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Histologic Changes of Pulmonary Arteries in Congenital Heart Disease with Left-to-Right Shunt (Part 1): Correlated with Preoperative Pulmonary Hemodynamics. Emphasizing the Significance of Pulmonary Arterial Concentration

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The hemodynamic findings related to the histologic changes in the small pulmonary arteries in congenital heart disease were analyzed with a left-to-right shunt. A lung biopsy was performed during the repair because of pulmonary arterial (PA) hypertension (mean PA pressure $\geq$15 mmHg) in 38 patients. There were 13 patients whose age ranged from 2 years to 25 years old. A preoperative cardiac catheterization was performed to locate the site of the defect and to determine the preoperative hemodynamic findings. Among them, 29 patients had pulmonary vascular resistance (PVR) > 2.5 unit/m^2. The lung biopsy specimens were investigated microscopically for the Heath-Edward grade, morphometric analysis of medial wall thickness (MWT) and the rate of the decrease in the pulmonary arteriolar concentration (PAC) obtained by the alvoelo-arterial ratio divided by patients' age. All patients were in the Heath-Edward grade I to III (29 patients in grade I). This grade correlated with the MWT, but did not correlate with a decrease in the PAC. The MWT and the rate of the decrease in the PAC did not accompany each other, but either one had the tendency dominate the pattern in individual patients. The MWT had a close correlation with the mean PA pressure and PVR, and an even closer correlation in patients with a high PVR and those older than 2 years of age. The rate of the decreased in the PAC showed a weak correlation with the shunt volume in patients over 2 years of age or with a large shunt. In the high flow group (PVR <2.5 unit/m^2, Qp/Qs >2.0, n=14) the MWT was significantly thinner and the rate of the decrease in the PAC was significantly higher than the high resistance group (PVR >2.5 unit/m^2, Qp/Qs2 <2.0, n=13). The rate of the decrease in the PAC correlated with the patients' age, but the MWT did not. The lung biopsy results in patients who had both left-to-right shunts and pulmonary hypertension showed that the rate of the decrease in the PAC was weakly related to the shunt volume and the MWT was related to the PA pressure and PVR. Either an increased MWT or the rate of the decrease in the PAC tended to dominate. These phenomena were prominent in patients older than 2 in whom a wide range of individual variations were noted in the morphometric pattern. The medial hypertrophy and the rate of the decrease in the PAC may be induced by different stimuli or that medial hypertrophy may play a role in preventing PAC decrease.

Key Words: Congenital heart disease with left-to-right shunt pulmonary artery, pulmonary hypertension, quantitative morphology correlation between pulmonary vascular change and function

INTRODUCTION

In the repair of congenital heart disease (CHD) with a left-to-right shunt, an increase in resistance due to a pulmonary vascular obstruction (PVO) presents as one of the largest obstacles. Structural abnormalities present in the lung can usually be predicted from the type of intracardiac abnormality, the age of the child, and the hemodynamic findings at cardiac catheterization.[1] It would be ideal to perform corrective surgery before the pulmonary vascular changes become irreversible, but there is no gold standard for assessing the reversibility of pulmonary vascular disease.[2,3] A PVO not only increases the operative mortality

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rate, but also closely affects the long-term prognosis of the surviving patients.[1,2]

Heath and Edward[4] were the first to classify the pulmonary vascular changes based on the pathologic findings of pulmonary artery (PA). The problems presented by these classifications were: 1) The results were not closely correlated with hemodynamics; 2) There were limitations in predicting the reversibility of the pulmonary vascular changes, which is closely related to the longterm prognosis after repair; 3) In ages under 2, most cases are classified as grade I or II, even those with high pulmonary vascular resistance (PVR).[5,6] A new morphometric analysis was proposed by Davies and Reid[7] to compensate for these limitations. This method can more precisely quantify the degree of medial hypertrophy of the muscular artery, thereby further subdividing the Heath-Edward Grade I and II. As a new concept, all the alveoli and arteries present in one microscopic field were counted to obtain the alveolo-arterial ratio. Because the radial count of alveoli in children with increased pulmonary blood flow (PBF) is in the normal range,[8,9] the alveolo-arterial ratio can be regarded as an index for assessing the pulmonary arterial concentration (PAC). However, the significance of the PAC related to the pulmonary hemodynamics or the long-term prognosis is unclear and is still controversial.

The aim of this study was to clarify the relationship between the preoperative hemodynamic pattern and the histologic changes in the PAs according to the Heath-Edward grading and morphometry including medial hypertrophy and the PAC. Thirty-eight patients from various age groups who all received a lung biopsy at the time of surgery were selected for this study. Contrary to the results of some reports,[9] a severe decrease in the PAC did not coincide the severity of the medial hypertrophy, but it did correlate with the magnitude of the shunt.

MATERIALS AND METHODS

Materials

A lung biopsy was done while performing a total repair of 38 CHD patients with a left-to-right shunt. Thirty-four patients were diagnosed with a ventricular septal defect (VSD). Among them, 1 had a patent ductus arteriosus and 2 had an aortic coarctation with a patent ductus arteriosus . Three patients had atrial septal defect, secundum type and 1 patient had a double outlet right ventricle with a subaortic VSD similar to the hemodynamics of a simple VSD. Twenty-six patients were males and 12 were females with ages ranging from from 2 months to 24 years (median 2.3 years). Among them, 13 were under 2 years and 25 were over 2 years. A lung biopsy was done because all patients had pulmonary arterial hypertension (mean PA pressure (15mmHg), and the PVR was > 2.5 unit/m^2 in 29 patients.

Preoperative cardiac catheterization

Cardiac repair was performed within 1 day to 7 months after a cardiac catheterization in all patients, and 34 received the repair within 4 weeks. Most patients were given a light cocktail (Phenalgan 0.5 mmg/kg + Thorazine 1 mg/kg + demerol 1mg/kg) as premedication 30 minutes before catheterization, and general anesthesia was achieved by injecting ketamine 1 - 2 mg/kg intravenously or 5-8mg/kg intramuscularly. Most patients breathed normal air through spontaneous respiration. A left and right heart catheterization was done simultaneously in all patients, thus obtaining the cardiac angiogram necessary to verify the defect site and any associated anomalies. The pressure and oxygen saturation were measured in both the left and right heart. The systemic and pulmonary blood flow was calculated by the Fick principle using the predicted oxygen consumption values.10 The amount of the left-to-right shunt was expressed as a pulmonic-to-systemic flow ratio (Qp/Qs). The PVR (unit/m^2) was calculated by the following formula:

$$\text{PVR (unit/m}^2\text{)} = \frac{\text{Mean PA pressure (mmHg)} - \text{Mean LA pressure (mmHg)}}{\text{Pulmonary blood flow (L/minute/m}^2\text{)}}$$

The correlation between the hemodynamic findings and the histologic changes in the PAs were investigated.

Lung biopsy and histologic observation

A lung biopsy was performed after stabilizing the hemodynamic status following the complete repair of the CHD. During the biopsy process the lung was inflated under 20 - 22 cm H_2O pressure, and approximately 1 cm^3 volume of lung tissue in the anterior segment of RUL was isolated using two C-clamps. The isolated tissue was incised and fixed in a Formalin solution as inflated for approximately 10 minutes, after which the C-clamps were released. After releasing the C-clamps, the tissue was further fixed for an additional 2 hours. Serial sections of the fixed tissue were produced after routine paraffin embedding The sectioned tissue was subsequently stained with hemotoxylin-eosin and elastic van Gieson solutions. The Heath-Edward grade, medial wall thickness and the alveolo-arterial ratio of the PAs were observed.

Medial wall thickness (MWT)

The medial muscular layer between the external and internal elastic lamina lying on the short axis was measured in the PAs, ranging in diameter from 50 - 100 μm. The external diameter of the arteries was measured between the external elastic lamina across the short axis of the vessel. Any partially muscularized PAs were excluded from the measurements. The percentage thickness was then calculated according to the following formula.

$$\text{MWT (\%)} = \frac{2 \times \text{Medial wall thickness}}{\text{External Diameter of PA}}$$

The rate of the decrease in the pulmonary arterial concentration (PAC)

The alveolo-arterial ratio was calculated by counting the total number of alveoli and PAs in a 100 × microscopic field. PAs as small as 20 - 50 μm in diameter were included in the count, and as many microscopic fields as possible were used (2 to 8 fields). For normal morphometric values for each age group we used the data reported by Rabinovitch et al.,[9] whose subjects were mostly Caucasian. As the normal value of the alveolar-arterial ratio varies with age, the alveolar-arterial ratio was divided by the normal values of the corresponding age reported by Rabinovitch et al.[9] to calculate the rate of the decrease in the PAC.

RESULTS

The correlation between the preoperative hemodynamics and the PA morphometric analysis findings for the 38 patients are shown in Table 1 and Fig. 1. The MWT (%) showed a significant

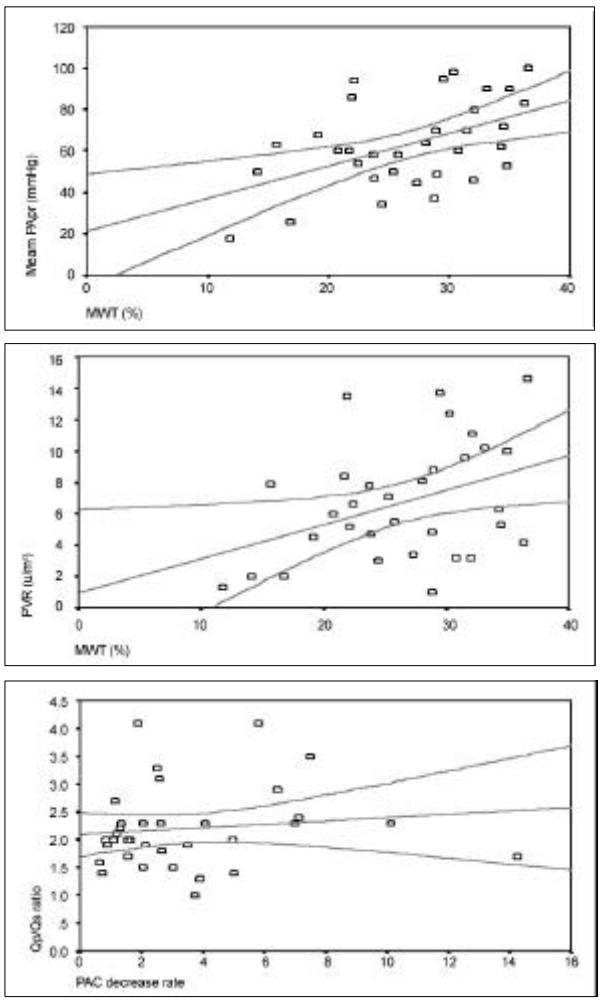

Fig. 1. The linear regression equation between the morphometric findings and the pulmonary hemodynamics. A) between the medial wall thickness (%) and the mean pulmonary arterial pressure (Y=1.56X + 21.55, r=0.55, $p <$ 0.001), B) between the medial wall thickness (%) and the pulmonary vascular resistance (Y=0.22X + 0.970, r=0.45, p <0.01), and C) between the rate of the decrease in the pulmonary arterial concentration and the Qp/Qs ratio (Y= 0.03X + 2.094, r=0.39, p <0.05).

Table 1. Summary of the Pearson Correlation Coefficient® between the Pre-operative Hemodynamics and Morphometric Findings

Hemodynamics	Morphometric findings	
	MWT (%)	Decrease rate of PAC
mPApr (mmHg)		
< 2 y.o	0.24	0.42
≥ 2 y.o	0.71*	0.16
all	0.55†	0.001
PVR (unit/m^2)		
< 2 y.o	0.21	0.02
≥ 2 y.o	0.55‡	0.17
all	0.45§	0.12
Qp/Qs ratio		
< 2 y.o	0.14	0.32
≥ 2 y.o	0.007	0.40‖
all	0.55	0.39‖

*p <0.0005, †p <0.001, ‡p <0.005, §p <0.01, ‖p <0.05.
< 2 y.o: 13 patients younger than 2 years of age.
≥ 2 y.o: 25 patients older than 2 years of age.
All, all 38 patients; MWT, medial wall thickness; PAC, pulmonary arteriolar concentration; mPApr, mean pulmonary arterial pressure (mmHg); PVR, pulmonary vascular resistance (unit/m^2); Qp/Qs ratio, pulmonic/systemic flow ratio.

correlation with the mean PA pressure and the PVR, and the rate of the decrease in the PAC showed a weak correlation. There was no significant difference between the hemodynamic and morphometric pattern in the patients either under 2 years of age (n=13) or over 2 years of age (n=25). The relationship between the MWT (%) and the hemodynamics was more significant in patients over 2 years of age (Table 1). The rate of the decrease in the PAC showed a significant correlation with the Qp/Qs ratio in patients over 2 years of age (Table 1). When the MWT(%) and the rate of the decrease in the PAC were compared (Fig. 2), there was a trend in each patient in which either the MWT(%) was more severe or the rate of the decrease in the PAC was more severe, and the reciprocal relationship was statistically significant (r=-0.37, p < 0.05). As the Heath-Edward grade increased, the MWT (%) increased, but the rate of the decrease in the PAC did not change constantly with this grade. Most patients belonged to Heath-Edward grade I (n=29), and among them, there were some cases showing a high rate of decrease in the PAC. One of the 3 patients belonging to Grade 0 had a high rate of decrease in the PAC, also 3 patients among the 5 grade II and III patients showed an almost normal value of the PAC (Fig. 2).

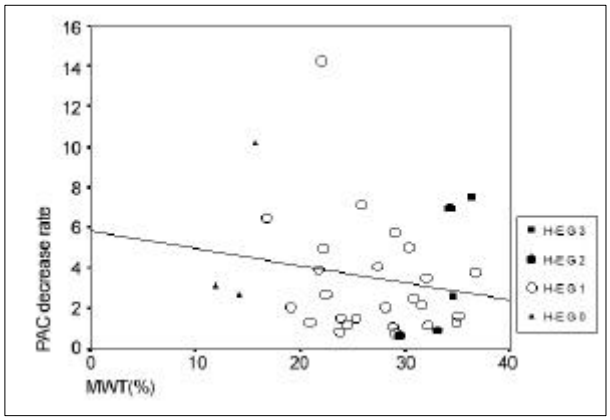

Fig. 2. The relationship between two morphometric findings and the Heath-Edward grade in each individual. The linear regression equation between the medial wall thickness (%) and the rate of the decrease in the pulmonary arteriolar concentration in a whole patient is shown (Y=-0.086X + 5.85, r=-0.37, p <0.05). H-E G, Heath-Edward grade.

On the basis of their preoperative hemodynamic patterns, 14 patients with Qp/Qs higher than 2.0, and a PVR lower than 5.9 unit/m^2 were grouped into the high flow group (average age; 6.2 + 7.4 years), while 13 patients with Qp/Qs < 2.0, and a PVR > 6 unit/m^2 were grouped into the high

resistance group (average age; 3.7 + 4.7 year). The remaining 9 patients were labeled as being in the mixed group (average age; 3.6 + 3.3 years) because they had Qp/Qs > 2.1 and PVR > 6 unit/m^2. The age of the 3 groups was not statistically different. Two patients had a low flow, and a low resistance pattern. The difference in the morphometric findings between the high resistance group and the high flow group was as follows; the MWT(%) and the rate of the decrease in the PAC were 28.8 ± 4.8 and 4.3 ± 2.9 in the high resistance group, 23.8 ± 6.8 and 10.2 ± 8.3 in the high flow group, and 28.5 ± 7.6, 8.6 ± 6.4 in the mixed group, respectively. The difference in both the MWT (%) and the rate of the decrease in the PAC between the high resistance group and the high flow group was statistically significant by t-test ($p < 0.05$). The linear correlation between the hemodynamics and the morphometry between the high flow subgroup and high resistance group was investigated. MWT (%) showed a linear correlation with the mean PA pressure and the PVR in the high resistance subgroup (Table 2, Fig. 3). In the high flow subgroup, the rate of the decrease in the

Table 2. Summary of the Pearson Correlation Coefficient® between the Morphometry and Hemodynamics in the High Resistance Subgroup (n=12)

Hemodynamics	Morphometric findings	
	MWT (%)	decrease rate of PAC
mPApr (mmHg)	0.70*	0.28
PVR (unit/m^2)	0.71*	0.26
Qp/Qs	0.10	0.57

*$p < 0.01$, †$p < 0.05$, Abb.; refer Table 1.

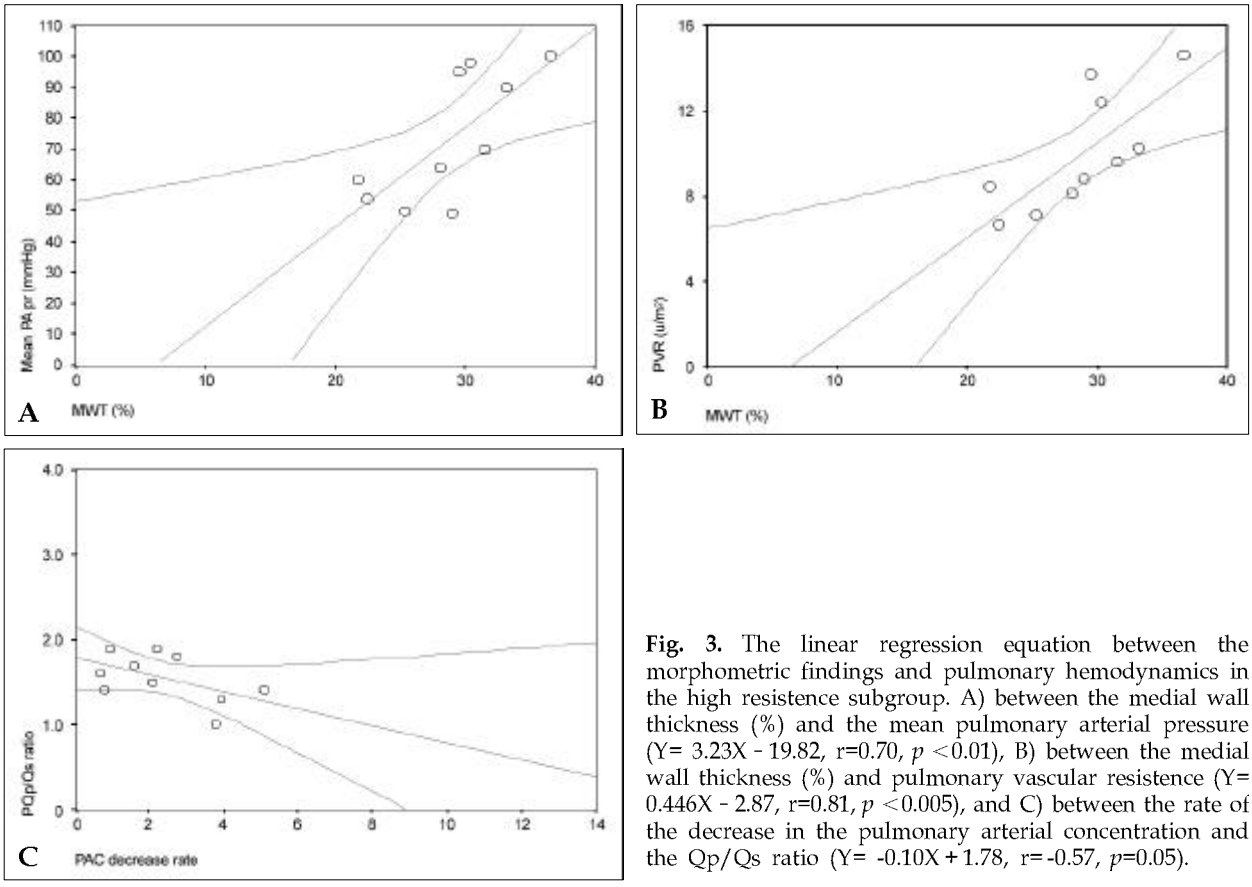

Fig. 3. The linear regression equation between the morphometric findings and pulmonary hemodynamics in the high resistence subgroup. A) between the medial wall thickness (%) and the mean pulmonary arterial pressure (Y= 3.23X - 19.82, r=0.70, $p < 0.01$), B) between the medial wall thickness (%) and pulmonary vascular resistence (Y= 0.446X - 2.87, r=0.81, $p < 0.005$), and C) between the rate of the decrease in the pulmonary arterial concentration and the Qp/Qs ratio (Y= -0.10X + 1.78, r= -0.57, p=0.05).

Table 3. Summary of the Pearson Correlation Coefficient® between the Morphometry and the Hemodynamics in the High Flow Subgroup (n=14)

Hemodynamics	Morphometric findings	
	MWT (%)	Decrease rate of PAC
mPApr (mmHg)	0.54*	0.06
PVR (unit/m^2)	0.36	0.20
Qp/Qs	0.11	0.67†

*$p<0.05$, †$p<0.01$, Abb.; refer Table 1.

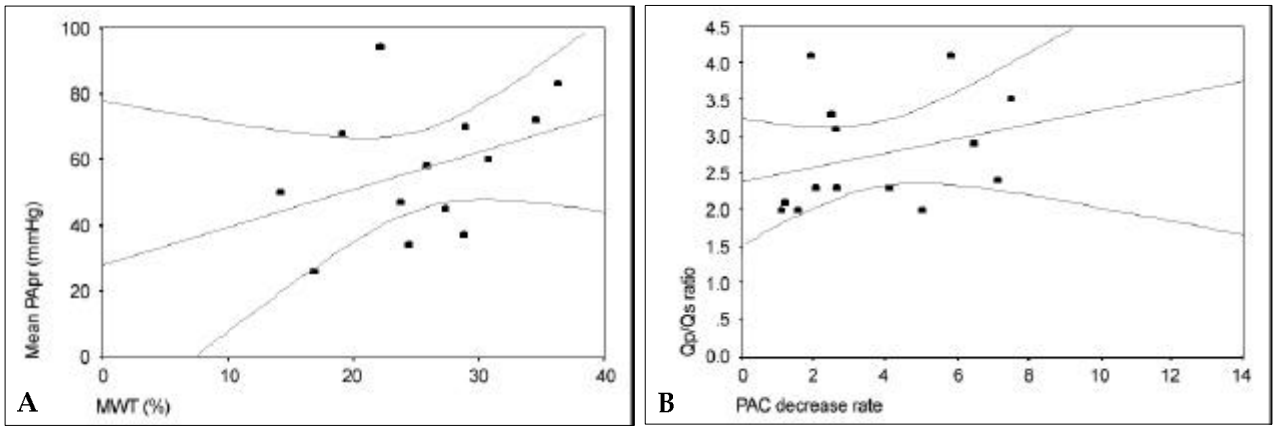

Fig. 4. The linear regression equation between the morphometric findings and pulmonary hemodynamics in the high flow subgroup. A) between the medial wall thickness (%) and the mean pulmonary arterial pressure (Y=1.137X + 28.138, r=0.54, $p<0.05$), B) between the rate of the decrease in the pulmonary arterial concentration and the Qp/Qs ratio (Y=0.086X + 2.277, r=0.67, $p<0.01$).

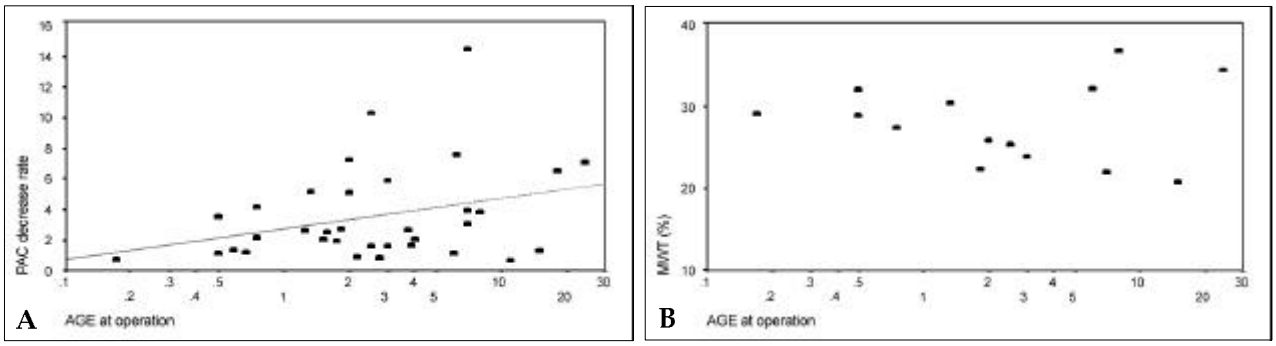

Fig. 5. The linear regression equation between the morphometric findings and the age of patients at the time of operation. A) the decrease rate of the pulmonary arterial concentration and the patient's age (Y=1.954X + 2.71, r=0.40, $p<0.05$), and B) the medial wall thickness (%) and age.

PAC showed a significant correlation with the Qp/Qs ratio (Table 3, Fig. 4).

The changes in the MWT (%) and the rate of the decrease in the PAC according to patients' age are shown in Fig. 5. Cases of a decreasing PAC began to be observed in patients over 2 years. In contrast, there were many patients over 2 who showed an increased MWT (%) but a near normal PAC. The decrease in the PAC at the time of the operation exhibited a significant correlation with patient's age (r=0.40, $p<0.05$). The MWT (%) was above 20% in all patients under 2 years of age, but there were cases where the MWT(%) was below 20% in the patients over 2 years of age. However

there was no significant linear relationship between MWT (%) and the patient age groups (r=-0.24, p=n.s.). Because the rate of the decrease in the PAC had a borderline relationship with the preoperative Qp/Qs, and the patient's at the time of the operation, multivariate analysis was undertaken to look for more important variants. The results showed a significant correlation with the pre-operative Qp/Qs at the 5% level and with the MWT (%) at the 7% level (R^2=0.32, F(33,3)= 5.18688, $p < 0.005$).

DISCUSSION

The subsegmental and pre-acinar PAs mostly completed their development by the sixth week of fetal life, but intra-acinar PAs continue to develop after birth following the development of alveoli.[11,12] During the first 18 months of life, the development of intrapulmonary arteries is most active, which exceeds the rate of alveolar development. Therefore, the ratio of the number of intrapulmonary arteries to the number of alveoli is highest (24 : 1) between birth and 2 months of age. However, this ratio diminishes as the child grows. It reduces to 12:1 by 2 years and 6:1 in adults.[9] The muscular layer begins to develop after the arteries develop, so in an infant most of the intra-alveolar arteries are non-muscular, and as the muscular layer develops it is gradually replaced by muscular arteries.[7,11]

In CHD patients with an increased PBF, there have been reports of precocious muscularization of the non-muscular PAs due to impaired development and remodeling, medial hypertrophy of the muscular arteries, and a decrease in the PAC.[8,9] The relationship between preoperative hemodynamic patterns and the histologic changes in the PAs in this study is that the MWT exhibited a significant correlation with the mean PA pressure and PVR, and this relationship was more significant in patients older than 2 years or in a high resistance subgroup. The rate of the decrease in the PAC showed a weak correlation with the Qp/Qs in patients older than 2 years or in the high flow subgroup. Hislop et al.[13] compared the histologic findings in 5 infants showing a typical clinical pattern of high flow and high resistance and obtained results consistent with ours. The high-flow group showed mild medial hypertrophy and a severe decrease in the PAC, while the high-resistance group demonstrated severe medial hypertrophy but an almost normal PAC.[13]

Variations in the characteristics of the MWT according to a patient's age and individual factors were recognized in this study. Patients younger than 2 years of age showed similar changes: moderate medial hypertrophy and a preserved PAC. Patients older than 2 years of age displayed a wide range of individual variations in both the MWT and PAC: A relatively large number of patients had a normal or mildly increased MWT and a severely decreased PAC, but some individuals had an increased MWT and a maintained PAC (Fig. 5A and B). In contrast, Rabinovitch et al.[9] reported that a severe decrease in the PAC always accompanied severe medial hypertrophy in all patients and closely correlated with the increased PVR. However, only half the subjects in their study were simple VSD patients and most were also younger than 2 years of age. Therefore, differences in the underlying cardiac defects and the age distribution between the 2 study groups may explain such contrasting results.

Severe muscularization of the PAs may reflect a characteristic response of an immature lung to an increased PBF[14,15] or individual variations in the rate of regression of the medial layer after birth.[16] Haworth et al.[17] suggested that in CHD patients with an increased PBF, a decreased PAC may result from a failure of the intra-alveolar PAs to multiply in the earlier stages of life because the diameter and concentration of their PAs had not changed much from this pattern at birth. Another possibility is that intimal proliferation can induce the obliteration and resorption of already developed PAs.[18,19]

The results of this study revealed that there was a tendency for the rate of the decrease in the PAC to be more severe with milder medial hypertrophy. The high-flow subgroup showed a severe rate of decrease in the r PAC with mild medial hypertrophy, but the high-resistance subgroup showed a reverse phenomenon. As the PAs in VSD are more likely to have severe medial hypertrophy at any PA pressure level and at any age, and a less severe PVO than in the transposi-

tion of great vessels, Yamaki & Wagenvoort[20] suggested the possible role of medial hypertrophy and precocious muscularization preventing the PA progressing to a PVO. While transposing great vessels, medial hypertrophy is suppressed by sustained vasodilation resulting from the high oxygen saturation of the PA blood, and intimal changes readily develop in the presence of the attenuated media.[20,21] Friedli et al.[2] stated that VSD patients showing a low resistance and a large amount of shunt volume in infancy, later converted to an increased resistance and PBF in the second year of life. However, patients with a high resistance and a low PBF in infancy exhibit normal resistance in early childhood. These reports and our results agree that medial hypertrophy and the rate of the decrease in the PAC are induced by different stimuli and the medial hypertrophy protects the pulmonary arteries from PVO in infancy. Which of these morphometric changes or how they contribute to progression to a higher Heath-Edward classification grade are not known.

The transit time through the pulmonary vascular bed is shortest in the high-flow and low-resistance hemodynamic group and becomes delayed as the PVR increases.[22] An increase in the blood flow velocity may act as an important pathogenic mechanism of endothelial damage in CHD with an increased PBF. In such defects, partial denudation of endothelial cells from the intra-alveolar arterioles has been demonstrated through electron microscopy.[23] Recent advances concerning the physiology of pulmonary hypertension have focused on chemical factors produced from and in response to different mediators by endothelial and smooth muscle cells. An increase in shear stress stimulates the endothelial cells to produce several modulators of the vascular tone.[19,24] There is an apparent progression from an endothelial dysfunction to a smooth muscle cell dysfunction as the vascular changes progress, both in animal experiments and in humans with CHD. Consequently, the smooth muscle cell migrates through the inner elastic layer into the intima. The arterial medial thickening due to this proliferation correlates with the PA pressure level. Endothelial proliferation and thrombosis contributes to the final obliteration of the small vessels.[19]

There are several pitfalls in interpreting a lung biopsy. Haworth and Reid8 verified in infants that morphometric analysis of a small piece of lung could reflect the pulmonary vascular changes of the entire lung, thus offering the efficacy of a lung biopsy in a PVO diagnosis. However, the pulmonary vascular changes in autopsy specimens have shown a different degree of changes in the pre-acinar and intra-acinar arteries with different types of CHD.[25] The lung portions obtained through a biopsy may not include the more proximal arteries, which make an interpretation of the PA histology variable.[25] Therefore, an adequate biopsy technique taking not only intra- but also pre-acinar vessels is essential. Gorenflo et al.[26] suggested that the alveoli/arteries ratio varied up to 43% from the mean. Consequently, it cannot be determined with adequate certainty in a biopsy specimen, because differentiation of the small venules from non-muscular arteries was not easy and the volume of biopsy specimens were not sufficient in a regular biopsy.[27] The normal value of the alveolo-arterial ratio in various age groups in Korea has not yet been reported. Therefore, the racial difference in the alveoloarterial ratio has not proven. Severe intimal fibrosis most likely did not regress after the correction,[28] so the specific task of morphometry to quantify intimal fibrosis still remains.

In conclusion, a histological evaluation of the PAs in CHD with a left-to-right shunt revealed that the medial hypertrophy and the rate of the decrease in the PAC did not accompany each other, but one or the other tended to dominate in individual patients. The degree of medial wall hypertrophy strongly correlated with the PA pressure and the PVR, while the rate of the decrease in the PAC correlated with the magnitude of the shunt and the age-at-operation. These phenomena were noted more distinctly in patients older than 2 years. It is plausible that the persistence of medial wall hypertrophy may play the role of preventing a decrease in the PAC. Therefore, a lung biopsy can assist in understanding the natural history of the pulmonary vascular changes, particularly in patients over 2 years of age with left-to-right shunt CHD.

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