Developmental Aspects of Pulmonary Circulation: Clinical Implications of Postnatal Maturation of Right Heart System

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DURING the latter half of the fetal life, right and left ventricles are connected in parallel and make together a high pressure ejection system (Fig. 1). The outputs and pressure values of both ventricles are approximately the same.¹ The fetus has very high pulmonary vascular resistance (PVR) and low pulmonary blood flow (Qp) which are derived mainly from the low blood oxygen tension (PO₂). PO₂ of pulmonary artery blood of normal fetus is about 18 mmHg.⁵ This low PO₂ also prohibits the ductus arteriosus to constrict. Low pH and high PCO₂ of normal fetal blood enhance the vascular action of physiological fetal hypoxemia, namely, the hypoxia foetalis. Fetal circulation is preserved by the characteristic blood gas status which is greatly different from the postnatal one. Morphologically, thick right ventricular wall, almost the same as left ventricular one, is characteristic.¹ Thick musculature of small pulmonary arteries and arterioles is also marked and becomes more and more prominent toward the end of gestation. Some conditions which bring abnormally high PO₂ of pulmonary artery blood in fetal life, e.g. transposition of great arteries (TGA), inhibit the increase of muscle thickness of pulmonary

vasculature to some extent.⁵ Premature babies also have relatively thin muscular layers immediately after birth. This probably is the reason why the premature babies with large left-to-right shunt, e.g. large ventricular septal defect (VSD) are liable to have congestive heart failure (CHF) earlier than full term babies with similar heart diseases disease do.⁵

After birth, the initiation of the lung respiration brings immediately a marked rise of PO₂, which causes a constriction of the ductus on one hand and a decrease of PVR on the other hand. The pulmonary blood flow increases greatly, then the left atrial pressure rises and in consequence the foramen ovale is closed. Both ventricles are reconnected in series consequently. Since then, right ventricle begins to proceed its own way as a part of the low pressure ejection system together with pulmonary vasculature. Morphologically, the media of pulmonary vasculature gradually diminishes in thickness after birth and at last loses its thick walled fetal feature, as *Civin* and *Edwards* pointed out.³ This metamorphosis begins on the first or the second day after birth and progresses quite rapidly during the first 2 or 3 weeks and then more slowly until it is about 12 or 18 months. The muscular layer of pulmonary arterial trunk shows also similar atrophy but more slowly.² The metamorphosis which normally occurs after birth is often called the maturation of pulmonary vasculature. The maturation occurs in the patients with various congenital heart diseases and sometimes modifies their clinical features. On the other hand, the maturation process will

Key Words:

- Pulmonary circulation
- Right ventricle
- Pulmonary vasculature
- Transposition of great arteries
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- Pulmonary stenosis
- Cor pulmonale
- Primary pulmonary hypertension

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Fig.1. Diagrammatic representation of the maturation process of the right heart system and its relation to the blood gas status. See the text for explanation.

be modified by the presence of various heart diseases⁴

A thinning of right ventricular wall also takes place after birth.¹ The decrease of right ventricular muscular weight is rapid and shows a good correlation with the fall of pulmonary artery pressure.¹ If one takes the right to left ventricular weight ratio as an indicator of the right ventricular metamorphosis, this change proceeds more slowly and lasts longer until 1 or 2 years of age. The ratio is approximately 1.0 immediately after birth and 1.5 at 3 weeks of age and reaches to 2.0 at the end of infancy.⁶ This is also a part of postnatal metamorphosis of right heart system, namely, the maturation of right heart in broader sense.

The unburdening of the right heart system due to the subsidence of pulmonary vascular constrictions is often considered as the causal factor of the maturation. However, this inference is not verified yet. We have some reason to think

that the maturation would occur even under a strong continuous burdening of right heart. This situation is often dangerous for the patient because a heart failure is often induced from it. This has been discussed by some authors in relation to the maturation of pulmonary vasculature^{4,5} We would like to mention here that the maturation of right ventricle also plays an important role on the course of congenital heart diseases.

METHODS

(1) Normal postnatal hemodynamic changes:

Sixteen consecutive cardiac catheterization data of normal heart in Kyushu University Hospital were examined as to pulmonary artery pressure and PVR index (PVRI). Because of paucity of the number of cases, additional 30 cases of small VSD which have pulmonary to systemic flow ratios (Q_p/Q_s) not larger than 1.5 were examined in the same manner.

Fig.2. Normal postnatal hemodynamic changes.

A. Normal postnatal change of systolic pressure of main pulmonary artery.
 B. Normal postnatal change of pulmonary vascular resistance index.

Fig.3. Qp/Qs and Rp/Rs of large ventricular septal defect. The age of onset of congestive heart failure is also shown in B.

A: Qp/Qs and age.

B: Rp/Rs and age. Age distribution of onset of CHF is also shown.

●: With congestive heart failure at the time of examination.

○: Without congestive heart failure at the time of examination.

Fig.4. Right ventricular systolic pressure in complete transposition of great arteries and postnatal age. Age distribution of onset of CHF is also shown.

●: With ventricular septal defect.
○: Without ventricular septal defect.

(2) Postnatal hemodynamic changes in large VSD:

One hundred thirty-six cases of large VSD were catheterized and examined concerning Q_p/Q_s , R_p/R_s (pulmonary to systemic resistance ratio) and the time of onset of CHF. P_p/P_s (pulmonary to systemic peak pressure ratio) were over 0.75 in all cases. The data of 100 of them were reported previously.⁷

(3) Postnatal hemodynamic changes in TGA:

Twenty-two cases of TGA were studied by cardiac catheterization. One of them was studied serially. The change of right ventricular systolic pressure by age was studied. All but two cases had ventricular septal defect.

(4) Postnatal changes in pure pulmonary valvular stenosis (PPS):

Twenty-three cases of PPS were studied by cardiac catheterization and by electrocardiography (ECG). They were divided into two groups. One of them is the younger age group which includes 12 cases of patients under 6 years of age. Another is the older group which has 11 cases of patients over 7 years of age. In the younger age group, there were 1 of 9 months, 1 of 2 years, 2 of 3 years, 2 of 4 years, 3 of 5 years and 3 of 6 years of age.

(5) Primary pulmonary hypertension and the right heart system:

Two sibling cases of this syndrome were studied by cardiac catheterization. The autopsy data were obtained in one case.

(6) Cor pulmonale and the right heart system:

Three cases of cor pulmonale due to upper airway obstruction were studied by cardiac catheterization.

RESULTS

(1) Normal postnatal hemodynamic changes:

The relations of age to pulmonary artery systolic pressure and to PVRI are shown in Fig. 2. They fall rapidly to normal within 2 months after birth. The data of normal heart and of small VSD are not essentially different.

(2) Postnatal hemodynamic changes in large VSD:

The data are summarized in Fig. 3. The age of onset of congestive heart failure is also shown in Fig. 3-B. A transient increase of Q_p/Q_s and a transient decrease of R_p/R_s are remarkable during 1 to 5 months of age. The occurrences of CHF are also concentrated to this period, but seems to begin a little earlier than the hemodynamic change.

Fig.5. Right ventricular voltage of ECG and pressure gradient between right ventricle and pulmonary artery in congenital pure pulmonary stenosis of different age groups.

TABLE I HEMODYNAMIC FINDINGS OF TWO SIBLING CASES OF PRIMARY PULMONARY HYPERTENSION

	M.M., 6mo. F.	M.S., 5mo. M.
	Pressure (mmHg)	Pressure (mmHg)
PA	100/53 (67.5)	95/50 (88)
RV	100/12.5 (47)	90/5 (38)
LV		62/7 (32)
RA	20.5/0 (12.5)	8/0 (5)
LA	15/0 (10.5)	16/0 (10)
FA	72.5/47.5 (53)	55/38 (45)
PAR	45.2 R.U.	89.7 R.U.
TSR	22.3 R.U.	48.4 R.U.
Rp/Rs	2.02	1.85

(3) Postnatal hemodynamic changes in TGA:

A transient decrease of right ventricular systolic pressure seems to occur immediately after birth and to last until about 6 months of age. Serial catheterization studies of a case which were performed on the 9th and the 21st days after birth showed the same tendency more remarkable. The occurrences of CHF begin quite

early before 1 month of age (Fig. 4).

(4) Postnatal changes in PPS:

In the older age group, the voltages of $Rv_1 + Sv_5$ are very well correlated with the right ventricular-pulmonary artery peak pressure gradients. On the other hand, in the younger age group, there is little correlation between the two factors (Fig. 5).

(5) Primary pulmonary hypertension and right heart system:

The hemodynamic data of the cases are shown in Table I. They presented very similar onsets, symptoms and signs including the fatal outcomes. Autopsy data were obtained only from younger brother. His right ventricle showed marked hypertrophy and dilatation, and the foramen ovale was patent. Even by elaborate microscopic studies no significant medial hypertrophy or intimal proliferation were found on the total pulmonary vascular system. There was no stenosis on the entire pulmonary artery system and on the further route of circulation.

(6) Cor pulmonale and right heart system:

The data were summarized in Table II. All 3 cases had congestive heart failure in spite of relatively mild pulmonary hypertension. Right ventricular hypertrophy (RVH) of ECG was mild except the third patient whose onset of disease was very early. Hypercapnia and hypoxemia were found in all cases.

Fig.6. Clinical and hemodynamic course of a patient with large ventricular septal defect

DISCUSSION

Our normal data including small VSD are fundamental ones for understanding the normal maturation, and are essentially the same as other reports on normal subjects.⁸⁻¹⁹ If one takes PVR itself instead of PVRI, the slope will extend further to about 5 years of age or more.¹³ The left heart system is known to show no such changes. Systemic blood pressure is somewhat low at birth and rises gradually to the level of older child within a week or two, but this is essentially different in pattern from the changes which take place in the right heart system.

The maturation process could be modified by several conditions. Babies born in high altitude often show delayed and incomplete maturation.⁵ Babies who have congenital heart diseases with large left-to-right shunt often show similar modification of maturation as the high altitude natives. We already showed that small left-to-right shunt does not influence over the normal maturation (Fig. 2). A very high pulmonary blood flow will cause a left atrial hypertension and then constriction of pulmonary arterioles.⁴ A

high PVR thus brought will cause a pulmonary hypertension which renders a pressure overload to the pulmonary vasculature and to the right ventricle. This overload is considered to be the cause of disturbed maturation. A delay and a premature set-back of maturation which could be called a regression to the fetal feature are common in the patient with a large left-to-right shunt. If some maturation occurs in such patient the shunt will increase and may induce a CHF. This regression probably has a defensive effect against the increase of the shunt.^{20,21} A volume overload to the left ventricle due to large Qp is considered to be responsible to the outbreak of CHF in the large VSD so far.⁴ This concept is quite reasonable in itself, however, we have to point out that in some cases the CHF really takes place without such situation. According to our data (Fig. 3-B), 29 cases out of 107 (27.1%) had CHF already before 1 month of age. Only one premature baby was contained in the 29 cases. The increase of Qp/Qs is not so remarkable within 1 month. A representative case is presented in Fig. 6. This baby showed typical

TABLE II HEMODYNAMIC, BLOOD GAS AND SOME OTHER FINDINGS OF COR PULMONALE DUE TO UPPER AIRWAY OBSTRUCTION

	Y.M. 2y. F.		M.Y. 2y. M.	T.K. 5mo.
	<i>Hypertrophy of tonsils</i>		<i>Hypertrophy of tonsils</i>	<i>Vascular Ring</i>
PA	38/19 (25)		45/20 (28)	
RV	50/10		48/12	75/10
PARI	3.0		3.2	3.6
CTR	0.62		0.62	0.71
pH	7.407	7.320	7.355	7.368
PaO ₂	87.1	50.0	40.8	36.2
SaO ₂	96.1	81.3	72.0	69.6
PaCO ₂	42.2	55.0	57.4	54.5
RVH	±		±	++
CHF	++		++	+
Onset	1.5/12 yr.		4 mo.	early neonatal
Outcome	Improved after tonsillectomy		Improved after tonsillectomy	Improved spontaneously

signs of CHF in her 2nd day of life. The symptoms were most flourished between 7 and 14 days with edema. Cardiac catheterization was performed in 28 days of age and it was revealed that her Qp/Qs was only 1.25. A left ventricular volume overload seems hardly to occur with such a small Qp/Qs. Engle's 9 autopsy cases of early death from VSD are very interesting in this respect.²² She presented several cases with both marked pulmonary vascular medial hypertrophy which suggests high PVR and the dilatation of right ventricle. It might be postulated here that the maturation of right ventricle which occurred under an overload would precipitate the outbreak of right ventricular failure. Our data concerning TGA are also interesting in this connection.

In TGA, the right ventricle has a responsibility to eject blood to the systemic circulation in place of the left ventricle. If a fall of right ventricular pressure takes place, a fall of aortic pressure follows directly and a serious threatening to life would be brought. We can now conclude from our data (Fig. 4) that the fall of right ventricular pressure really occurs in accordance with the

time during which the normal maturation of right heart should take place. Sudden appearance of CHF in very early weeks is a common ominous event in the baby with TGA. *Tynan* showed recently that the maturation of pulmonary vasculature normally occurs in TGA with intact ventricular septum, and that a gradual fall of pulmonary artery pressure and an increase of Qp are generally seen. However, Qp/Qs seems to remain under 2 in most of his cases and scarcely reaches to 3. Pulmonary artery systolic pressure is between 20 and 50 mmHg in most patients.²³ The sudden outburst of fatal CHF cannot be explained on this basis. In cases of TGA with VSD, there may be a higher Qp and a higher pulmonary artery pressure. However, the fall of right ventricular pressure as was seen in our cases cannot be explained by the analogy of usual large VSD because the latter shows no transient fall of left ventricular or aortic pressure. We can infer here again that an intrinsic process of maturation occurs on the right ventricular muscle in spite of unfavourable consequence. The other notorious congenital heart disease which have

fatal heart failure in the first week of life as TGA is the hypoplastic left heart syndrome?²⁴ One should remind here that the right ventricle again has the role of maintenance of systemic circulation through the patent ductus and the maturation of right ventricle will bring danger if it occurs.

Also in PPS, the early occurrence of heart failure is well known. It is transient in character. The maturation of pulmonary vasculature occurs excessively in this disease²⁷ but has no positive meaning for the clinical course. The maturation of right ventricular muscle only has the meaning.

Several papers concerning the natural history of PPS are published. However, we can see an apparent contradiction between the electrocardiographic progression and the fairly stationary hemodynamic course in these data.^{25,26} It is also known that there are scattered cases with severe obstruction and without marked right ventricular hypertrophy of ECG. Especially in newborns and in infants, such cases with discrepancy are common. *Rowe* and *Mehrizi* say that in neonates with severe PPS there are considerable number of cases with mild or no right ventricular hypertrophy of ECG, and in general, some degree of reduction in right ventricular cavity size and tricuspid valve ring size is characteristic for such cases.³⁰ It is reasonable to think that the ECG finding reflects the state of cardiac muscle in some way. In our data (Fig. 5), it is suggested that the state of ventricular muscle in young subject is something different from that of older subject even under the same hemodynamic situation. This observed inhibition of ventricular hypertrophy persists too long to be regarded as the phenomenon related to the maturation, but the relation could not be denied. The maturation may be a versatile and long lasting biological phenomenon. The normal value of voltages of Rv_1 and Sv_5 are rather greater in the younger age group from the neonatal period than in the older age group.³¹ Therefore, our data cannot be explained by the difference of normal ECG values by age.

These findings are previously not reported and need larger number of cases to confirm. However, these are sufficient to suggest that an age factor exists between the ventricular overload and the ventricular hypertrophy. The maturation and the hypertrophy are opposite concepts to each other. The former inhibits the latter. This is also related to the problem of the reactivity of the right heart musculature against various loads.

The essential process occurring in PPS is a transient postnatal atrophy followed by a re-hypertrophy of the right ventricular musculature under a pressure overload, and this is well comparable to the change of pulmonary vascular media in the case with a large VSD.

We would like to discuss on the peculiar cases of primary pulmonary hypertension to elucidate the reactivity of pulmonary vasculature. They had rather typical features as the juvenile type of primary pulmonary hypertension described by *Thilenius et al.*²⁸ They thought that the disease process is present at birth in most cases of childhood from their histological data of pulmonary vasculature which had the fetal patterns. *Heath* and *Edwards* have the same opinion.²⁹ But our case of autopsy is quite different from most of the previously reported cases by the lack of morphological evidence of the pulmonary vascular obstruction, in spite of the presence of severely increased resistance of the pulmonary vasculature. There are no other ways than to conclude that the pathogenetic factor of this case should be entirely functional one. Severe diffuse constrictions of the resistance vessels of the pulmonary circulation should be postulated. The maturation must have occurred already on his pulmonary vasculature, provided that he ever had normal fetal features at birth. It may be possible to infer that he would get some medial hypertrophy of pulmonary vessels if he could survive longer. The maturation of right ventricle seems to have occurred already also at the time of the onset of the disease process. This would make some difference from the cases of PPS as to the size of ventricular cavity for instance, but is not certain.

The individual difference of the reactivity of pulmonary vasculature should be considered in two different directions, one the constrictive reactivity against various stimulating factors and the other the morphological adaptability against overloads. The patient might have a high functional and a low morphological reactivity.

The functional reactivity of the pulmonary vasculature is known to be different with ages, species and individuals. It is suggested that the pulmonary vasculature of fetus and neonates of many animals is much more susceptible to a hypoxia especially in early postnatal days before the maturation fully occurs than in the later stages of life.³²⁻³⁴

Kato et al. compared newborn minipigs to newborn puppies and concluded that only the

former had significant reactivity to the left pneumonectomy and to the hypoxia.⁴¹ The difference of pulmonary vascular reactivity by different species was shown by this study.

We also have 3 cases of cor pulmonale due to chronic upper airway obstruction. Such type of cor pulmonale is uncommon in adults but the mechanisms are not different. Tonsillar hypertrophy, for instance, is a condition which affects the pulmonary function and induces an alveolar hypoventilation. If a right ventricular hypertrophy and a heart failure follow this condition without other cardiopulmonary diseases, it is reasonable to call it the cor pulmonale.³⁵⁻³⁹ In our cases, only the last one seems to have the pathogenetic factor congenitally and have much higher pulmonary artery pressure, more severe right ventricular hypertrophy of ECG and milder heart failure than in the other cases. In this case, the maturation process of right heart might be modified in the newborn period. In the other two cases with tonsillar hypertrophy, the maturation process must have fully occurred already at the time of the onset of the pathologic process. Pulmonary hypertension and right ventricular hypertrophy are mild and it seems to be insufficient to cause the severe heart failure which actually occurred equally in both cases. Hypoxemia accompanied by hypercapnia is characteristically common and it may be well suspected as the causal factor of cor pulmonale. However, this blood gas change seems to affect not through the induction of pulmonary hypertension and consequent right ventricular hypertrophy as often believed, but through rather direct way to the right ventricular function. There are number of facts which suggest the existence of cardioactive and vasoactive substances derived from the pulmonary circulation.⁴⁰ The function of the right heart system should be studied biochemically in future. Such studies will also disclose the fundamental process of the maturation of right heart.

SUMMARY

The postnatal maturation of pulmonary vasculature which occurs early neonatal stage brings a decrease of pulmonary artery pressure and of pulmonary vascular resistance as shown in our study on the normal subjects. The presence of small ventricular septal defect (VSD) did not affect the normal maturation pattern. In some severe congenital heart diseases the maturation

also occurs but is modified to some extent. The maturation occurred in a case of large VSD causes transient increase of pulmonary blood flow as seen in our data and the latter may act as a precipitating factor for the onset of congestive heart failure. However, we showed that there are a number of cases which have heart failure prior to the increase of pulmonary blood flow. The traditional concept of maturation cannot be applicable for such cases to explain the development of heart failure. We proposed a broader concept of the maturation of the right heart containing the maturation of right ventricular musculature, and showed that it is effectively applicable for the explanation of the hemodynamic transition and the onset of heart failure in large VSD, transposition of great vessels (TGA) and pure pulmonary stenosis (PPS). A transient postnatal decrease of right ventricular pressure in TGA and a discrepancy existing between the hemodynamic severity and the grade of ECG findings in young children with PPS were found and discussed. The pathologic physiology of maturation containing the reactivity of pulmonary vasculature, the right ventricular function and the heart failure was discussed on the ground of the above mentioned data and the added cases of primary pulmonary hypertension and cor pulmonale.

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