

# Histologic Changes of Pulmonary Arteries in Congenital Heart Disease with Left-to-Right Shunt (Part 2): Emphasis on the Significance of Pulmonary Arterial Concentration in the Correlation with Pulmonary Hemodynamics after Repair

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We performed this study to assess the correlation of residual pulmonary hypertension in the immediate postoperative period with that in the late follow-up period, to assess the histologic changes of pulmonary arteries (PA) at the time of repair for patients with congenital heart disease consisting of left-to-right shunt, and to clarify the role of lung biopsy in determining the operability and reversibility of pulmonary vascular changes. Lung biopsy was performed during repair in 38 patients, with a wide range of age, who had congenital left to right shunt and pulmonary hypertension. All were Heath-Edward grade III or less. Morphometric study included measurement of medial wall thickness (MWT) and decrease rate of pulmonary arterial concentration (PAC). Mean PA pressure in the immediate postoperative period was measured in all 38 patients. Follow-up cardiac catheterization was performed in 15 patients (average 3.8 years after repair). At operation, 5 patients of this late follow-up group were under 2 years of age and the other 10 were 2 or more. During catheterization, pulmonary hemodynamic reaction was observed both under room air inhalation and after inhalation of hypoxic gas FiO<sub>2</sub> 0.15. Mean PA pressure and pulmonary vascular resistance (PVR) in the immediate postoperative period had a significant correlation with PA pressure and PVR values before the operation, but not with morphometry, Heath-Edward grade, or with pulmonary hemodynamics in late follow-up. During the late follow-up study, 5 of the 15 patients had pulmonary hypertension (defined

as mean PA pressure  $\geq 15$  mmHg) under room air inhalation, and PA hypertension was induced in 4 additional patients after hypoxic gas inhalation. There was no incidence of PA pressure or PVR values registering above the preoperative level. The degree of PA hypertension showed a correlation with the rate of PAC decrease and also with patients' age-at-operation. Multiple regression analysis showed that both the rate of PAC decrease and the age-at-operation contributed significantly to the degree of PA hypertension. Some of the patients over age 2 had a decreased rate of PAC above the regression line, which none of the patients under age 2 experienced. In patients with Heath-Edward grade III or less, residual pulmonary hypertension in the immediate postoperative period was not correlated with histology, but in late follow-up, it was with PAC and the age-at-operation. Therefore, a decrease of PAC is assumed to be a totally or partially irreversible pulmonary vascular change depending on the patient's age-at-operation, while medial hypertrophy is thought to be a reversible pulmonary vascular change. Lung biopsy could play an important role in determining the reversibility of pulmonary vascular obstruction, particularly in patients older than 2 years.

Ed- re highlights above: such hyphenation is optional, but if used then it should be applied consistently throughout the paper. As 3 of the 4 entries in the abstract use it, I have maintained it consistently below.

**Key Words:** Congenital heart disease with left-to-right shunt pulmonary artery, pulmonary hypertension, quantitative morphology, post-operative follow-up

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## INTRODUCTION

In congenital heart disease (CHD) with left-to-

right shunt, the defect is best repaired before pulmonary vascular changes become irreversible, but predicting the reversibility of pulmonary vascular obstruction (PVO) through clinical evidence or cardiac catheterization has its limitations and is not always accurate.<sup>1,2</sup> Although the role of lung biopsy to determine operability in these patients is still inconclusive, it can be done either preoperatively or simultaneously during repair to solve this problem. According to the Heath-Edward scale,<sup>3</sup> a grade higher than IV is considered irreversible and contraindicates complete repair. But some patients with grade III or lower may also show progressive PVO after repair,<sup>4</sup> so predicting PVO reversibility on the basis of the Heath-Edward scale alone also has its limitations. Supplementation of morphometric analysis to Heath-Edward grade in patients with grade III or lower may complement prediction of residual PVO.<sup>5</sup>

We performed lung biopsy at the time of repair for CHD with left-to-right shunt, and also performed a follow-up cardiac catheterization study, averaging 3.8 years after repair, to look for histologic evidence of pulmonary arteries (PA) that most closely correlated with residual PVO in patients with Heath-Edward grade III or lower.

## MATERIALS AND METHODS

### Materials

Lung biopsy was performed on 38 patients receiving repair for left-to-right shunt. They were studied for pulmonary hemodynamics immediately after the operation (n=38) and also at an average 3.8 years (3-4.2 years) after the repair (n=15). None of the 15 patients in the latter group demonstrated residual left-to-right shunt. The patients' ages at the time of late follow-up ranged from 4-27 years (median 6 years) and all repaired main cardiac defects were VSD, but coarctation of the aorta coexisted in 1 patient and another had accompanying patent ductus arteriosus.

### Method of lung biopsy and histologic observation

These examinations proceeded as previously

described in Part 1 of the present study

### Hemodynamic study on the second postoperative day

Catheters were introduced via the anterior wall of the right ventricle and pulmonary vein at the time of operation to monitor the pressure and oxygen saturation of the right and left heart. On the second postoperative day, mean PA pressure and the pulmonic-to-systemic resistance ratio (Rp/Rs) were calculated after the patient had been weaned off the mechanical ventilator and the hemodynamics had been stabilized.

$$\text{Rp/Rs ratio} = \frac{\text{Mean PA pressure (mmHg)} - \text{Mean LA pressure (mmHg)}}{\text{Mean aortic pressure (mmHg)} - \text{Mean RA pressure (mmHg)}}$$

### Late follow-up cardiac catheterization

Premedication and anesthesia during cardiac catheterization were performed as previously described in part 1 of the present study.<sup>6</sup> The patients were studied under spontaneous room air respiration. Both the right heart and left heart were studied simultaneously to measure oxygen saturation of the PA and right atrium for confirmation of the absence of residual left-to-right shunt. The aortic, PA, right atrial and pulmonary venous wedge (PVW) pressures were all measured, cardiac output was calculated by thermodilution method, and pulmonary vascular resistance (PVR) was calculated by the following formula.

$$\text{PVR (unit/m}^2\text{)} = \frac{\text{Mean PA pressure (mmHg)} - \text{Mean PVW pressure (mmHg)}}{\text{Cardiac index (L/minute/m}^2\text{)}}$$

All patients were restudied after 10 minutes of spontaneous respiration with FiO<sub>2</sub> 0.15 gas mixture held in a Douglas bag, via a mask with a one-way valve, followed by reevaluation of their pulmonary hemodynamic responses to hypoxic gas inhalation. The results under room air respiration and after hypoxic gas inhalation were compared. Systemic arterial gas study was undertaken to monitor arterial oxygen tension 4,

8, and 10 minutes after the start of hypoxic gas inhalation, and the aortic and PA pressures were also monitored at the same time. About 9 minutes and a half minutes after the start of hypoxic gas inhalation, the pressures and cardiac output were studied as previously described for an additional two minutes under continuous inhalation of hypoxic gas.

### The correlation between hemodynamic pattern and PA histologic changes

Hemodynamic results of the second postoperative day and at an average 3.8 years after repair were correlated with the preoperative hemodynamics, age-at-operation, Heath-Edward grade and morphometric findings of lung biopsy specimens obtained at the time of repair.

## RESULTS

### Correlation between hemodynamics of the second postoperative day and histology

Postoperative mean PA pressure and Rp/Rs ratio each showed a correlation with preoperative mean PA pressure ( $r=0.39$ ,  $p<0.0005$ ) and PVR ( $r=0.51$ ,  $p<0.001$ ), respectively, but neither did with medial wall thickness percentage (MWT) (Fig. 1) or with the decrease rate of pulmonary arteriolar concentration (PAC). No remarkable

difference in the strength of this linear correlation was seen between patients either younger or older than 2 years. Twenty eight patients with Heath-Edward grade I had mean PA pressure  $24.5 \pm 11.2$  mmHg, and Rp/Rs ratio  $26.3 \pm 15.6\%$ . Few patients belonging to other grade groups, but 2 out of the 4 patients with Heath-Edward grade 0, who had almost normal PAC, demonstrated almost normal postoperative hemodynamics, while the other 2 patients with decreased PAC showed postoperative mean PA pressure of 34 and 19 mmHg. Postoperative PA pressure and Rp/Rs ratio of the 2 patients in grade II were no higher than those in grade I. The two patients in grade III had mean PA pressure of 28 and 74 mmHg, and Rp/Rs ratio of 22.3% and 90.2%.

### Correlation between hemodynamics of the late follow-up period and histologic changes

Systemic arterial oxygen tension ( $\text{PaO}_2$ ) during inhalation of room air, and at 4, 8 and 10 minutes after inhalation of  $\text{FiO}_2$  0.15 gas mixture are shown in Table 1. The levels of  $\text{PaO}_2$  and oxygen saturation of arterial gas were lowest at 4 and 8 minutes, but slightly recovered at 10 minutes. Arterial pH and  $\text{PaCO}_2$  level did not change significantly during the procedure (Table 1). Continuously monitoring of PA pressure and aortic pressure showed that aortic pressure did not change significantly (under room air inhalation, average 80.2 mmHg; after 10 minutes exposure to

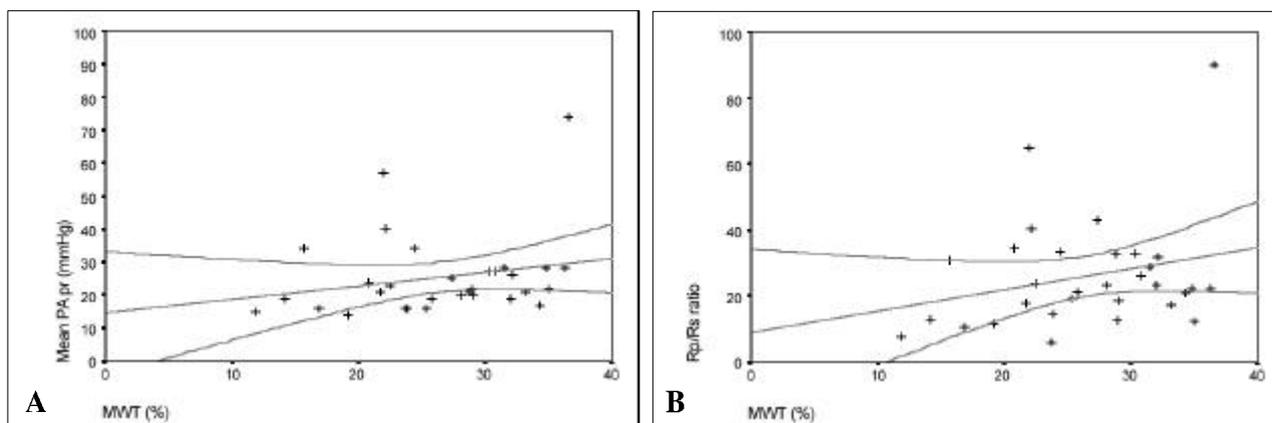


Fig. 1. Linear regression equation between morphometry and pulmonary hemodynamics at the 2nd post-operative day. A), between medial wall thickness (%) and mean pulmonary arterial pressure ( $Y=0.416X + 14.482$ ,  $r=0.322$ ,  $p=0.07$ ), and B), between medial wall thickness(%) and pulmonic/systemic resistance ratio ( $Y= 0.646X + 8.976$ ,  $r=0.193$ ,  $p=0.28$ ).

**Table 1.** Arterial Gas Study Results under Room Air Inhalation and after Hypoxic Gas Inhalation in Late Follow-up Patients (n=15)

Arterial Blood Gas	Under room air	FIO <sub>2</sub> 0.15 inhalation for			Repeated measures ANOVA ( <i>p</i> -value)
		4 min	8 min	10 min	
PaO <sub>2</sub> (mmHg)	91.3 ± 13.5	78.3 ± 20.7*	77.5 ± 20.3*	82.7 ± 16.8	0.057
SAT (%)	96.1 ± 1.7	90.2 ± 9.5 <sup>†</sup>	93.7 ± 4.9*	91.3 ± 9.8	0.062
pH (unit)	7.39 ± 0.04	7.35 ± 0.05	7.36 ± 0.05	7.36 ± 0.04	0.723
PaCO <sub>2</sub> (mmHg)	40.1 ± 3.5	42.4 ± 4.4	45.1 ± 8.2	42.5 ± 3.5	0.226

Values are mean ± 1 SD: \* *p*<0.05, <sup>†</sup>*p*<0.01 by contrast compared to the values under room air.

FIO<sub>2</sub>; fraction of inspired oxygen, Min; minute, PaO<sub>2</sub>; systemic arterial oxygen tension, SAT; arterial oxygen saturation, PaCO<sub>2</sub>; systemic arterial carbon dioxide tension.

**Table 2.** Changes of Hemodynamic Status under Room Air Inhalation and Hypoxic Gas Inhalation in Each Subgroup of Late Follow-up Patients

Hemodynamics	Group 1 (n=6)	Group 2 (n=4)	Group 3 (n=5)	Kruskal-Wallis test ( <i>p</i> -value)
m PA pr (mmHg)				
Room air	17.3 ± 3.0	15.8 ± 3.0	23.4 ± 5.0	0.042
Hypoxia	19.7 ± 2.7*	21.0 ± 2.9*	27.8 ± 7.4	0.092
CI (L/minute/m <sup>2</sup> )				
Room air	5.2 ± 1.0	4.6 ± 0.9	4.8 ± 1.0	0.556
Hypoxia	5.6 ± 1.5	4.7 ± 0.5	3.8 ± 1.1*	0.876
PVR (unit/m <sup>2</sup> )				
Room air	1.3 ± 0.3	2.0 ± 0.4	3.1 ± 0.6	0.003
Hypoxia	1.5 ± 0.3	3.0 ± 0.5*	4.7 ± 1.5*	0.003

Values are mean ± S.D.

Wilcoxon test (\**p*<0.05) difference from the values under room air inhalation.

m PA pr, mean pulmonary arterial pressure; CI, cardiac index; PVR, pulmonary vascular resistance.

hypoxic gas inhalation, average 75.7 mmHg; *p* > 0.05). By comparison, PA pressure increased steadily after the start of hypoxic gas inhalation and reached the maximum level after 8 or 10 minutes. Five patients showed PVR values greater than 2.5 unit/m<sup>2</sup> under room air inhalation, while the remaining 10 showed lower values. Four of these 10 patients demonstrated PVR increases above 2.5 unit/m<sup>2</sup> after hypoxic gas inhalation. The 15 patients were grouped into the following 3 subgroups in accordance with degree of PVR change under room air respiration/inhalation and after hypoxic gas inhalation; 6 with normal PVR both under room air respiration/inhalation and after hypoxic gas inhalation to subgroup 1, 4 showing increased PVR only after hypoxic gas inhalation to subgroup 2, and 5 showing increased

PVR under room air inhalation and further elevation after hypoxic gas inhalation to subgroup 3. Ten minutes after inhalation of hypoxic gas, the average level of PaO<sub>2</sub> and oxygen saturation diminished more in subgroup 3 than either subgroup 1 or 2, but the difference was considered statistically insignificant (*p* > 0.05).

Mean values of PA pressure, cardiac index and PVR on the late follow-up study are presented in Table 2. Under room air respiration/inhalation and after hypoxic gas inhalation, mean PA pressure was significantly elevated in subgroup 3 compared to the other two subgroups by Kruskal-Wallis test, and mean PA pressure was significantly different between baseline and hypoxic condition in both subgroup 1 and 2 by Wilcoxon test. On the other hand, although the cardiac

**Table 3,** Difference of Various Preoperative Statuses in Each Subgroup of Late Follow-up Period

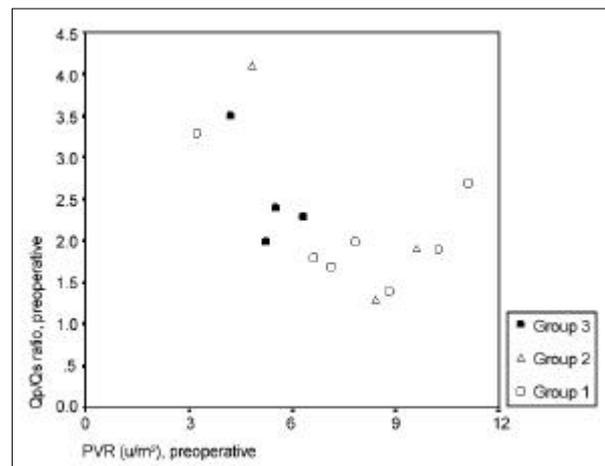
Hodynamics	Group 1 (n=6)	Group 2 (n=4)	Group 3 (n=5)	Kruskal-Wallis test ( <i>p</i> -value)
Age-at-operation (year)	2.5 ± 1.9	3.1 ± 2.7	7.1 ± 9.7	n.s.
Preoperative hemodynamics				
m PA pr (mmHg)	64.5 ± 16.8	62.5 ± 9.5	73.4 ± 15.0	n.s.
PVR (unit/m <sup>2</sup> )	8.0 ± 2.8	7.4 ± 2.1	5.1 ± 0.9	n.s.
Qp/Qs ratio	2.2 ± 0.7	2.1 ± 1.0	2.6 ± 0.6	n.s.
POD#2 hemodynamics				
m PA pr (mmHg)	21.0 ± 4.7	23.5 ± 3.1	24.6 ± 9.6	n.s.
Rp/Rs ratio	19.8 ± 8.8	20.8 ± 7.1	20.7 ± 3.1	n.s.
Morphometry				
PAC decrease rate	2.6 ± 1.3	7.3 ± 3.2	15.6 ± 5.5	0.003
MWT(%)	29.0 ± 3.8	26.1 ± 4.8	28.0 ± 6.8	n.s.

Values are mean ± S.D., abb.; refer Table 1 & 2.

POD#2, postoperative second day; Qp/Qs ratio, pulmonic/systemic flow ratio; Rp/Rs ratio, pulmonic / systemic resistance ratio; PAC, pulmonary arterial concentration; MWT, medial wall thickness in %.

index exhibited no difference among the 3 subgroups for room air respiration/inhalation or after hypoxic gas inhalation by Kruskal-Wallis test, it was significantly decreased to 77.4% after hypoxic gas inhalation, compared to that under room air inhalation, in subgroup 3 by Wilcoxon test. The values of PVR under room air inhalation and after hypoxic gas inhalation were significantly different among the three subgroups by Kruskal-Wallis test, and the value after hypoxic gas inhalation was significantly higher than that under room air inhalation in subgroups 2 and 3 by Wilcoxon test.

Various pre- and post-operative factors were compared (Table 3). The age-at-operation showed no significant difference between each subgroup. Hemodynamic values of preoperative and immediate postoperative periods did not show statistically significant differences, but when the scattergram was drawn for preoperative Qp/Qs ratio and PVR (Fig. 2), the patients with Qp/Qs ratio higher than 2:1 and a mild increase of PVR (high-flow subgroup) tended to belong in subgroup 3 in the late follow-up study, while patients with high resistance (high-resistance subgroup) had a tendency to belong in subgroup 1 or 2 in the late follow-up study. The value of preoperative PVR displayed no meaningful difference from the PVR value of post-hypoxic gas inhalation in the late follow-up period for subgroup 3. Mean PA pressure at late follow-up was higher than that of



**Fig. 2.** Scattergram delineating preoperative hemodynamics of individual patients according to the grouping in the late follow-up period (average 3.8 years after repair).

the second postoperative day for 3 of the 5 subgroup 3 patients (2nd postoperative day mean PA pressure 17, 19 and 19 mmHg, late follow-up mean PA pressure 20, 30 and 22 mmHg for these 3 patients), and their left atrial pressure was normal at the late follow-up. In subgroups 1 and 2, on the contrary, only 1 patient showed further elevation of mean PA pressure to that of the immediate postoperative period, but left atrial pressure was also elevated (15 mmHg) which indicates that pulmonary venous hypertension was a possible primary cause. Regarding histolo-

gic changes of lung biopsy at the time of operation, there were no significant differences in MWT (%) between each group, but there were for the PAC decrease rate for each subgroup ( $p=0.003$ ) (Table 3, Fig. 3). Two belonged to Heath-Edward grade II, 1 to grade III, and the remaining 12 to grade I (Fig. 3). The single patient with grade II and showing almost normal PAC revealed a normal PVR value in the late follow-up study.

The linear correlation between PVR in late follow-up and the rate of PAC decrease was quite high both under room air inhalation ( $r=0.72$ ,  $p<0.001$ ) and after  $\text{FiO}_2$  0.15 gas mixture inhalation ( $r=0.71$ ,  $p<0.0005$ ) (Fig. 4). As PVR was also correlated with the age-at-operation (under room air inhalation  $r=0.66$ ,  $p<0.01$ , after hypoxic gas inhalation  $r=0.76$ ,  $p<0.005$ ) (Fig. 5), multiple regression analysis was performed and the results demonstrated that both the rate of PAC decrease and the age-at-operation contributed significantly (room air inhalation,  $R_2 = 0.77$ ,  $F(12.2) = 20.2158$ ,  $p < 0.0005$ , after hypoxic gas inhalation,  $R_2 = 0.88$ ,  $F(12.2) = 42.8220$ ,  $p < 0.000005$ ). The multiple linear regression equation is as follows: under room air inhalation;  $\text{PVR} = 0.080$  (age-at-operation) +  $0.080$  (PAC decrease rate) +  $1.065$ , after hypoxic gas inhalation;  $\text{PVR} = 0.177$  (age-at-operation) +

$0.138$  (PAC decrease rate) +  $1.090$ . The regression lines representing  $\text{PVR} = 2.5$  unit/ $\text{m}^2$  according to this formula for both room air and hypoxic gas inhalation are drawn in Fig. 6. The patients with a rate of PAC decrease above these regression lines are presumed to have residual PVO after repair. When these lines were overlapped with the linear equation line between the rate of PAC decrease and the age-at-operation (Part 1), the equation lines bisected with the opposite direction of slope at around 2 years of age (Fig. 6).

## DISCUSSION

Early surgical repair of CHD has decreased the incidence of irreversible pulmonary vascular disease. However, the potential reversibility of pathological lesions is not synonymous with operability. Patients with potentially reversible disease can die from pulmonary hypertensive crises, which characteristically occur immediately after, or during the first few days following cardiac repair in young children who have a high pulmonary blood flow (PBF) preoperatively.<sup>6,7</sup> In this study, immediate postoperative hemodynamics had a close correlation with preoperative mean PA pressure and PVR, but not with the histologic findings. Administration of vasodilators in some patients to overcome such pulmonary vasoconstriction may decrease the correlation between histologic parameters and immediate postoperative hemodynamics. The correlation between immediate post-operative PA pressure and histologic grading varied among various investigators. Some reported correlation with severe medial hypertrophy of the peripheral PAs, but with little if any intimal proliferation,<sup>7,8</sup> while others reported correlation with the Heath-Edward grade.<sup>5,9,10</sup> Fried et al.<sup>9</sup> also found correlation with arterial density after closure of VSD, while Rabinovitch et al.<sup>5</sup> found no correlation with morphometric findings. The number of cases in Heath-Edward grades other than grade I were too few in the present study to confirm the possibility of pulmonary hypertensive crisis or reversibility related to the pathologic changes such as intimal hyperplasia.

Endothelial dysfunction of PA, which occurs

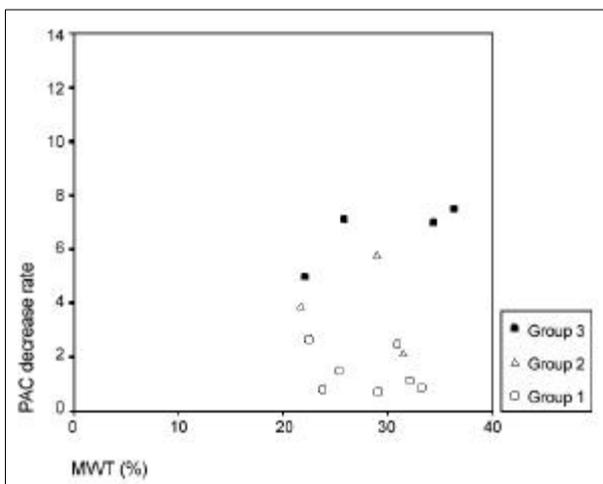


Fig. 3. Scattergram delineating histologic findings of lung biopsy at the time of repair according to the grouping in the late follow-up period. The mean values of morphometric findings in each group are shown in Table 4. The numbers over the circles indicate the Heath-Edward grade. The unmarked circles indicate the cases belonging to Heath-Edward grade 0 or I.

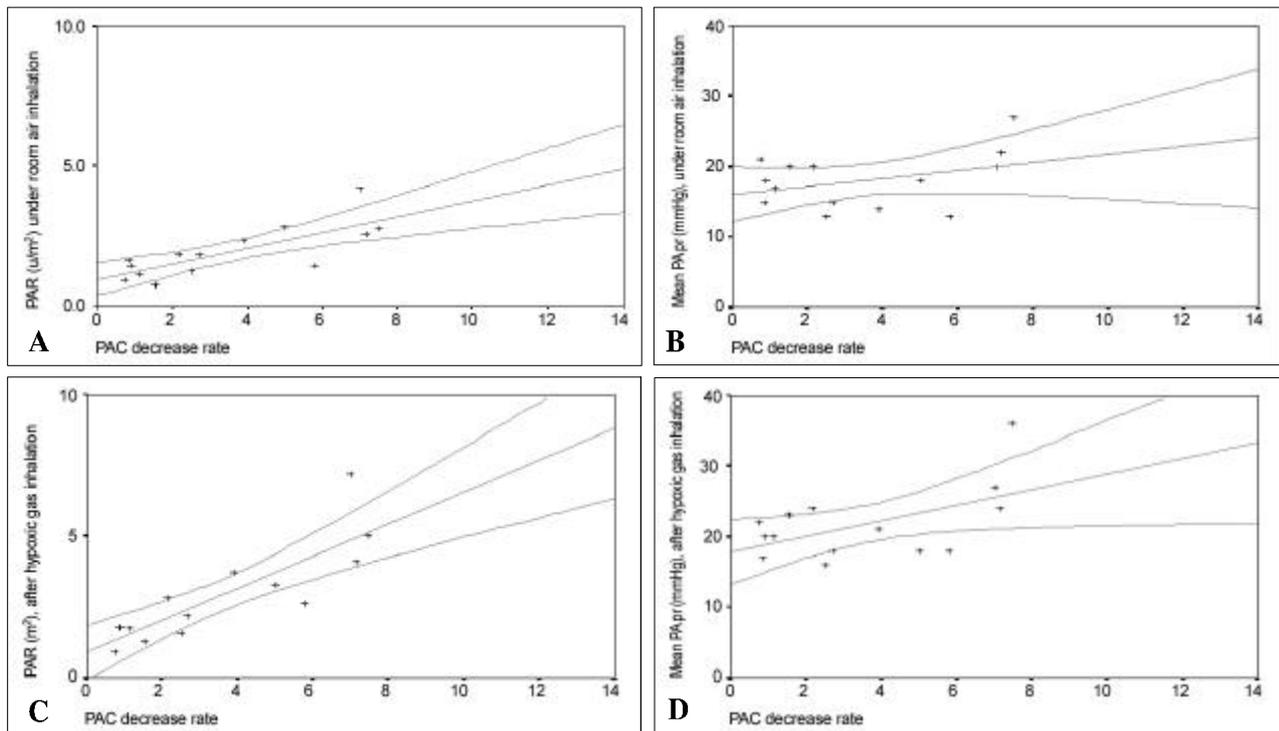


Fig. 4. Linear regression equation between the PAC decrease rate in histology and pulmonary hemodynamics in the late follow-up period. A), between PAC decrease and PVR under room air inhalation ( $Y=0.280X + 0.997$ ,  $r=0.780$ ,  $p<0.001$ ), B), between PAC decrease and mean pulmonary arterial pressure under room air inhalation ( $Y=0.568X + 16.088$ ,  $r=0.332$ ,  $p=0.23$ ), C), between PAC decrease and PVR after hypoxic gas inhalation ( $Y=0.566X + 0.890$ ,  $r=0.849$ ,  $p<0.0005$ ), and D) between PAC decrease and mean pulmonary arterial pressure after hypoxic gas inhalation ( $Y=1.114X + 17.825$ ,  $r=0.496$ ,  $p<0.05$ ).

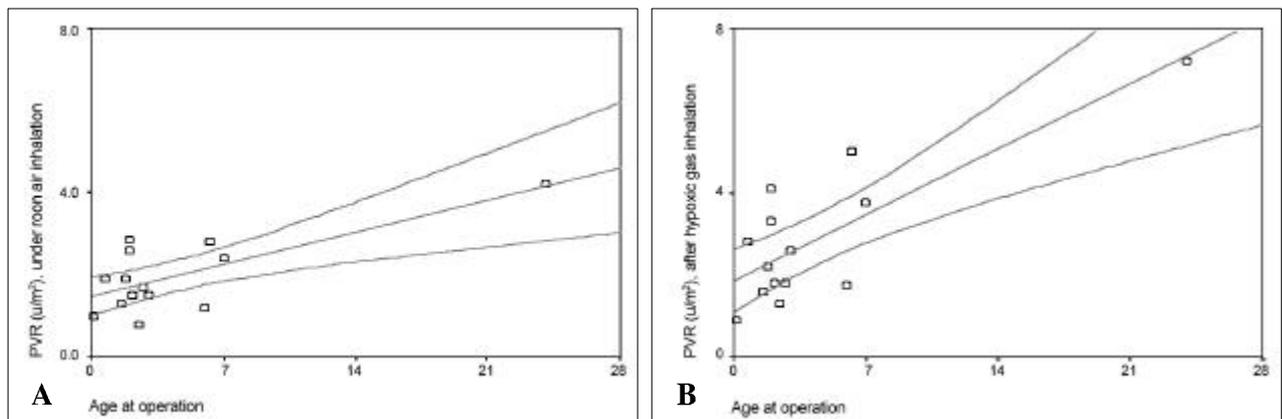


Fig. 5. Linear regression equation between age-at-operation and PVR in the late follow-up period. A), between PVR under room air inhalation and age-at-operation ( $Y=0.112 X + 1.480$ ,  $r=0.72$ ,  $p<0.005$ ), and B), between PVR after hypoxic gas inhalation and age-at-operation ( $Y=0.228 X + 1.853$ ,  $r=0.71$ ,  $p<0.005$ ).

before the onset of significant pulmonary hypertension or histologic evidence of smooth muscle dysfunction,<sup>11</sup> may contribute to the development of hypertensive crisis as a result of impaired endothelial/smooth muscle cell interaction.<sup>8,10</sup> In addition,

pulmonary endothelial function may be further disrupted during cardiopulmonary bypass through a variety of mechanisms. Insufficient blood supply of the vasa vasorum of PA endothelium, microemboli, neutrophil activation and

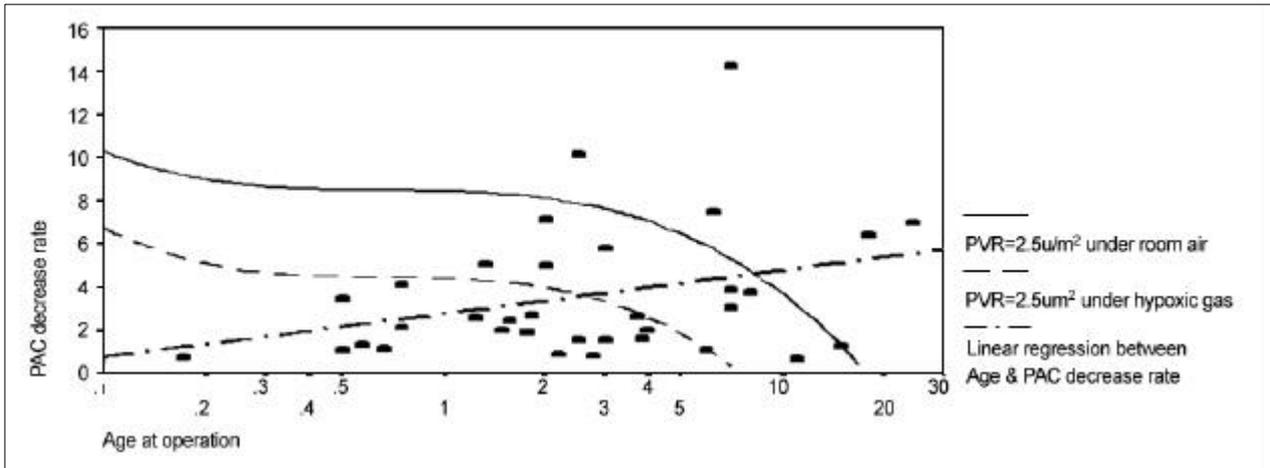


Fig. 6. Two linear lines with negative slope indicate the multilinear regression equation lines between PVR, rate of PAC decrease and age-at-operation under room air inhalation ( $PAC = -age-at-operation + 18$ ) or after hypoxic gas inhalation ( $PAC = -1.28 \text{ age-at-operation} + 10.2$ ) in the late follow-up period, when PVR is set to 2.5 unit/ $m^2$ . The linear line with positive slope indicates the linear equation line between PAC decrease rate and age-at-operation ( $PAC \text{ decrease rate} = 1.954 \text{ (age-at-operation)} + 2.713$ ,  $r=0.40$ ,  $p<0.05$ )

sequestration, interruption of normal PBF, excessive thromboxane production, hypoxic vasoconstriction, and platelet adhesion have all been suggested as potential mechanisms.<sup>7,8</sup> The duration of total cardiopulmonary bypass may be important.<sup>8</sup>

There is no gold standard for assessing the reversibility of pulmonary vascular disease. Progressive pulmonary hypertension occurs in some children despite successful early repair. In patients who received repair, PVR would return to normal levels when it was less than 50% of systemic levels, but the change was unpredictable and even increased when this value was more than 50%.<sup>2,12</sup> The increase of cardiac output may be less than normal after exercise,<sup>13-15</sup> and either PA pressure or PVR may increase excessively after exercise or hypoxic gas inhalation.<sup>13,14</sup> Age-at-operation was said to be the most crucial factor in determining long-term outcome.<sup>7</sup> Since the risk of PVO remarkably increases when cardiac defect is repaired after 2 years of age,<sup>16</sup> and postoperative mortality in infancy has been greatly reduced through recent advances in cardiac surgery, the modern trend is to repair simple left-to-right shunt lesions as early as possible, not only to prevent PVO but also to promote the normal pulmonary vascular development in early life.<sup>17</sup> But complicated anomalies such as transposition of a great vessel tend to be complicated by PVO early in infancy.<sup>18</sup> Also, a Rastelli operation or

Fontan operation performed in complicated CHD has to be delayed until after a certain level of development is reached. In Korea, there are still some patients living with unrepaired simple cardiac defects due to their birth before the introduction of the medical insurance system. Therefore, the interpretation of lung biopsy is still important in understanding the fate of PVO after repair, and thus in selecting the time and method of operation.

The patients in this study with residual or hypoxia-induced pulmonary hypertension in late follow-up tended to have had a large shunt volume and mild increase of PVR preoperatively, while the patients without residual pulmonary hypertension tended to have had a small shunt volume high PVR and. Friedli et al.<sup>16</sup> also reported that the risk of PVO was high in infants with large shunt volume, while infants with high resistance showed good prognosis in general. These results suggest rapid progress of PVO by high shunt flow, a trend in agreement with the results of our study even in patients over 2 years of age.

The reversibility of PVO probably depends on whether histologic changes can be reversed, or whether this reversibility factor depends on the patient's age-at-operation. The decrease of PAC is believed to be an important predictor of long-term PVO persistence. Medial hypertrophy had no clear-cut correlation with hemodynamics in the

late follow-up study. Immediate postoperative hemodynamics would not be an accurate predictor of long-term prognosis. In patients with VSD, medial PA hypertrophy has been observed to regress after PA banding.<sup>19</sup> It has also been demonstrated through animal experiments that the progress of medial hypertrophy and PAC decrease take quite different courses from each other after release from stimuli which cause PA hypertension.<sup>20-25</sup> Rats exposed to hypoxic gas showed both regression of the muscular layer and loss of precocious muscularization of non-muscular arteries during the recovery phase but PAs with obliterated lumen generally disappeared permanently.<sup>20-22</sup> Rats fed with *Crotalaria* also showed regression of medial hypertrophy but a fixed value for PAC during the recovery phase.<sup>23-25</sup> We postulate from the result of our study that while medial hypertrophy can regress, the decreased PAC value remains unchanged after repair of cardiac defect and becomes an important predictor of long-term PVO residue. However, Gorenflo et al.<sup>26</sup> reported that intimal fibrosis was associated with persistent PVR, but that morphometric findings did not correlate with it. They also denied the reliability of PAC using lung biopsy.

The value of PVR in the late follow-up of this study was found through multiple regression analysis to be correlated not only with PAC decrease, but also with patient age-at-operation. So the earlier the defect was repaired, the lower was the value of PVR in the late follow-up period if the rate of PAC decrease was identical. Rabinovitch et al.<sup>5</sup> reported similar results with infants younger than 9 months recovering to normal level after repair, even when PAC diminished, but with recovery being incomplete in the older age group. The development of PAs was found to be most active during the first 18 months in humans.<sup>18</sup> In an experiment using piglets, PAs were observed to develop more actively in younger piglets than in older ones following the repair of experimentally created left-to-right shunts.<sup>27,28</sup> So PVO reversibility seems to depend on the ability of the PA development process to catch up with the decrease of PAC, an ability which is more feasible with younger patients.

The linear regression line representing PVR at 2.5 unit/m<sup>2</sup> under room air respiration/inhalation

and after hypoxic gas inhalation related to the rate of PAC decrease and age-at-operation is shown in Fig. 4. It is evident that none of the 6 patients less than 1 year of age belong to the area above the regression line (PVR 2.5 unit/m<sup>2</sup> after hypoxia), but 2 of the 6 between 1 and 2 years age and 15 of the 26 after 2 years of age belong above this line. As the patients' ages increased, the proportion of patients with decreased PAC increased, but the degree of PAC decrease that can be recovered as PA develops was found to be restricted. These 2 opposing trends seem to bisect each other around 2 years of age, and offer an explanation for why repair of VSD should be done before and no later than 2 years.<sup>16</sup>

Other possibilities related with the age may be persistence of intimal fibrosis,<sup>26</sup> increase of vascular stiffness due to extracellular matrix remodeling<sup>29</sup> or the amount of smooth muscle cells in PA.<sup>30</sup> Mild intimal fibrosis is potentially reversible, but concentric intimal fibrosis that occluded more than 1/5 of the vessel lumen most likely did not regress after corrective operation.<sup>31</sup> The residual intimal changes may have induced endothelial cell dysfunction and impaired vascular reactivity.<sup>10,32</sup> Rats exposed to hypoxic gas revealed hypertrophy of endothelial cells, smooth muscle cells and also fibroblasts in adventitia with simultaneous synthesis of connective tissue.<sup>33</sup> In the recovery phase, hypertrophied cells reverted to normal, but with persistent deposition of elastin and collagen in the vessel wall,<sup>20,33,34</sup> which was left with decreased extensibility. Similar histologic evidence was reported in patients with congenital left-to-right shunt.<sup>29</sup> Under hypoxic gas inhalation, acute pulmonary vascular response depends on the amount of smooth muscle formation in PAs, thus the older the patients were, the larger was the PVR increase.<sup>30</sup> So the influence of patient's age at the time of operation on PVR after hypoxic gas inhalation may represent an additional effect brought on by the age of the patient at the time of follow-up study.

In conclusion, in a group of widely age spread CHD patients with left-to-right shunt, the authors performed lung biopsy at the time of repair, and correlated the histologic findings with the pulmonary hemodynamics of the immediate postoperative period and the late follow-up period. PA

pressure in the immediate postoperative period was closely correlated with preoperative PA pressure and PVR, but not with morphometry. Late follow-up catheterization done an average of 3.8 years after repair revealed that the degree of residual pulmonary hypertension was correlated with the decrease of PAC and the age at the time of repair. Medial hypertrophy is thought to be reversible, but decrease of PAC is thought to be irreversible, or at least partially reversible, depending on patient age-at-operation. Therefore, the rate of PAC decrease is an important determinant for long-term prognosis. Lung biopsy could play an important role in the determination of PVO reversibility, particularly in patients older than 2 years.

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