develop more quickly than in VSD. With regard to the question why the media is thinner in TGA, we have speculated that in this condition the oxygen saturation of pulmonary arterial blood is much elevated, which suppresses medial hypertrophy by continually dilating the vessels. We previously demonstrated that in a patient with the isolated origin of right pulmonary artery, medial hypertrophy of small pulmonary arteries in the right lung was much less remarkable than in the left lung, and concluded that fully oxygenated blood in the right pulmonary artery might suppress medial hypertrophy, which otherwise could occur in response to high pressure (Yamaki et al. 1983b). This may be supporting the speculation.

In the present study we have compared the IPVD scores and medial thickness of small pulmonary arteries in cases of congenital MS, TGA and VSD. We have

Fig. 3. Various grades of medial thickening of small pulmonary arteries about 100 μ m in diameter in cases of TGA (a), VSD (b) and congenital MS (c). Note the difference in medial thickness. Elastica-Goldner stain $\times 200$.

found that the thickest media occurs in congenital MS, followed by TGA and VSD. Again the oxygen saturation of the small pulmonary arteries seems to provide an explanation for this finding. Since in congenital MS, ordinary venous blood enters the pulmonary arteries, the oxygen saturation is the lowest among the three conditions. On the other hand, in TGA, the blood that enters the pulmonary arteries has already been oxygenated, having the highest oxygen saturation. As a consequence, the media of small pulmonary arteries in TGA is in a state of constant dilation due to high oxygen saturation, which suppresses hypertrophy of the media. In contrast, in congenital MS, the unsaturated venous blood flowing in the pulmonary arteries leaves them in a state of constriction, allowing the media to thicken in response to increased pulmonary arterial pressure, reaching the highest medial thickness. An experimental study by Dingemans and Wagenvoort (1978) may support the occurrence of severe medial hypertrophy in congenital MS. They considered that hypoxia of small pulmonary arteries caused vasoconstriction and led to hypertrophy of the media. Although the age of the TGA patient in the present study was the lowest, intimal changes were the severest, followed by VSD and then congenital MS. This is thought to be due to the fact that the media is the thinnest in TGA, and the attenuated vascular walls induce the intimal changes that appear from an early stage. In contrast, the intimal changes is thought to be suppressed by the medial hypertrophy in congenital MS.

We think that clinically, the suitability of a surgical operation should be made based on the severity of intimal lesions (Yamaki et al. 1980, 1993). In this view, the total correction is recommended to perform at an early stage in cases of TGA when pulmonary hypertension is found, because pulmonary arterial lesions develop the earliest among the three types of disease. In contrast, the operation can be somewhat delayed in VSD; in congenital MS it is possible to wait for a somewhat longer period. It is nevertheless important to note that in the pulmonary arterial vessels with extreme medial hypertrophy, as seen in our congenital MS case, vasospasms can be easily induced, giving rise to necrosis of the media. In light of this danger, it is desirable not to wait too long.

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