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Correlation between Quantitative Morphometric Pulmonary Vascular Structures and Postoperative Transpulmonary Pressure Gradient following Fontan Procedure

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= Abstract = **The prognosis of Fontan operation mainly depends on the pulmonary vascular resistance, but it is difficult to know it preoperatively. According as the pulmonary vascular resistance is proportional to the transpulmonary pressure gradient, we measured transpulmonary pressure gradient and percentage medial thickness with lung biopsy tissues, and examined the correlation between them.**

Thirty four patients who had undergone Fontan operation from Feb. 1989 to Dec. 1991 were subject to lung biopsy in order to measure Heath-Edward grade and the pulmonary arterial percentage medial thickness by quantitative morphometric analysis. And we examined the correlation between the postoperative transpulmonary pressure gradient and the pulmonary arterial percentage medial thickness. The difference of percentage medial thickness depending on age or shunt operation was also examined. Data showed no difference between Heath-Edward grade 0 and other grades in the transpulmonary pressure gradient. The patients undergone shunt operation did not show any difference in the percentage medial thickness compared to ones who did not.

However, the study showed significant correlation between postoperative second day transpulmonary pressure gradient and percentage medial thickness in pulmonary arterial diameter of 20~50 μM with the correlation coefficient of 0.445 (p=0.03).

We conclude that pulmonary vascular resistance is generated mainly by diameter 20~50 μM pulmonary arteries, and it partly depends on their percentage medial thickness. This result suggests that assessment of the percentage medial thickness of 20~50 μM pulmonary arteries on lung biopsy is helpful in prediction of postoperative transpulmonary pressure gradient and prognosis following Fontan operation.

Key Words: *Percentage Medial Thickness*

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INTRODUCTION

The Fontan procedure, connection of right atrium either to the pulmonary artery or via subpulmonary ventricular chamber, provides a physiologic correction for tricuspid atresia and other types of single ventricle. Because the morbidity and mortality of Fontan operation mostly depends on the pulmonary vascular resistance, the patients with elevated pulmonary vascular resistance may not be suitable candidates for Fontan operation. Even mild elevation will result in "right heart" failure after Fontan-type procedure for tricuspid atresia and related lesions (Juaneda and Haworth 1984: Mayer 1986: Mair 1985). Therefore, preoperative evaluation of pulmonary vascular resistance is very important for the patient's outcome. But, the level of pulmonary vascular resistance determined by preoperative cardiac catheterization reflects the pulmonary circulation at one time only. And in patients with either severe subpulmonary stenosis or atresia, it may be very difficult to enter the pulmonary artery and to obtain pressure measurements (Rabinovitch 1981a).

Rabinovitch et al. (1978, 1984) asserted a new grading system of pulmonary vascular changes using morphometric analysis of lung biopsy tissue. In her report, quantitative morphometric data were correlated with hemodynamic data.

We applied this quantitative technique of analysis to examine the lung biopsy tissue prepared at the time of operation and calculated the percentage medial thickness in order to examine the relationship between transpulmonary pressure gradient (pressure gradient between right and left atrium) and percentage medial thickness. We also examined the relationship between Heath-Edward grade and transpulmonary pressure gradient, and the effect of surgically created systemic-to-pulmonary shunt on percentage medial thickness.

MATERIALS AND METHODS

1) Patients

Among the patients who had undergone Fontan operation from Feb. 1989 to Dec. 1991, thirty four patients were included in this study. The inclusion criteria were as follow: patient 1) who had no pressure gradients between right atrium and pulmonary artery, 2) who had no pressure gradients between pulmonary vein and left atrium, and 3) who had no atrioventricular regurgitation by echocardiography. Preoperative cardiac catheterization was performed to all patients, but pulmonary artery catheterization was possible in 15 patients.

Their ages at operation ranged from 15 months to 150 months and mean age was 40.94 months. Seven patients were less than 24 months. Gender ratio was 22 males to 12 females. Patient's mean body weight was 13.694±4.12kg and mean hemoglobin level was 17.26±2.14mg/dl. Before Fontan operation, 18 patients had systemic-to-pulmonary artery shunt; 11 in left, 5 in right Blalock-Taussig shunt, and 2 in central shunt. Mean duration between shunt operation and Fontan operation was 26. 44 month (see Table 1,2).

2) Measurement of transpulmonary pressure gradient

Under general anesthesia, Leader catheter was inserted and located in right atrium through subclavian vein. After operation, another Leader catheter was located in left atrium through right upper pulmonary vein. In case that there was no pressure gradient between right atrium and pulmonary artery after Fontan operation, mean right atrial pressure (RAP) was equal to mean pulmonary arterial pressure (PAP), and mean right atrial pressure was substituted for mean pulmonary arterial pressure. Mean left and right atrial press-

Table 1. Preoperative patient profile

	Mean	SD	Range
Age(mo.)	40.94	29.79	15 ~150
Weight(kg)	13.69	4.12	8.1~ 26.0
Hemoglobin (mg/dl)	17.26	2.14	12.2~ 22.8
Duration of shunt(mo.)	26.44	6.97	16 ~ 38

SD, standard deviation

Table 2. Patient numbers in each groups

	Numbers
Age≤24 mo.	7
>25 mo.	27
Shunt	18
Right BT	5
Left BT	11
Central	2
HE grade	
grade 0	15
grade 1	17
grade 2	2

BT, Blalock-Taussig; HE, Heath-Edward.

ure were checked at the immediate postoperation, postoperative first, and second day morning. Transpulmonary pressure gradient (△P) which is the difference between right and left atrial pressure was calculated.

Lung biopsy was performed after intracardiac repair was completed and protamine was administered. The lungs were fully inflated at the pressure of 30~40cm of water. Two curved clamps were placed on the upper medial aspect of the right lung. The tissue between the clamps was incised and the distal clamp containing the inflated tissue was immediately submerged in 10% neutral formalin solution. After formalin fixation for 10 hours, the tissue was sequentially processed in ethyl alcohol and in xylene, and then embedded in paraffin. Five micrometer sections were stained with hematoxylin eosin and elastin Van Gieson stain for the detail evaluation of the changes in vascular structure.

Microscopically, the external diameter of arteries was measured with VIDAS Kontron Image Analyzer (Zeiss company, Germany) between external elastic laminae across the shorter axis of vessel. Medial thickness was measured from external to internal elastic laminae. Percentage medial thickness was then calculated according to the following equation;

$$\frac{2 \times \text{wall thickness}}{\text{external diameter}} \times 100 = \% \text{ medial thickness}$$

For each biopsy, all fields in the section were examined at 200× power. Arteries were grouped according to their external diameters of 20~50μM, 51~100μM and 101~200μM and percentage medial thickness was calculated for each size group. Median value of percentage medial thickness of each group was used in statistics. $W_{20\text{-}50}$, $W_{51\text{-}100}$, and $W_{101\text{-}200}$ were percentage medial thickness of arterial diameter of 20~50μM, 51~100μM, and 101~200μM, respectively. All biopsies were done under the parent's consent.

Data were analyzed with the SAS (SAS Institute Inc., Cary, N. C.) at the Seoul National University, College of Medicine. Data were compared between groups by paired t-test and Wilcoxon rank sum test. Pearson test was used for correlation. A p-value less than 0.05 was considered statistically significant. All data were expressed as mean± standard deviation.

RESULTS

1) Mean transpulmonary pressure gradients; △P

The mean values of transpulmonary pressure gradient of immediate postoperation (△P0), postoperative first day (△P1), and postoperative second day (△P2) were 9.29±2.60 cmH_2O, 8.98±2.34 cmH_2O, and 9.25±2.12 cmH_2O, respectively. There were no statistical significances between the groups (see Table 3).

2) Mean percentage medial thickness; W

The mean values of percentage medial thickness of arterial diameter of 20~50μM ($W_{20\text{-}50}$), 51~100μM ($W_{51\text{-}100}$), and 101~200μM ($W_{101\text{-}200}$) were 33.43±9.06%, 24.65±8.47%, and 20.90±7.35%, respectively. There were no statistical significances between the groups (see Table 3).

3) Comparison of percentage medial thickness according to ages

In the less than 24 months aged group, the mean values of percentage medial thickness were 32.64% ($W_{20\text{-}50}$), 23.28% ($W_{51\text{-}100}$), and 25.28% ($W_{101\text{-}200}$), respectively. In the more than 25 months aged group, the mean values of percentage medial thickness were 33.65% ($W_{20\text{-}50}$), 24. 97% (W_{51}

Table 3. Mean value of transpulmonary pressure gradient and percentage medial thickness

	Mean	SD
ΔP0(cmH_2O)	9.29	2.60
ΔP1	8.98	2.34
ΔP2	9.25	2.12
$W_{20\sim50}$(%)	33.44	9.06
$W_{51\sim100}$	24.65	8.47
$W_{101\sim200}$	20.90	7.35

ΔP0, Immediate postoperative transpulmonary pressure gradient(cmH_2O); ΔP1. ΔP2, Postoperative first and second day transpulmonary pressure gradient(cmH_2O); $W_{20\sim50}$, $W_{51\sim100}$, $W_{101\sim200}$% medial thickness of pulmonary arterial diameter of 20~50μM, 51~100μM, 101~200μM(%).

100), and 19.59% ($W_{101-200}$), respectively. The p values between two groups were 0.732, 0.866, and 0.121, respectively, and there were no statistical significances.

4) Comparison of postoperative transpulmonary pressure gradients to Heath-Edward grade (HE grade)

Of all patients, the number of HE grade 0 was 15, grade I was 17, and grade II was 2. The △P0, △P1, and △P2 of HE grade 0 were 9.43cmH_2O, 15cmH_2O, and 9.50cmH_2O, respectively. The △P0, △P1, and △P2 of HE grade I or II were 9.18cmH_2O, 8.83cmH_2O, and 9.02cmH_2O, repectively. The △Ps of HE grade 0 were slightly higher than those of HE grade I or II, but the p-values between two groups were 0.609, 0.818, and 0.179, respectively, and there were no statistical significances between two groups (see Table 4).

5) Comparison of percentage medial thickness between the patients with or without shunt

The mean duration of shunt operation was 26.44 months. The W_{20-50}, W_{51-100}, and $W_{101-200}$ of patients with shunt were 35.22%, 24.94%, and 20.72%, respectively. The W_{20-50}, W_{51-100} and $W_{101-200}$ of patients without shunt were 31.64%, 24.36%, and

Table 4. Comparison of postoperative transpulmonary pressure gradients to Heath-Edward grade

	HE grade 0	HE grade I, II	p
ΔP0	9.43±3.20	9.20±2.15	0.609
ΔP1	9.16±2.41	8.83±2.35	0.819
ΔP2	9.50±2.46	9.02±1.83	0.179

ΔP0=Immediate postoperative transpulmonary pressure gradient(cmH_2O); ΔP1, ΔP2=1st. and 2nd. day postoperative transpulmonary pressure gradient (cmH_2O); HE grade=Heath-Edward grade

21.06%, respectively. The p-values between two groups were 0.291, 0.235, and 0.980, respectively, and there were no statistical significances (see Table 5).

6) Correlations between mean postoperative transpulmonary pressure gradient (△P) and mean percentage medial thickness (W)

The correlation coefficients between mean percentage medial thickness and mean postoperative transpulmonary pressure gradient were examined. There was statistically significant correlation only between △P2 and W_{20-50}. Its correlation coefficient was 0.445 (p=0.03). The slope and the intercept were 0.127 and 5. 270, respectively. The equation was $\triangle P2 = 0.127W_{20-50} + 5.270$ (see Fig. 1).

Table 5. Comparison of percentage medial thickness between the patients with and without shunt

	Shunt(−)	Shunt(+)	p
$W_{20\sim50}$	35.22±6.91	31.46±10.73	0.291
$W_{51\sim100}$	24.94±6.26	24.36±10.44	0.235
$W_{101\sim200}$	20.72±7.30	21.06± 7.66	0.980

$W_{20\sim50}$, $W_{51\sim100}$, $W_{101\sim200}$% medial thickness of pulmonary arterial diameter of 20~50μM, 51~100μM, 101~200μM(%).

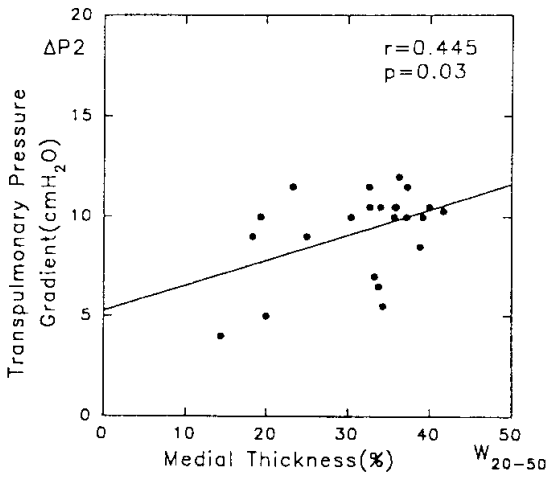

Fig. 1. Scattergram and linear regression of △P2 and W_{20-50}
W_{20-50} correlated with △P2 and correlation coefficient was 0.445 ($p=0.03$). The slope and intercept was 0.12 and 5.270, respectively.
(△P2; Postoperative second day transpulmonary pressure gradient
W_{20-50}; Percentage medial thickness of pulmonary arterial diameter of 20~50μ M)

DISCUSSION

Patients with congenital heart defect complicated by pulmonary vascular changes and elevated pulmonary vascular resistance may have some limitations for corrective surgery. Moreover, if the patient is a Fontan candidate, the pulmonary vascular resistance is the most critical factor for postoperative mortality and morbidity. In case of pulmonary vascular resistance less than 2U · M^2, almost all patients were survived (Mayer 1986), and with that of 2-4U · M^2, patients' survival is selective (Mair 1985). If the pulmonary vascular resistance is more than 4U · M^2, Fontan operation is contraindicated. Therefore, preoperative cardiac catheterization for the evaluation of patient's hemodynamic status including pulmonary vascular resistance is important for Fontan candidate, but the results are sometimes very unsatisfactory. The reasons for that are: (1) assumed values of oxygen consumption under 3 years of age are far less accurate (2) when the saturation in pulmonary artery is very high, calculations of pulmonary blood flow according to the Fick's equation are misleadingly high, and as a result the level of pulmonary vascular resistance is often underestimated, (3) the contribution of the bronchial collateral circulation is hard to access, (4) direct assessment of pulmonary arterial pressure through pulmonary venous wedge pressure measurement has not proved to be reliable, (5) the level of pulmonary vascular resistance determined at preoperative cardiac catheterization reflects the behavior of the pulmonary circulation at one time only and may not be representative, (6) in patients with either severe subpulmonary stenosis or atresia and surgically created systemic-to-pulmonary arterial shunt, it may be difficult to enter the pulmonary artery and to obtain pressure measurements; in this case, the catheter itself may impede pulmonary blood flow and pulmonary arterial pressure may be falsely decreased. In some patients, because of the size or configuration of the systemic to pulmonary arterial anastomosis, it may not be possible or appropriate to enter the pulmonary artery at all (Rabinovitch 1978: Rabinovitch 1981a). Actually we could not perform preoperative pulmonary artery catheterization of 19 patients in our cases. It is, therefore, necessary to have an alternative way to assess pulmonary circulation.

An evaluating method of the morphologic state of the pulmonary vascular bed in lung tissue to assess the severity of pulmonary vascular disease was introduced by Heath and Edward. This grading system of pulmonary vascular change is helpful but has drawbacks. First, the severe structural changes (grade IV and higher) are uncommon in the first 2 years of life, even in the presence of marked elevation of pulmonary vascular resistance. Second, those advanced changes, if present, are not evenly distributed throughout the lung parenchyma so that they may not be found in a small piece of biopsy tissue (Rabinovitch 1978 : Rabinovitch 1981a). Our results showed that there was no significant transpulmonary pressure

gradient difference between Heath-Edward grade 0 and grade I, II. Therefore, we think that Heath-Edward grading system may not be proper to explain the relationship between vascular structural changes and pulmonary vascular resistance or hemodynamic data.

Many studies were done to find out the developmental change of pulmonary vascular structures according to pulmonary blood flow (Hislop and Reid 1972: Hislop and Reid 1973a & b: Haworth 1977a: Haworth 1977b: Haworth and Reid 1977 Haworth and Reid 1978: Haworth and Macartney 1980: Haworth and Hislop 1983: Haworth 1984). Rabinovitch and co-workers (Rabinovitch 1978) introduced a new grading system of pulmonary vascular changes called quantitative morphometric analysis. According to this system, there are three progressively severe stages. Grade A: There is either only abnormal extension of muscle into peripheral pulmonary arteries, or, in adition, mild increase in wall thickness of normally muscular arteries (less than 1.5 times normal). Grade B: As in grade A, there is increased extension of muscle, but, in addition, there is more severe medial hypertrophy of normally muscular arteries. When medial wall thickness is greater than 1.5 but less than 2 times normal, it is called early grade B. When medial wall thickness is more than twice normal, it is called late grade B. Grade C: In addition to the findings of late grade B, arterial concentration is reduced and usually arterial size is also reduced. Patients with these changes have the elevation in pulmonary vascular resistance up to greater than 3.5U · M^2.

Although not all the structural changes are always present, the changes of grade C are always combined with grade B (Meyrick and Reid 1980), and almost all patients with grade C are not suitable for Fontan operation. Therefore, the degree of medial hypertrophy is an important factor for patient selection and postoperative prognosis of Fontan operation. Moreover, this structural changes assessed by morphometric analysis have been shown to be related to the hemodynamic findings in very young children (Haworth and Reid 1978: Haworth 1984).

Generally, pulmonary vascular resistance is proportional to the pressure gradient between right and left atrium (Smith 1990). In the patient who is performed Fontan operation with no pressure gradient between right atrium and pulmonary artery and with no AV valve regurgitation and no ventricular dysfunction, the transpulmonary pressure gradient is due to pulmonary vascualr resistance. If right atrial pressure is more 5 mmHg higher than left atrial pressure, the lung is probably restrictive and this case is not suitable for Fontan operation (Kirklin and Barrett-Boyes 1986). Therefore, if we can predict postoperative transpulmonary pressure gradient preoperatively, it will be helpful to select patient and to predict outcome.

In order to find the relation between morphometric findings and hemodynamic data, we examined percentage medial thickness and transpulmonary pressure gradient. Our results showed that the percentage medial thickness of pulmonary arterial diameter of 20~50μM was significantly correlated with postoperative second day transpulmonary pressure gradient. Based upon our results, we conclude two probable assumptions. First, the pulmonary vascular resistance is dependent on pulmonay arteries with diameter of 20~50μM. According to the study of Haworth and Hislop (1983), these arteries are corresponding to normal alveolar duct arteries or respiratory bronchiolar arteries. Generally, it is thought that terminal bronchiolar arteries are most resistant vessels, because they are more muscular than other vessels. But, our study showed a different result. We think that the reasons for this difference are due to; 1) poor growth of pulmonary vessels because of the decresed pulmonary blood flow in Fontan candidates (Hislop and Reid 1973: Haworth and Reid 1977: Haworth and Macartney 1980: Rabinovitch 1981b: Johnson and Haworth 1982), 2) non injected biopsy study of our cases (Haworth and Hislop 1983), and 3) the differences of normal values between caucasian and orientals. Unfortunately, we have no our normal values of peripheral pulmonary vascular structures, but we think that orientals are more or less smaller in pulmonary arterial size than caucasians. Second, this correlation is shown in postoperative second day. In immediate postoperation and postoperative first day, the myocardial function is so depressed by extracorporial circulation that the de-

pressed myocardium may affect left atrial pressure (Burrows 1988). The disturbed pulmonary function due to the increased pulmonary vascular permeability or minute collapse may also affect pulmonary arterial pressure and left atrial pressure. And the pulmoanry vascular resistance is sometimes transiently elevated for 12~36 hours after cardiopulmonary bypass and then return to normal (Kirklin and Barrett-Boyes 1986). We assume that these impaired functions are recovered in postoperative second day and the correlation between transpulmonary pressure gradient and percentage medial thickness appears at that time.

Eighteen patients had systemic-to-pulmonary shunt before Fontan operation. The types of shunt operation were sixteen Blalock-Taussigs and two centrals. The mean duration between shunt operation and Fontan operation was 26.44 months. The effect of surgically created shunt on the percentage medial thickness was not significant. Rabinovitch and co-workers (Rabinovitch 1981b) reported that surgically created shunt caused abnormal extension of muscle into periperal arteries and increased muscularity of normally muscular arteries. But, in their cases, four of eight patients were performed Waterstone or Potts operation and the duration of shunt was 4 to 5 years. In our series, all patients except two were performed Blalock-Taussig operation and the duration of shunt was short. We conclude that short duration of Blalock-Taussig shunt does not affect the percentage medial thickness.

The absolute values of left and right atrial pressure are variable with patient status, position, and administration of fluid, however, the difference between two atrial pressure is rarely affected by these factors. Also, any site of lung, except lingular segment, represents the whole lung vascularity as to the degree of muscularity of arteries (Haworth and Reid 1978). Therefore, we conclude that preoperative assessment of pulmonry arterial percentage medial thickness using quantitative morphometric analysis is useful to select patient as well as to predict the outcome.

Conclusively, preoperative lung biopsy and assessment of the percentage medial thickness of pulmonary arterial diameter of 20~50μM may be useful to predict postoperative transpulmonary pressure gradient. However, since their correlation coefficient was as low as 0.445, other factors, such as smooth muscle extension to peripheral arteries and size or number of peripheral arteries, might also affect pulmonary vascular resistance and postoperative transpulmonary pressure gradient. Further evaluation of these factors is required.

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