SURGERY FOR CONGENITAL HEART DISEASE

PULMONARY VASCULAR RESISTANCE DURING EXERCISE LATE AFTER REPAIR OF LARGE VENTRICULAR SEPTAL DEFECTS

Relation to age at the time of repair

Postoperative pulmonary artery pressure and resistance were assessed during exercise in 32 patients late after repair of large ventricular septal defect with pulmonary hypertension. Nineteen patients had a preoperative pulmonary-to-systemic resistance ratio of between 0.15 and 0.50 (group 1) and 13 had a ratio between 0.50 and 0.96 (group 2). Age at the time of operation was 0.9 to 13.0 years (4.6 ± 3.6) in group 1 and 0.8 to 15.8 years (4.3 ± 4.2) in group 2. Age at the time of restudy was 9 to 21 years (14.5 ± 3.0) in group 1 and 9 to 22 years (13.5 ± 4.1) in group 2. Pulmonary artery pressure was measured in the supine position at rest and during exercise, as were the measurements underlying the calculations of pulmonary vascular resistance. Mean pulmonary artery pressure was 13 to 21 mm Hg (17 ± 2) and 10 to 26 mm Hg (20 ± 5) in groups 1 and 2, respectively, at rest, and this increased to 17 to 27 mm Hg (22 ± 3) and 14 to 39 mm Hg (27 ± 7) in groups 1 and 2, respectively, during exercise ($p < 0.05$). Pulmonary vascular resistance was 0.51 to $3.40 \text{ U} \cdot \text{m}^2$ (1.93 ± 0.63) and 0.79 to $3.31 \text{ U} \cdot \text{m}^2$ (2.05 ± 0.65) in groups 1 and 2 at rest. It was 0.58 to $2.24 \text{ U} \cdot \text{m}^2$ (1.36 ± 0.57) and 0.81 to $3.85 \text{ U} \cdot \text{m}^2$ (2.18 ± 0.97) in groups 1 and 2 during exercise ($p < 0.01$). Postoperative pulmonary vascular resistance during exercise correlated well with age at the time of repair in both groups ($r = 0.65$, $p < 0.05$ in group 1; $r = 0.86$, $p < 0.001$ in group 2). These data suggest that 85% of patients with a preoperative pulmonary-to-systemic resistance ratio of between 0.15 and 0.50 would have normal pulmonary vascular resistance during exercise when operated on at younger than 3.8 years old and 85% of those with a preoperative pulmonary-to-systemic resistance ratio of more than 0.50 would have normal pulmonary vascular resistance during exercise when operated on at younger than 1.1 years. (J THORAC CARDIOVASC SURG 1995;109:1218-24)

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The prognosis of large ventricular septal defect (VSD) with pulmonary hypertension after surgical closure has been documented. Age and pulmonary vascular resistance (PVR) at the time of repair have been shown to be incremental risk factors that relate to outcome and regression of pulmonary hypertension.^{1,2} However, most of the data available were obtained at resting status, and little infor-

mation is available about late postoperative PVR during the stress of exercise.³⁻⁵ We therefore assessed pulmonary hemodynamics during exercise, as well as at rest, late after closure of large VSD with pulmonary hypertension and analyzed the relation of age and PVR at the time of repair to postoperative PVR during the stress of exercise.

Material and methods

Thirty-two patients were studied to evaluate pulmonary hemodynamics at rest and during exercise late after closure of large VSD. Patients with coexisting patent ductus arteriosus or atrial septal defect were included in this study, but those with atrioventricular septal defect were excluded. No patient had a chromosome aberration. All patients had pulmonary hypertension before operation (mean pulmonary artery pressure equal to or greater than 25 mm Hg). Preoperative mean pulmonary artery pressure ranged from 25 to 90 mm Hg (57 ± 16 ; mean

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Table I. Preoperative hemodynamic data

	Age at time of repair (yr)	PAm (mm Hg)	Pp/Ps	Qp/Qs	Rp/Rs
Total (n = 32)	0.8-15 (4.5 ± 3.8)	25-90 (57 ± 16)	0.27-1.10 (0.80 ± 0.21)	1.04-3.10 (1.65 ± 0.46)	0.15-0.96 (0.45 ± 0.20)
Group 1 (n = 19)	0.9-13 (4.6 ± 3.6)	25-80 (49 ± 14)	0.27-0.98 (0.70 ± 0.21)	1.05-3.10 (1.85 ± 0.48)	0.15-0.48 (0.32 ± 0.11)
Group 2 (n = 13)	0.8-15 (4.3 ± 4.2)	43-90 (67 ± 11)	0.69-1.10 (0.94 ± 0.12)	1.04-1.64 (1.36 ± 0.19)	0.51-0.96 (0.64 ± 0.12)
p Value	NS	<0.05	<0.05	<0.05	<0.05

p Value obtained from comparison between groups 1 and 2.

PAm, Mean pulmonary artery pressure; Pp/Ps, pulmonary-to-systemic peak pressure ratio; Qp/Qs, pulmonary-to-systemic flow ratio; NS, not significant.

Table II. Postoperative data (1)

	Age at time of restudy (yr)	Interval (yr)	HR (beats/min)		Increasing rate of HR (%)	S _v O ₂ (%)	
			Rest	Exercise		Rest	Exercise
Total (n = 32)	9-22 (14.1 ± 3.5)	4-14 (9.6 ± 2.8)	60-111 (88 ± 15)	99-162 (134 ± 18)	118-186 (154 ± 17)	62.0-84.5 (78.0 ± 5.6)	36.0-66.8 (56.9 ± 7.8)
Group 1 (n = 19)	9-21 (14.5 ± 3.0)	5-14 (9.9 ± 2.9)	60-111 (86 ± 17)	99-162 (129 ± 20)	118-186 (152 ± 19)	62.0-84.5 (78.0 ± 6.0)	40.8-66.8 (57.3 ± 7.3)
Group 2 (n = 13)	9-22 (13.5 ± 4.0)	4-13 (9.2 ± 2.6)	69-110 (92 ± 12)	116-156 (141 ± 13)	136-186 (156 ± 15)	67.8-84.0 (78.0 ± 5.0)	36.0-65.8 (56.3 ± 8.8)
Normal subjects (n = 7)	10-22 (15.3 ± 4.1)		52-114 (91 ± 20)	108-176 (141 ± 25)	121-242 (162 ± 42)	71.8-85.1 (76.5 ± 4.8)	37.2-64.6 (48.5 ± 9.4)
p Value	NS	NS	NS	NS	NS	NS	NS

p Value of "interval" was obtained from comparison between groups 1 and 2; p values of other data were obtained from comparison among three groups.

Interval, Period between operation and restudy; HR, heart rate; S_vO₂, mixed venous oxygen saturation; NS, not significant.

plus or minus standard deviation of the mean) and the pulmonary-to-systemic systolic pressure ratio was 0.27 to 1.10 (0.80 ± 0.21). The pulmonary-to-systemic blood flow ratio was 1.04 to 3.10 (1.65 ± 0.46) and the pulmonary-to-systemic resistance ratio (Rp/Rs) was 0.15 to 0.96 (0.45 ± 0.20). The patients were divided into two groups according to whether they had an Rp/Rs of less than or more than 0.5.^{5,6} Group 1 consisted of 19 patients who had a preoperative Rp/Rs between 0.15 and 0.50 and group 2 of 13 patients with an Rp/Rs between 0.50 and 1.0. Ages at the time of repair (Table I) were 0.9 to 1.3 years (4.6 ± 3.5) in group 1 and 0.8 to 15.8 years (4.3 ± 4.0) in group 2 (not significant).

Surgical technique. The VSD was closed through a right ventriculotomy, a right atriotomy, or the pulmonary valve during moderately hypothermic cardiopulmonary bypass. Intermittent aortic crossclamping was used before 1978 and since 1978 cold hyperkalemic crystalloid cardioplegic solution has been used for myocardial protection.

Postoperative cardiac catheterization. Cardiac catheterization late after operation was done with patients mildly sedated but awake. The catheter was advanced through the right ventricle into the pulmonary artery and into the wedged position. The wedge pressure was measured followed by pressures in the pulmonary artery, the right ventricle, and the right atrium. Then a catheter was inserted into the femoral artery and advanced into the left

ventricle. The pressures in the left ventricle and ascending aorta were measured. Oximetry and cineangiography determined that neither intracardiac left-to-right or right-to-left shunts were present. Cardiac output was measured with the indicator-dilution method by injection of indocyanine greens into the pulmonary artery and sampling from the femoral artery. PVR was calculated as unit per meter squared in the usual manner. The same kinds of studies were obtained during exercise. Moderate exercise stress (about 1 watt/kg) was calibrated with bicycle ergometry in the supine position in each patient. The postoperative cardiac catheterization was done 4 to 14 years (9.6 ± 2.7) after the repair. Age at the time of restudy was 9 to 21 years (14.5 ± 3.0) and 9 to 22 years (13.5 ± 4.0) in groups 1 and 2, respectively (not significant). Interval between the operation and restudy was 5 to 14 years (9.9 ± 2.8) and 4 to 13 years (9.2 ± 2.5) in groups 1 and 2, respectively (not significant) (Table II). Normal values of PVR both at rest and during exercise were obtained from seven normal subjects who had undergone catheterization because of functional murmur. Ages of normal subjects were not different from those of patients in groups 1 and 2 at restudy.

The purpose of this study and of the stress test was explained to all patients or to their parents, or both, and informed consent was obtained.

Statistics. All data were expressed as mean plus or minus the standard deviation of the mean. Comparison of

Table III. Postoperative data (2)

	Cardiac index (L/min/m ²)		PAm (mm Hg)		PVR (U · m ²)	
	Rest	Exercise	Rest	Exercise	Rest	Exercise
Total	2.45-7.26	4.91-14.75	10-26	14-39	0.51-3.40	0.58-3.85
(n = 32)	(4.62 ± 1.19)	(7.97 ± 2.44)	(18 ± 4)	(24 ± 6)	(1.98 ± 0.63)	(1.70 ± 0.85)
Group 1	2.45-6.34	4.91-14.25	13-21	17-27	0.51-3.40	0.58-2.24
(n = 19)	(4.28 ± 1.07)	(7.90 ± 2.14)	(17 ± 2)	(22 ± 3)	(1.93 ± 0.63)	(1.36 ± 0.57)
Group 2	3.21-7.26	4.94-14.75	10-26	14-39	0.79-3.31	0.81-3.85
(n = 13)	(5.11 ± 1.23)	(8.06 ± 2.93)	(20 ± 5)	(27 ± 7)	(2.05 ± 0.65)	(2.18 ± 0.97)
Normal subjects	3.52-7.34	5.09-12.00	10-19	11-20	0.41-2.76	0.73-1.57
(n = 7)	(5.20 ± 1.72)	(8.41 ± 2.62)	(14 ± 3)	(16 ± 4)	(1.50 ± 0.88)	(1.17 ± 0.36)
p Value						
Group 1 vs normal	NS	NS	<0.01	<0.001	NS	NS
Group 2 vs normal	NS	NS	<0.01	<0.005	NS	<0.05

PAm, Mean pulmonary artery pressure; NS, not significant.

the data at rest and during exercise was made by the paired *t* test. Hemodynamic data between two groups were compared with the unpaired *t* test. Comparison among continuous variables in more than two groups was made by one-way analysis of variance. The relationships between age at the time of repair and pulmonary hemodynamics were evaluated by linear regression analysis as were the associations between preoperative data and postoperative PVR at rest and during exercise. The variables that were significantly related to the postoperative PVR at rest or during exercise in linear regression analysis were then evaluated in stepwise multiple regression analyses. Statistical significance was considered present at *p* < 0.05. The normal range for PVR was defined as the mean value plus or minus 2 standard deviations obtained from control subjects. Upper limits of the normal PVR were 3.3 units · m² at rest and 1.9 units · m² during exercise.

Results

Postoperative hemodynamic profile. Patients in three groups (group 1, group 2, and normal group) had similar hemodynamic data both at rest and during exercise, including heart rate, increasing rate of the heart rate, mixed venous oxygen saturation, and cardiac index (Tables II and III).

Associations with preoperative data and postoperative PVR at rest and during exercise. According to linear regression analyses, postoperative PVR at rest correlated with age at the time of repair (*p* < 0.001) and age at the time of restudy (*p* < 0.02). Postoperative PVR during exercise was correlated with age at the time of repair (*p* < 0.0003), age at the time of restudy (*p* < 0.05), preoperative Rp/Rs (*p* < 0.005) (Fig. 1), and mean pulmonary pressure (*p* < 0.005). In multiple regression analysis, age at the time of repair (*p* < 0.005) was a significant predictor of postoperative PVR at rest. Both age at the time of repair (*p* < 0.001) and preoperative

Rp/Rs (*p* < 0.001) were also significant predictors of postoperative PVR during exercise (Table IV).

Mean pulmonary artery pressure. Mean pulmonary artery pressure increased during exercise (both groups *p* < 0.05), more so in groups 1 and 2. In both groups the values were about normal both at rest and during exercise (Table III). However, neither in group 1 nor in group 2 did mean pulmonary artery pressure at rest or during exercise correlate with age at the time of repair.

PVR. PVR decreased during exercise overall and in patients in group 1, and differences in PVR during exercise between group 1 and normal subjects could have been caused by chance alone. However, during exercise PVR did not decrease in group 2 and was greater than that in normal subjects (*p* < 0.05) (Table III).

Relationship between postoperative PVR at rest and age at the time of repair. Postoperative PVR at rest correlated well with age at the time of repair overall (Fig. 2, A). It did not correlate with age at the time of repair in group 1 (Fig. 2, B), but correlated well with that in group 2 (Fig. 2, C). These correlations demonstrated that 85% of the patients had normal PVR at rest late after repair even when they had had an Rp/Rs more than 0.5 and had repair before age 10 years.

Relationship between postoperative PVR during exercise and age at the time of repair. During exercise, postoperative PVR correlated well with age at the time of repair overall in both groups (Fig. 3). These correlations demonstrated that 85% of the patients with a preoperative Rp/Rs between 0.15 and 0.50 had normal response of PVR during exercise when operated on at younger than age 3.8 years and, also, that 85% of the patients with a preoperative

Fig. 1. Relationship between postoperative PVR during exercise and preoperative Rp/Rs. There was significant correlation between them ($r = 0.563$, $p < 0.005$). Ex, Exercise.

Table IV. Relationship between postoperative PVR and preoperative data according to linear regression analysis and multiple regression analysis

Variables	Rest		Exercise	
	Correlation coefficient	p Value	Correlation coefficient	p Value
Linear regression analysis				
Age at time of repair	0.5537	0.0010	0.5919	0.0003
Age at time of restudy	0.4228	0.0157	0.3986	0.0236
Interval	0.2170	0.2326	0.2993	0.0957
PAm	0.2317	0.2016	0.4832	0.0050
Rp/Rs	0.1282	0.4841	0.5626	0.0033
Pp/Ps	0.2721	0.1315	0.3141	0.0797
Qp/Qs	0.1653	0.3657	0.3030	0.0915
Stepwise multiple regression analysis				
Age at time of repair	0.5537	0.0010	0.6729	0.00003
Rp/Rs		NS	0.6119	0.00025

Interval, Period between operation and restudy; PAm, mean pulmonary artery pressure; Pp/Ps, pulmonary-to-systemic peak pressure ratio; Qp/Qs, pulmonary-to-systemic flow ratio; NS, not significant.

Rp/Rs more than 0.50 had normal PVR during exercise when operated on at younger than 1.1 years old.

Discussion

Surgical "cure" of patients with large VSD with pulmonary hypertension (defined as surviving the early postoperative period and being alive late after operation with essentially normal pulmonary artery pressure) was reported to be obtained when surgical closure was done within 2 years of age.^{2,7} However, normal pulmonary artery pressure in this definition

was pressure measured at rest, not during exercise. The normal response of pulmonary circulation to exercise is a decrease in PVR.^{8,9} Therefore a normal pulmonary hemodynamic response can be said to be present, in a strict sense, only when the response to exercise is normal. However, we do not know that there is a difference in prognosis between patients with normal pulmonary vascular responses only at rest and those having normal responses even during exercise.

Some reports demonstrated an increase in pulmonary artery pressure during exercise in patients who

Fig. 2. **A,** Relationship between postoperative PVR at rest and age at time of repair overall. *Dashed lines* enclose plus or minus standard error (roughly equivalent to 70%) in this and in **C**. There was significant correlation between them ($r = 0.530, p < 0.005$). **B,** Relationship between postoperative PVR at rest and age at time of repair in group 1. **C,** Relationship between postoperative PVR at rest and age at time of repair in group 2. There was significant correlation between them as follows: postoperative PVR = $1.532 + 1.129 \log(\text{age at time of repair} = \text{year})$ ($r = 0.583, p < 0.05$).

Fig. 3. A, Relationship between postoperative PVR during exercise and age at time of repair overall. There was significant correlation between them as follows: postoperative PVR = $0.605 + 0.997 \log(\text{age at time of repair})$ ($r = 0.607, p < 0.001$). B, Relationship between postoperative PVR during exercise and age at time of repair in group 1. There was significant correlation between them as follows: postoperative PVR = $0.827 + 1.015 \log(\text{age at time of repair})$ ($r = 0.651, p < 0.05$). C, Relationship between postoperative PVR during exercise and age at time of repair in group 2. There was significant correlation between them as follows: postoperative PVR = $1.200 + 2.134 \log(\text{age at time of repair})$ ($r = 0.857, p < 0.001$). Ex, Exercise.

underwent surgical closure of a large VSD at an older age.^{3,4} However, there is still a paucity of this kind of information, especially about pulmonary vascular responses to exercise in patients who underwent closure of a large VSD at a very young age.

This study confirms the results of the previous report that patients with severe pulmonary hypertension caused by a large VSD should be operated on at less than 2 years of life.² However, our results refine this statement, because they demonstrate that a large VSD with moderately or severely high PVR should be closed when the patient is younger than 1 year old. Patients with a large VSD with mildly elevated PVR appear to have a good response even when the operation is delayed until age 3.8 years, although we would recommend repair at an earlier age.

Mixed venous oxygen saturation during exercise in patients in the present study was 36% to 84% ($60\% \pm 11\%$) and exercise load would be maximal when mixed venous oxygen saturation was less than 30%¹⁰; therefore, the exercise stress test used in this study was not maximum but moderate. Cardiac index during exercise in patients in this study significantly increased and was comparable to that of normal subjects. Some patients had pulmonary hypertension during exercise, suggesting good ventricular performance even during exercise.

The PVR rather than the Rp/Rs may be preferable for evaluating pulmonary vascular status. However, the resistance ratio is still clinically useful for assessing the severity of intrinsic PVR when operability is assessed in congenital bidirectional shunts. This ratio takes into account miscellaneous factors (catecholamine level and blood viscosity) that affect both pulmonary and systemic vascular beds.^{6,11} Therefore we still use this resistance ratio at preoperative assessment of pulmonary vascular obstructive disease. On the other hand, the PVR was measured at postoperative study in this study and should be more appropriate when pulmonary vascular responses to exercise are assessed in subjects without shunt.

In conclusion, this study demonstrated that a large VSD with PVR of more than an Rp/Rs of 0.5 should be closed while the patient is younger than 1 year old. This is also preferable in those with an Rp/Rs less than 0.5, but even when operation is delayed to the age of 4 years normal pulmonary vascular responses to moderate exercise are usually present late after operation.

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