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Clinical Studies on Results of Repair of Ventricular Septal Defect Associated with Severe Pulmonary Hypertension

Mortality and Hemodynamic Changes in Various Age Groups

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Introduction

Ventricular septal defect (VSD) is the most common congenital heart anomaly, comprising approximately 25 per cent of all congenital heart disease as isolated defect[1]. Not uncommonly, infants with large VSD die in the first year of life as a result of intractable congestive heart failure and pulmonary complications. These patients with intractable congestive heart failure or pulmonary complications not responsive to vigorous medical management require surgical treatment in early infancy.

There have been two ways to manage these infants surgically, one being the primary repair and the other being two-staged correction consisting of the pulmonary artery banding[2] and the subsequent total correction. Until recently, pulmonary artery banding has been prefered for surgical management of these infants by many surgeons[3~9] because of the poor operative results[10~13] in the primary repair.

The technique of surface-induced deep hypothermia and limited cardiopulmonary bypass was reported by HIKASA, SHIROTANI and colleagues[14] in 1967. Since then, primary repair of VSD in infancy has been performed in many institutions[15~20,33] using this technique with better operative results. At the present time, however, patients with large VSD associated with severe pulmonary hypertension still pose the great challenges in the surgical treatment of VSD even with an improved techniques, while

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in other circumstances good operative results have been obtained with relative ease.

Furthermore, there has been no general agreement at what age the pulmonary vascular change begins and how it develops. The major unsolved problem with the patients with pulmonary vascular disease is selection of time for performance of the surgical procedure.

The purpose of this paper is to analyze the operative results and the postoperative hemodynamic changes with reference to the age of patients and the degree of pulmonary vascular disease, and to determine the optimal age for primary repair of isolated VSD from a viewpoint of surgical risk and pulmonary vascular disease.

Materials and methods

A) Materials.

During the seven-year period from September 1968 to December 1975, the primary repair of isolated VSD was performed in 420 patients at Hyogo Kenritsu Amagasaki Hospital. Materials used in the present investigation were 181 patients associated with severe pulmonary hypertension among these 420 patients. Ninety-three patients were male and 88 were female. The patients ranged in age from 3 months to 11 years and were divided by age into six groups : less than 6 months of age (18 patients), 6 to 11 months (62 patients), 1 year (49 patients), 2 years (23 patients), 3 years (10 patient) and over 4 years of age (19 patients). The range and average of body weight in each age group are shown in Table I.

Table I. Range and average of body weight in various age groups in patients subjected to repair of ventricular septal defect with severe pulmonary hypertension

Age Group	Body Weight (kg)	
	range	average
0-5 mo. (av. 5.2 mo.)	4.1- 6.6	5.5
8-11 mo. (av. 9.5 mo.)	3.9-10.0	6.7
1 yr.	5.7-11.2	8.5
2 yr.	6.0-14.5	10.3
3 yr.	9.0-15.0	12.2
Over 4 yr. (av. 6.6 yr.)	13.5-34.0	18.7

B) Cardiac catheterization.

All of the patients underwent routine cardiac catheterization and angiocardiography prior to the operation. It was carried out under light sedation with pethidine, promethazine and thiopenthal in infants, and under local anesthesia while awake in older children. Pressures were obtained using Statham P23Db strain gauges at a reference level on third of chest thickness below the sternum, and were recorded on an Electronics for Medicine DR 8 recorder. Oxygen saturations and contents were assessed using Van Slyke analysis. The pulmonary artery was entered in all of patients, and simultaneous systemic pressures were obtained from a catheter inserted to aortic root or by puncturing femoral artery. Oxygen saturation in pulmonary venous blood was assumed to be 95 per cent when it could not be obtained. The calculations using the data obtained by cardiac catheterization were made as follows:

1) Ratio of pulmonary to systemic pressure (P_P/P_S) = $\frac{P_{PA}\ syst}{P_{SA}\ syst}$

2) Ratio of pulmonary to systemic blood flow (Qp/Qs)

$$= \frac{\dot{V}o_2}{C_{PVO_2}-C_{PAO_2}} \Big/ \frac{\dot{V}o_2}{Ca_{O_2}-Cv_{O_2}} = \frac{Ca_{O_2}-Cv_{O_2}}{C_{PVO_2}-C_{PAO_2}}$$

3) Ratio of pulmonary to systemic vascular resistance (Rp/Rs)

$$= \frac{P_{PAm}-P_{LAm}(\text{or } P_{PCm})}{Q_P} \Big/ \frac{P_{SAm}-P_{RAm}}{Q_S} = \frac{P_{PAm}-P_{LAm}(\text{or } P_{PCm})}{P_{SAm}-P_{PCm}} \cdot \frac{1}{Q_P/Q_S}$$

P syst	: systolic pressure	PA	: pulmonary artery
Pm	: mean pressure	PV	: pulmonary vein
$\dot{V}o_2$	: oxygen consumption	SA	: systemic artery
Qp	: pulmonary blood flow	RA	: right atrium
Qs	: systemic blood flow	LA	: left atrium
C	: oxygen contents	PC	: pulmonary capillary
		a	: arterial blood
		v	: mixed venous blood

The author classified the patients undergoing the repair of VSD in each age group according to the degree of Pp/Ps and Rp/Rs. For the purpose of this study, pulmonary hypertension was defined as severe when Pp/Ps exceeded 0.75, while it was defined minimal (not any or mild) or moderate when Ps/Ps was less than 0.75. And patients were considered to have minimal (not any or mild) pulmonary vascular disease when Rp/Rs is less than 0.5, moderate pulmonary vascular disease when this ratio was 0.5 to 0.75, and severe pulmonary vascular disease when this ratio was greater than 0.75. Based on the hemodynamic status, 181 out of 420 patients were associated with severe pulmonary hypertension. These patients were divided into additional three subgroups in each age groups : group I with Rp/Rs less than 0.5, group II with Rp/Rs of 0.5 to 0.75, and group III with Rp/Rs greater than 0.75.

The postoperative catheterization was carried out in 108 patients out of 161 survivors 1 month after repair. Observing the patients in out-patient clinic, the repeat catheterization was performed 1 year after repair in 17 patients, who showed an unsatisfactory decrease in Pp/Ps and Rp/Rs at the time of the first postoperative catheterization. One of these 17 patients underwent another cardiac catheterization in 4 years after repair.

C) Operative techniques.

Operations were performed with normothermic or mild hypothermic cardiopulmonary bypass in 135 patients. Improvement of intracardiac exposure was obtained by intermittently cross-clamping the aorta for periods of 10 minutes with perfusing blood temperature at 32°C. In the remaining 46 patients with body weight less than 10 Kg, repair was made during complete circulatory arrest using deep hypothermia with surface-cooling and limited cardiopulmonary bypass. Table II gives an outline

Table II. Hypothermic procedure for repair of ventricular septal defect

1)	Premedication	Atropine sulfate	0.02 mg/kg
		Pethidine	1-2 mg/kg
2)	Anesthesia :	Halothane	0.5-1.0%
		Carbon dioxide	0-3%
		Nitrous oxide	50%
		Oxygen	50%
		Alcuronium	0.5 mg/kg
3)	Chlorpromazine : 0.5 mg/kg i.v. drip		
4)	Potassium : 1mEq/kg i.v. drip, during surface cooling		
5)	Surface cooling by blanket and ice bags down to 25°C (R.T.)		
6)	Bypass cooling down to 23°C		
7)	Circulatory arrest within 30 minutes		
8)	Bypass rewarming up to 33°C		
9)	Surface rewarming up to 36°C		

of this hypothermic procedure. The lowest average rectal temperature was 22°C with a range from 20°C to 24°C, and the average duration of circulatory arrest was 35 minutes with a range from 18 to 55 minutes. In early period in this series the hypothermic procedure was performed in the patients under 10 Kg of body weight, whereas this technique has been used in the patients under 6 Kg of body weight since 1969. Transventricular repair of VSD was performed through vertical, oblique, or transverse ventriculotomy incisions. Defects were closed by direct suture or use of a patch of prosthetic knitted Teflon or duplicated autopericardium with interrupted mattress sutures all around the defect, taking the precautions for avoidance of the area occupied by the bundle of His.

D) Lung specimen.

Lung specimen was obtained from the middle lobe or lower lobe of the lung at the time of operation in 23 patients with severe pulmonary hypertension. The specimen was fixed in 10% Formalin solution and stained with Hematoxylin-Eosin, Van Gieson, Orcein, and/or Azan method. Small muscular pulmonary artery, ranging from 800 to 1000 micron in external diameter, was examined histologically (Fig. 1). The thickness of media and its external diameter were measured, and the ratio of the former to the later (mean medial thickness) was calculated as follows :

$$\text{mean medial thickness} = \frac{m_1+m_2}{2} + \frac{m_3+m_4}{2} \Big/ \frac{d_1+d_2}{2}$$

Results

A) Incidence of severe pulmonary hypertension and associated anomalies.

The incidence of severe pulmonary hypertension was highest (100 per cent) in the group less than 6 months of age, and decreased accompaning with an increase in age (Fig. 2).

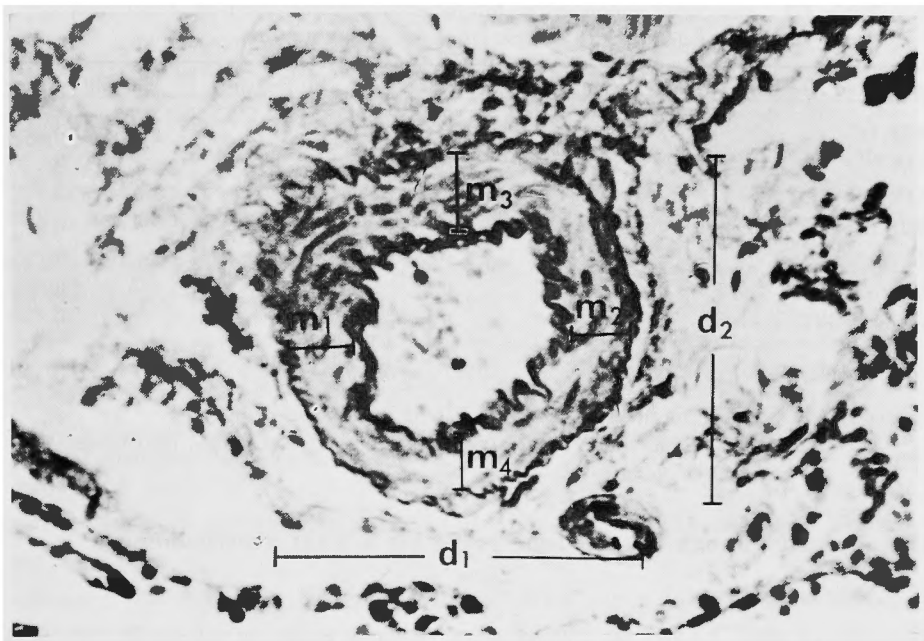

Fig. 1 Small muscular pulmonary artery is demonstrated. Thickness of media was measured as distance between internal and external elastic fibers (m_1, m_2, m_3, m_4)

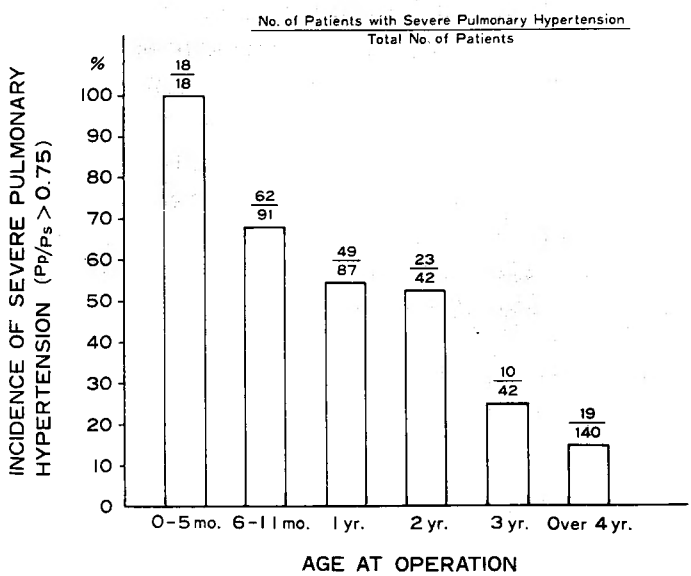

Fig. 2 Incidence of severe pulmonary hypertension in various age groups in 420 patients who underwent repair of ventricular septal defect

Eighty-eight patients had certain associated anomalies, some of which were corrected concomitantly with repair of VSD (Table III). The commonest associated anomaly was patent foramen ovale which was corrected in 15 of 57 patients both

Table III. Associated anomalies in 181 patients operated upon for ventricular septal defect with severe pulmonary hypertention

Associated Anomaly	No. Patients	Corrected	No. Deaths	Mortality Rate %
PFO	57	15	11	19.3
PDA	8	8	0	0
PDA and PFO	4	4	2	50.0
ASD (II)	10	10	0	0
MI	3	0	0	0
Dextrocardia	2	0	0	0
Bilateral SVC	4	0	0	0
Total	88	37	13	14.8

Legend PFO, Patent foramen ovale. PDA, Patent ductus arteriosus. ASD (II), Secundum type of atrial septal defect. MI, Mital insufficiency. SVC, Superior vena cava.

transatrially and through the tricuspid valve via a right ventriculotomy.

B) Hospital mortality.

There were two deaths in 239 patients (0.8 per cent) in whom Pp/Ps was less than 0.75 (Table IV). Mortality, when Pp/Ps exceeded 0.75, was related to the degree of pulmonary resistance (Table V). When Rp/Rs was less than 0.5, 7 of 91 patients (7.7 per cent) died, 2 of the nonsurvivors being less than 6 months of age, 6 to 11 months and 1 year of age respectively, and 1 of these being 3 years of age at the time of operation. Seven of 55 patients (12.7 per cent) with Rp/Rs of 0.5 to 0.75 died, 2 of the nonsurvivors being less than 6 months, 3 being 6 to 11 months, and 1 being 1 year and 3 years of age respectively. Six of 35 patients (17.1 per cent) with Rp/Rs greater than 0.75 died postoperatively, 3 of the nonsurvivors being 6 to 11 months, 1 being 1 year, and 2 being over 4 years of age. Mortality rate with respect to age when Pp/Ps exceeded 0.75 was 22.2 per cent in patients less than 6 months, 12.9 per cent in patients of 6 to 11 months, 8.2 per cent in patients of 1 year, 0 per cent in

Table IV. Hospital mortality after repair of ventricular septal defect in various age groups

Category	No. of Patients						Total	Mortality Rate (%)
	0-5 mo.	6-11 mo.	1 yr.	2 yr.	3 yr.	Over 4 yr.		
Pp/Ps≦0.75	0	29(1)	38(0)	19(0)	32(0)	121(1)	239(2)	0.8
Pp/Ps>0.75	18(4)	62(8)	49(4)	23(0)	10(2)	19(2)	181(20)	11.0
Total	18(4)	91(9)	87(4)	42(0)	42(2)	140(3)	420(22)	5.2[a]

Legend : a, Overall. Pp/Ps, Ratio of pulmonary peak pressure to systemic peak pressure. Parenthesis indicates No. of deaths.

Table V. Hospital mortality after repair of ventricular septal defect with severe pulmonary hypertension according to the degree of the ratio of pulmonary to systemic vascular resistance in various age groups

Category	No. of Patients						Total	Mortality Rate (%)
	0-5 mo.	6-11 mo.	1 yr.	2 yr.	3 yr.	Over 4 yr.		
Rp/Rs <0.5	8(2)	29(2)	29(2)	14(0)	4(1)	7(0)	91(7)	7.7
Rp/Rs 0.5-0.75	8(2)	19(3)	10(1)	7(0)	5(1)	6(0)	55(7)	12.7
Rp/Rs >0.75	2(0)	14(3)	10(1)	2(0)	1(0)	6(2)	35(6)	17.1
Total	18(4)	62(8)	49(4)	23(0)	10(2)	19(2)	181(20)	11.0[a]

Legend ; a, Overall. Rp/Rs, Ratio of pulmonary to systemic vascular resistance. Parenthesis indicates No. of deaths.

patients of 2 years, 20 per cent in patients of 3 years, and 10.5 per cent in patients over 4 years of age.

To compare the mortality rate in early and later series in this study, 181 patients were divided to 89 in early series during the period from Sept., 1968 to Jan., 1971, and to 92 in later series during the period from Feb., 1971 to Dec., 1975 (Table VI). In later series, there were no hospital deaths in 47 pateitns with Rp/Rs less than 0.5 and 28 patients with Rp/Rs of 0.5 to 0.75, there being two deaths in 17 patients (11.8 per cent) with Rp/Rs greater than 0.75. One of these patients was operated on at the age of 10 months with Pp/Ps and Rp/Rs greater than 1.0, in whom VSD was multiple, and died of respiratory and renal failure on the second postoperative day. Postmortem examination revealed hypoplastic left ventricle in this case. The other underwent repair at the age of 11 years with Pp/Ps and Rp/Rs greater than 1.0 and died suddenly on the fifth postoperative day following uneventful course during

Table VI. Hospital motlaity after repair of ventricular septal defect with severe pulmonary hypertension in early and later series in various age groups

Category	Sept., 1968-Jan., 1971								Feb., 1971-Dec., 1975							
	No. of Patients						Total	Mortality Rate (%)	No. of Patients						Total	Mortality Rate (%)
	0-5mo.	6-11mo.	1yr.	2yr.	3yr.	Over 4yr.			0-5mo.	6-11mo.	1yr.	2yr.	3yr.	Over 4yr.		
Rp/<0.5	6(2)	19(2)	13(2)	2(0)	1(1)	3(0)	44(7)	15.9	2(0)	10(0)	16(0)	12(0)	3(0)	4(0)	47(0)	0
Rp/Rs0.5-0.75	5(2)	12(3)	3(1)	2(0)	2(1)	3(0)	27(7)	25.9	3(0)	7(0)	7(0)	5(0)	3(0)	3(0)	28(0)	0
Rp/Rs 0.75	2(0)	9(2)	3(1)	1(0)	1(0)	2(1)	18(4)	22.2	—	5(1)	7(0)	1(0)	—	4(1)	17(2)	11.8
Total	13(4)	40(7)	19(4)	5(0)	4(2)	8(1)	89(18)	20.2[a]	5(0)	22(1)	30(0)	18(0)	6(0)	11(1)	92(2)	2.2[a]

Legend : a, Overall. Rp/Rs, Ratio of pulmonary to systemic vascular resistance. Parenthesis indicates No. of deaths.

early postoperative period. Overall mortality rate was 2.2 per cent in later series, while it was 20.2 per cent in early series.

C) Location of VSD.

The anatomic classification of VSD proposed by BECU and co-workers[21] and implemented by KIRKLIN and his associates[22] has been adopted (Fig. 3). Table VII indicates operative mortality according to the type of VSD. Type II occupied 75 per cent of patients and the mortality rate was highest (50 per cent) in complex type of IV and II.

D) Cause of death.

There were twenty operative deaths (11 per cent) in the entire series (Table VIII). Four of these resulted from respiratory insufficiency, four from cerebral damage

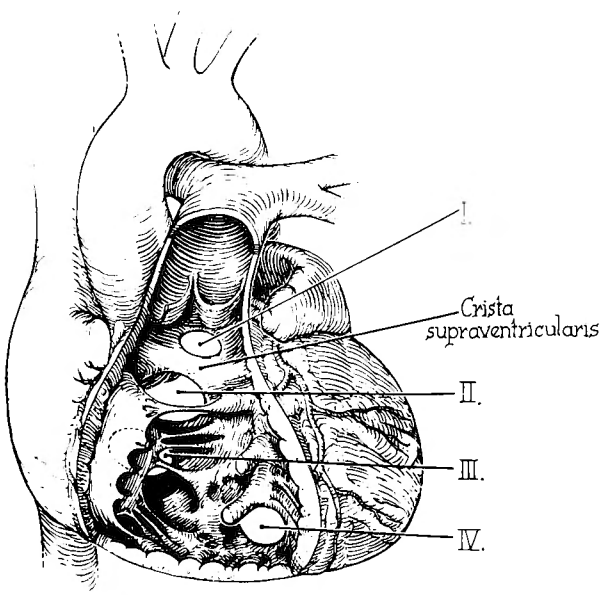

Fig. 3 Anatomic classification of ventricular septal defect

Table VII. Type of repaired ventricular septal defects and mortality encoutered in patients with severe pulmonary hypertension

Type of Defect	No. Patients(Per Cent)	No. Deaths	Mortality Rate %
I	23(12.7)	0	0
I + II	12(6.6)	2	16.7
II	137(75.7)	15	10.9
III	4(2.2)	1	25.0
IV	3(1.7)	1	33.3
IV + II	2(1.1)	1	50.0
Total	181(100)	20	11.0[a]

a, Overall.

Table VIII. Causes of deaths following repair of ventricular septal defect with severe pulmonary hypertension

Causes of Deaths	No. Patients
Respiratory insufficiency	4
Cerebral damage	4
Acute renal failure accompanied with excessive hemolysis	4
Low cardiac output	2
Pulmonary edema	2
Hemorrhage from stomach and intestine	1
Hemorrhage from liver	1
Vomitting and aspiration	1
Unexplained sudden death	1
Total	20

mainly due to air embolism, and four from acute renal failure accompanied with excessive hemolysis. Two occurred from progressive reduction in cardiac output, two from heart failure with pulmonary edema. One patient died from massive hemorrhage from stomach and intestine, 1 from hemorrhage from liver which was found at autopsy, and 1 from vomitting and aspiration. Unexplained sudden death was seen in 1 patient, which was already described.

E) Postoperative hemodynamic changes.

1) Pp/Ps. Changes in Pp/Ps following repair of VSD related to age and Rp/Rs are shown graphically in Fig. 4.

In group I where Rp/Rs is less than 0.5, Pp/Ps fell in all of 51 patients of all age groups 1 month after repair and reached the normal range(less than 0.3)in 13, mildly elevated (0.3 to 0.5) in 34, and moderately elevated (0.5 to 0.75) in 4. There was no patient less than 6 months of age with Pp/Ps remained moderately or severely elevated (greater than 0.75). There were no significant differences in the extent of fall of Pp/Ps among each age groups. One of patients less than 6 months of age was recatheterized 1 year after repair and changed from the mild range to normal range.

In group II where Rp/Rs is 0.5 to 0.75, Pp/Ps fell in all of 35 patients of all age groups 1 month after repair and reached the normal range in 3, mildly elevated in 22, and moderately elevated in 10. There were no patients less than 6 months of age with Pp/Ps remaining in moderate range. There was a significant decrease in Pp/Ps in any patient recatheterized 1 year after repair, 5 patients having changed from the moderate to the mild range and 3 from the mild to normal range.

In group III where Rp/Rs is greater than 0.75, Pp/Ps fell in all of 22 patients of all age groups 1 month after repair and reached mildly elevated in 12, moderately elevated in 6, and remained severely elevated in 4 with a decrease to a certain extent. One patient, 8 months of age at the operation, and 2 patients in 1 year of age changed from the mild range to normal range at the time of recatheterization 1 year

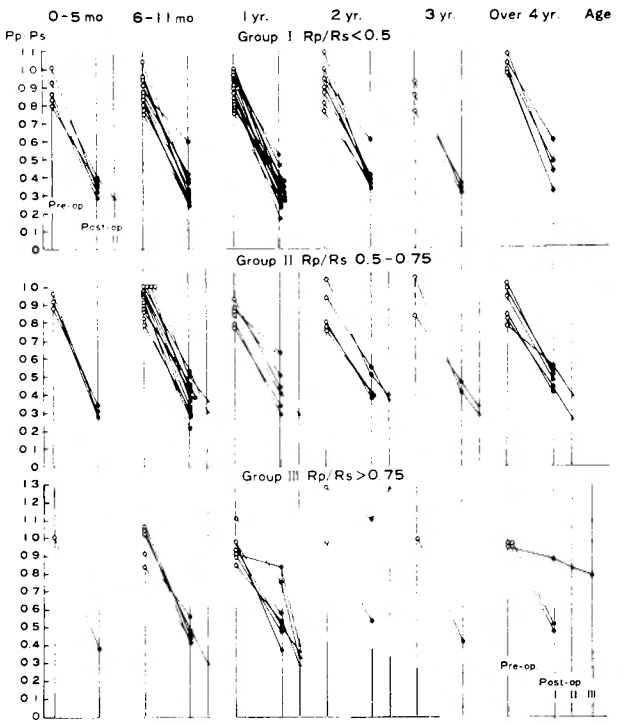

Fig. 4 Chages in Pp/Ps following successful repair of ventricular septal defect with severe pulmonary hypertension related to age and Rp/Rs

after repair. Two patients in 1 year of age changed from the severe range to normal range at recatheterization. In one of patients in 2 years of age, Pp/Ps remained severely elevated with a decrease to some extent 1 month after repair and showed severe elevation 1 year after repair. In one of patients, operated on at the age of 4 years, Pp/Ps remained severely elevated with a slight gradual decrease at the time 1 month, 1 year, and 4 years after repair.

2) Rp/Rs. The ratio of pulmonary to systemic resistance revealed a similar trend to fall in all the patients 1 month after repair except 1 patient of 2 years of age in whom it rose from 0.78 to 0.83 (Fig. 5). When he was recatheterized 1 year after repair, there was a marked increase in Rp/Rs to 1.13. Using the criteria based on Rp/Rs, he had severe pulmonary vascular disease before and shortly after operation and died of pulmonary dysfunction due to severe pulmonary vascular disease which rapidly progressed following repair of VSD. One of patients, 4 year-old at operation, has had severe pulmonary vascular disease even in 4 years after operation, which suggests that pulmonary vascular obstructive change has become irreversible. Among 108 patients who underwent postoperative catheterization 1 month after repair, 51 belonged to group I, 35 to group II and 22 to group III preoperatively (Table IX). Pulmonary vascular disease changed from the mild to the minimal or normal range

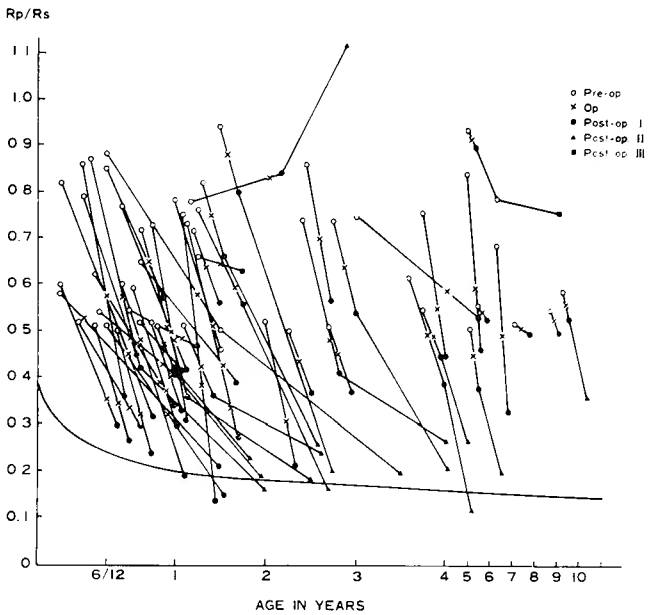

Fig. 5 Changes in Rp/Rs after successful repair of ventricular septal deeect with moderate and severe pulmonary vascular disease. The heavy line represents the normal maturation line for pulmonary vascular resistance.

Table IX. Degree of pulmonary vascular disease before and after repair of ventricular septal defect with severe pulmonary hypertension

Group	Before Op.			After Op. (1mo.) P.V.D.		
	Rp/Rs	P.V.D.	No. Patient	Not Any or Mild	Moderate	Severe
I	<0.5	Mild	51	51	—	—
II	0.5–0.75	Moderate	35	29	6*	—
III	>0.75	Severe	22	9	9+	4‡
	Total		103	89	15	4

Legend : Rp/Rs, Ratio of pulmonary to systemic vascular resitance. P.V.D., Pulmonary vascular disease.

* In 4 patients, all were over 4 years old, became "Mild" at recatherization 1 year after operation.

\+ In 4 patients, all were 1 year old, became "Mild" at recatherization 1 year after operation.

‡ In 1 patient, 1 year old, became "Mild" at recatherization 1 year after operation, and 1 patient, 8 years old, with persistent shunt, died in 7 months after operation.

in all of 51 patients in group I, from the moderate to the mild range in 29 of 35 patients in group II, 6 patients in group II remaining in the moderate range with a decrease to some extent. Nine patients in group III changed from the severe to the mild range, 9 from the severe to the moderate range, 4 remaining in the severe range

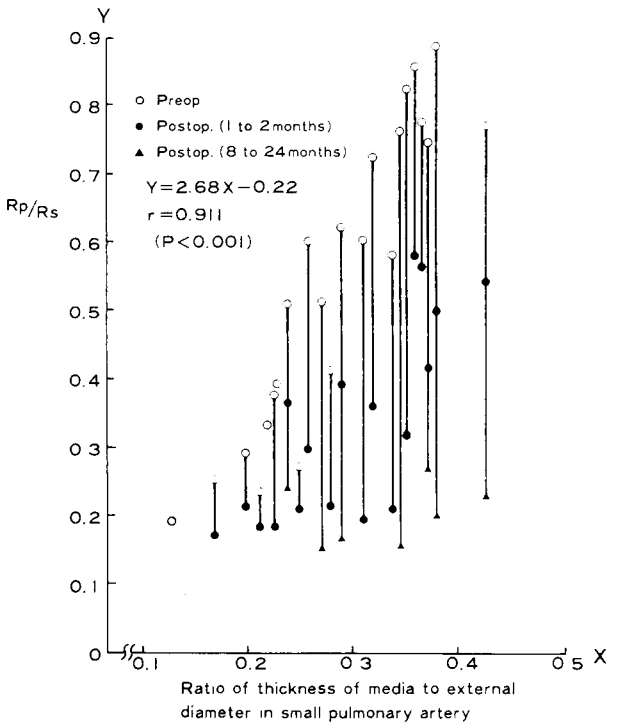

Fig. 6 Correlation between Rp/Rs and mean medial thickness (ratio of thickness of media to external diameter in small pulmonary artery)

with a decrease in Rp/Rs to some extent. At recatheterization 1 year after repair, pulmonary vascular disease changed from the moderate to the mild range in 4 patients in group II, from the moderate to the mild range in 4 patients and from the severe to the mild range in 1 patient in group III.

F) Late death.

There have been four late deaths (2.5 per cent of the survivors) among 161 patients surviving the operation. One patient died from complete heart block, 1 from arrhythmia during the catheterization, 1 from progressive pulmonary vascular disease, and 1 from congestive heart failure due to a large amount of left-to-right shunt through residual VSD.

G) Histological assessment of lung specimen.

The histological examination of lung specimen, obtained at the time of operation in 23 patients, revealed grade I to III pulmonary vascular changes according to the classification of HEATH and EDWARDS[23]. Two patients with Rp/Rs greater than 0.75 who died following repair, 2 year-old boy and 11 year-old girl, showed grade IV to VI change at autopsy. There was a good positive correlation between preoperative Rp/Rs and mean medial thickness, the correlation coefficient being 0.91 ($P < 0.001$) as shown in Figs. 6.

Discussion

Since the first primary repair of VSD was performed by LILLEHEI and his associates[24] in 1954, many reports about the results of the primary repair of VSD had appeared in the early days of cardiopulmonary bypass, in which the mortality rate was between 30 and 50 per cent[10~13]. Because of these poor results, the primary repair in infancy has been abandoned by many surgeons with a few exceptions[10,14,25], and the two-staged correction has been employed in most cardiac centers during the past 2 decades.

A number of reviews were reported about the pulmonary artery banding and its efficacy with operative mortality rate between 5 to 25 per cent[3~5,7,8]. Serious complications following pulmonary artery banding were also reported by many investigators, such as obstruction of right ventricular outflow[6], deformity of pulmonary artery[26], thrombus formation beneath the band resulting in severe obstruction[27], thickening of pulmonary valve leaflets[7,27], rupture of pulmonary artery[28], and subaortic stenosis[29]. Subsequent repair of VSD and debanding has brought the operative mortality rate between 5 and 30 per cent[3~5,7~9,30]. GIROD[8] reported combined mortality rate of pulmonary artery banding and subsequent total correction being 15 per cent. Other authors[4,5,7] reported higher combined mortality, mainly because of higher stage-two mortality.

HIKASA[31] reported his encouraging experience in the primary repair of VSD in 55 patients under 1 year of age with mortality rate of 7 per cent using deep hypothermia with surface cooling and limited cardiopulmonary bypass. BARRATT-BOYES[32] reported no deaths of 11 correction of VSD in infants less than 1 year of age with use of similar hypothermic technique. CASTANEDA[33] reported three operative deaths of 9 patients under 3 months of age performed under deep hypothermia. VENUGOPAL and SUBRAMANIAN[17], using a similar technique, reported no deaths in 22 infants, 15 of these being associated with severe pulmonary hypertension. MURAOKA[20] published a mortality rate of 9.4 per cent in 96 patients under 2 years of age with use of deep hypothermic procedure. BONCHEK[34] reported one operative death out of 11 corrections of VSD in infants less than 2 years of age, using cardiopulmonary bypass. CHING[35] reported a 33 per cent operative mortality rate in a whole series of 75 patients less than 12 months of age with an improved mortality rate of 22 per cent in 18 pateints for recent 5 years, utilizing extracorporeal circulation with moderate hypothermia.

The risk of the operative intervention for VSD has been greatly influenced not only by the age of the patient, but also by the degree of pulmonary hypertension and of pulmonary vascular disease. It has been generally concluded that the patients with pulmonary hypertension and pulmonry vascular disease increase the hazards of surgical repair of VSD. HALLMAN[12] reported a 26 per cent operative mortality rate in 175 patients with severe pulmonary hypertension (Pp/Ps greater than 0.80). In a

series of 185 patients with severe pulmonary hypertension (Pp/Ps greater than 0.75), CARTMILL[13] reported a 15 per cent operative mortality in 86 patients with Rp/Rs less than 0.45, 13 per cent in 86 patients with Rp/Rs of 0.45 to 0.75, and 54 per cent in 13 patients with Rp/Rs greater than 0.75. IBACH[36] reported a 40 per cent mortality rate in 21 patients with Pp/Ps greater than 0.75. In a review reported by CHING[35], the mortality rate was 23 per cent in 70 patients less than 24 months of age with Pp/Ps greater than 0.75. DUSHANE[37] has recently published the encouraging reports on the operative results in patients with severe pulmonary hypertension (Pp/Ps greater than 0.79). There were two operative deaths out of 9 patients (22 per cent) less than 6 months of age, one death out of 23 (4 per cent) between 6 and 12 months of age, and one death out of 19 (5 per cent) between 13 and 24 months of age. In author's present investigation of VSD associated with severe pulmonary hypertension (Pp/Ps greater than 0.75), the operative mortality rate in the entire series was 22.2 per cent in patients less than 6 months of age, 12.9 per cent in patients of 6 to 11 months of age, and 8.2 per cent in patients of 1 year of age, while the operative risk was acceptably low (0.75 per cent) regardless of age in the patients with Pp/Ps less than 0.75. In later series of this study from 1971 to 1975, however, only two patients with severe pulmonary vascular disease died following repair among 92 patients with severe pulmonary hypertension including 5 patients less than 6 months, 22 of 6 to 11 months, and 30 of 1 year of age. The striking decrease in the mortality rate in the patients with severe pulmonary hypertension in later series seems related mainly to the improved management of congestive heart failure or repiratory failure prior to operation, the near absence of excessive hemolysis and cerebral air embolism, and the reduced incidence of low cardiac output syndrome or pulmonary complications.

Considering the fact that the primary repair of isolated VSD with severe pulmonary hypertension can be performed with acceptably low operative risk regardless of the patient's age or body weight as seen in later series in this study, the spotlight must be focused on the selection of the optimal time for the primary repair to restore the pulmonary hemodynamics to normal or near normal as soon as possible following operation. There has been no clear agreement about the onset of pulmonary vascular disease and its development. Some investigators[38,39] have shown a decrease in pulmonary vascular resistance after repair-although not usually to normal levels-in every case, irrespective of the degree of preoperative elevation. Other investigators[13,40,41] have found that pulmonary vascular resistance raised after repair in some cases with pulmonary hypertension. And, when the long-term follow-up studies are available, it seems clear that some patients among older children have progressive pulmonary vascular disease in spite of the repair of VSD. FRIEDLI and his coworkers[42] reported the follow-up studies in 25 survivors with preoperative Rp/Rs more than 1/3 in 1 to 11 years after repair. Seven of 10 patients (70 per cent) who were operated on after age 2 years showed an increase in Rp/Rs and 3 of these died

of EISENMENGER syndrome due to progressive pulmonary vascular disease. On the contrary, patients who underwent the repair before age 2 years had normal pulmonary vascular resistance. DUSHANE and KIRKLIN[37] published a surprising reports about the late changes in pulmonary vascular disease and indicated that none of 18 patients who were less than 2 years old when operated on showed an increase in pulmonary vascular resistance, while 14 of 50 patients (28 per cent) who were older than 2 years when operated on showed an increase in pulmonary vascular resistance. Reviewing these reports, however, it is clear that there has been a few patients so far who underwent the repair of VSD associated with severe pulmonary hypertension at the age less than 6 months or 6 to 11 months, and who underwent the follow-up examinations of the hemodynamic changes. In the author's investigation, 10 of 14 survivors who were operated on at the age less than 6 months and 30 of 54 survivors who were operated on at the age of 6 to 11 months were examined 1 month after repair and all of these except one showed significant decrease in both Pp/Ps and Rp/Rs to normal or near normal range. It seems particularly noteworthy that one patient, operated on at the age of 5 months, with severely elevated Rp/Rs (0.86) which was suspected due to the immaturation of the pulmonary vascular bed[47] showed a significant decrease in both Pp/Ps and Rp/Rs to near normal range, although the lung specimen was not obtained. One of patients who underwent the repair at the age of 2 years showed progressive pulmonary vascular disease and died of EISENMENGER syndorme 13 months after repair. Another patient, who were 4 years old when operated on, showed persistent severe pulmonary vascular disease on long-term follow-up. It is concluded, based on the follow-up studies on hemodynamic changes after repair of VSD in this study, that pulmonary vascular disease can progress or remain stationary following operation in some instances who are operated on after 2 years of age with preoperative Rp/Rs greater than 0.75, and that the later the repair is performed, the less likely the pulmonary vascular resistance will approximate normal levels following operation.

The assessment of pulmonary vascular disease is essentially a histological one, as described and graded according to its severity by HEATH and EDWARDS[23,43,44]. In this series, lung specimen was obtained in 23 patients ranging in age from 4 months to 3 years, and demonstrated grade I to III pulmonary vascular changes in all of them. None of these showed grade IV or more vascular changes, althouth a small number of patients was examined. Postmortem examination of 2 year-old boy and 11 year-old girl when operated on with preoperative Rp/Rs greater than 0.75, revealed grade IV or more vascular changes. There was a good correlation between Rp/Rs and mean medial thickness observed in the small muscular pulmonary artery in these patients with correlation coefficient of 0.91. In addition, all of these except 5 patients showed a significant decrease in Rp/Rs 1 month after repair. Three of 5 patients were examined later and showed a significant decrease in Rp/Rs to near normal level.

It is suggested from these facts that Rp/Rs and thickness of media in small muscular pulmonary artery correlates well when pulmonary vascular obstructive changes are within grade III, and that the changes within grade III are reversible as indicated by HEATH and EDWARDS[44]. WAGENVOORT[45] and NAEYE[46] have reported in their histological studies that the pulmonary vascular obstructive disease of grade IV or more occurs after the patient reaches 2 years of age.

When considered of these histological findings combined with hemodynamic changes observed in the present investigation, it must be concluded that the repair of VSD associated with severe pulmonary hypertension and severely elevated Rp/Rs (greater than 0.75) should be performed before the patient has reached 2 years of age. The patients with severe pulmonary vascular disease of Rp/Rs greater than 1.0 and with right-to-left shunt dominant are not candidates for the repair of VSD. The repair of VSD with severe pulmonary hypertension with Rp/Rs less than 0.75 is permitted at any time before 3 years of age, but should be done preferably at the age between 1 and 2 years, because the operative risk has been found equally low at any age as seen in later series in this investigations, and because progressive pulmonary vascular disease may occur even in patients of this category after 2 years of age.

With regards to the type of surgical procedure, it is concluded that the definitive primary repair should be the method of choice for the treatment of certain cases of symptomatic VSD in infancy because it can be performed with less risk than pulmonary artery banding.

Summary

Evaluation of the operative risk and postoperative hemodynamic changes was made in the primary repair of isolated VSD with severe pulmonary hypertension which was performed in 181 patients during the period from September, 1968 to December, 1975 at Hyogo Kenritsu Amagasaki Hospital.

1) The operative mortality rate in entire series related to the patient's age and to the degree of pulmonary vascular disease. Namely, the mortality rate in each age group was 22.2 per cent (less than 6 months), 12.9 per cent (6 to 11 months), 8.2 per cent (1 year), 0 per cent (2 years), 20 per cent (3 years), and 10.5 per cent (over 4 years) respectively. The overall mortality rate was 11 per cent.

The mortality rate was 7.7 per cent in the patients with mild pulmonary vascular disease (Rp/Rs less than 0.5), 12.7 per cent in the patients with moderate pulmonary vascular disease (Rp/Rs 0.5 to 0.75), and 17.1 per cent in the patients with severe pulmonary vascular disease (Rp/Rs greater than 0.75).

2) The mortality rate observed in later series in this investigation, showed a striking decrease and no relation to the patient's age or body weight but to the degree of pulmonary vascular disease. There were no deaths in 75 patients with mild or moderate pulmonary vascular disease, and there were two deaths in 17

patients (11.8 per cent) with severe pulmonary vascular disease, overall mortality in later series being 2.2 per cent.

3) The cardiac catheterization was carried out in 108 patients among 161 survivors 1 month after repair. Late changes in hemodynamics were examined by recatheterization in 17 of these patients 1 year after repair. The results showed a fall in Pp/Ps and Rp/Rs in all the patient except one, in whom both Pp, Ps and Rp, Rs rose 1 year after repair performed at the age of 2 years. This patient died of progressive pulmonary vascular disease. The majority of patients showed a various degree of residual pulmonary vascular disease, but it is definitely indicated that Pp/Ps and Rp/Rs have shown more rapid fall to normal or near normal range in young infants than did in older children.

4) The lung specimen, obtained in 23 pateints at the time of operation, revealed pulmonary vascular changes of grade I to III in all of them. There was a good correlation between preoperative Rp, Rs and mean medial thickness in small muscular pulmonary artery. Postmortem examination of 2 year-old boy and 11 year-old girl when operated on revealed grade IV or more vascular changes.

5) In view of operative risk and pulmonary vascular disease, VSD with severe pulmonary hypertension and severely elevated Rp/Rs (greater than 0.75) should be repaired before the patient has reached 2 years of age.

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和文抄録

高度肺高血圧症を伴う心室中隔欠損症根治手術の臨床的研究

とくに手術成績ならびに術後血行動態の推移に関する年令別検討

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心室中隔欠損症（VSD）は先天性心奇形のうちで最も発生頻度が高く，したがって最もしばしば外科治療の対象となる疾患である．本症の手術成績および遠隔成績を左右する重要な因子として患者の手術時年令，肺高血圧の程度および肺血管の閉塞性病変の程度が挙げられる．乳児期における一期的根治手術の成績がきわめて不良であったため，従来は肺動脈絞扼術とそれに次ぐ二期的根治手術がその外科治療の主流をなしてきた．近年，ようやく乳児期の一期的根治手術が行われるようになったが，6カ月未満あるいは1才未満の根治手術症例の絶対数はいまだ少なく，それらの術後血行動態の推移を追跡した報告もきわめて少ない．一方，肺血管の閉塞性病変がいつ始まり，いかに推移するかに関しては幾多の報告があるか，確固たる意見の一致をみていない．著者は昭和43年9月より昭和50年12月までの約7年間に兵庫県立尼崎病院心臓センターで行われた420例のVSDに対する一期的根治手術のうち，肺・体動脈収縮期圧比（Pp/Ps）が0.75以上の高度肺高血圧症を伴った181例を対象として，年令別ならびに肺血管病変の重症度の指標としての肺・体血管抵抗比（Rp/Rs）別に，手術成績と術後の血行動態の推移を検索し，次のような結果および結論をえた．

1. 手術時年令と手術成績：死亡率は，6カ月未満で22.2%と最も高いが，必ずしも年令とは相関しなかった．昭和46年2月以降の後期では，92例中10カ月と11才（いずれもRp/Rs 0.75以上）の2例を失ったのみで（死亡率2.2%），手術成績は年令とは無関係にきわめて良好であった．

2. Rp/Rsと手術成績：死亡率は，Rp/Rs 0.5以下で7.7%，0.5—0.75で12.7%，0.75以上で17.1%と明らかに高肺血管抵抗群ほど成績は不良であった．しかし，後期においてはRp/Rs 0.5以下の36例および0.5～0.75の28例に死亡例はなく，Rp/Rs 0.75以上の17例中2例の死亡（死亡率11.8%）のみで，後期の全体死亡率は2.2%と良好であった．後期におけるこれら手術成績の著しい向上は，術前術後における呼吸循環管理や開心術に対する補助手段の改善，とくに術後呼吸管理の進歩によるものである．

3. 手術時年令と術後Pp/PsおよびRp/Rsの推移：6カ月未満症例ではRp/Rs如何にかかわらず術後1カ月で全例Pp/Ps，Rp/Rsともに正常値あるいは正常値近くまで下降した．6～11カ月症例では，大部分の症例で正常値あるいは正常値近くまで下降したが一部下降の不良な症例があった．しかし，これらも術後1年では正常値へと下降していた．1才症例では，Rp/Rs 0.5以下症例の下降は全例良好であるが，Rp/Rs 0.5以上の症例の中には下降不良な症例があった．しかしこれらも1年後には正常値近くまで下降していた．2才，3才および4才以上では，Rp/Rsの値にかかわらず正常値近くまで下降する症例と，下降はするがなお中等度あるいは高値を維持する症例があり，2才の1症例（Rp/Rs 0.75以上）は，術後肺血管病変がさらに進行して遠隔死した．4才の1例（Rp/Rs 0.75以上）では術後4年においてもなお高度の肺血管病変を呈していた．一般的には，手術時年令が若いほど肺循環はよりすみやかに正常に復する傾向が認められた．

4. 肺生検や剖検による肺血管病変の判定：生存例23例において手術時肺生検を施行した．全例Heath-Edwards重症度分類Ⅰ度～Ⅲ度の可逆性病変を呈し，これら症例の肺細小動脈の中膜の厚さとRp/Rsはよく相関し（相関係数0.911，$P<0.001$），かつ術後Rp/Rsは良好な下降を示した．剖検時にHeath-EdwardsⅣ度以上の不可逆性病変を示した症例は，2才および11才の2例にすぎないが，2才児ですでに不可逆性肺血管病変を呈する症例のあることは注目に値する．

5. 肺血管の閉塞性病変は2才未満では可逆性の変化が主であり，2才を越えると，Rp/Rsが0.75以上を示す症例のうちには不可逆性の変化が進行し，VSD閉鎖後もなお進行する症例のあることが判明した．したがってRp/Rs 0.75以上の高肺血管抵抗を示す症例は，患者が2才に達するまでに根治手術を行うべきである．