The Spectrum of Pulmonary Vascular Disease in Transposition of the Great Arteries

By Peter H. Viles, M.D., Patrick A. Ongley, B.M., Ch.B., and Jack L. Titus, M.D., Ph.D.

SUMMARY
Obstructive pulmonary vascular disease (PVD) was evaluated in lung sections taken at autopsy in 53 patients with complete transposition of the great arteries. Twenty-three had intact ventricular septa and 30 had ventricular septal defects. Children of similar age and associated defects had widely differing degrees of PVD and presented a spectrum of disease. In a small number of patients, the presence of pulmonic stenosis (congenital or acquired by pulmonary artery banding in infancy), a small ventricular septal defect, or a large atrial septal defect was not protective against the development of severe PVD. The findings of this study demonstrate the need for thorough hemodynamic evaluation of patients with complete transposition of the great arteries prior to repair by present technics. In addition, operation should probably be performed as soon as technically feasible.

Additional Indexing Words:
Ventricular septal defect  Pulmonary stenosis  Pulmonary hypertension
Pulmonary banding

The Development of obstructive pulmonary vascular disease (PVD) may preclude successful surgical correction of various forms of congenital heart disease, including complete transposition of the great arteries in which PVD may develop rapidly. The present study of the pulmonary vessels of patients who died in recent years with transposition of the great arteries demonstrates that a spectrum of PVD exists in patients of similar ages and associated lesions.

Methods
Data were reviewed on patients who had transposition of the great arteries and came to autopsy at the Mayo Clinic in the 5-year period 1961 through 1965. Gross specimens were examined, and those showing dextrotransposition of the great arteries with the aorta arising anteriorly from the infundibulum of the right ventricle and with fibrous continuity between the mitral valve (left atrioventricular valve) and the pulmonary valve were selected. In 52 cases there was sufficient lung tissue for review. In addition, one case in which death occurred in 1967 was included as an example of a late death following surgical repair by the Mustard technic. Levo-cardia was present in all cases. Specifically excluded from this study were instances of transposition of the great arteries associated with tricuspid atresia, common ventricle, origin of both great arteries from the right ventricle, and levo-transposition of the great arteries (corrected transposition).

The presence of atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA) was noted. If the atrial septum had been excised at operation, the surgeon's operative note was reviewed to ascertain the preoperative status. Valvular or subvalvular pulmonic stenosis (PS) was judged to be present only when there was clear evidence of obstruction in these areas.

From the Mayo Clinic and Mayo Foundation: Section of Pediatrics and of Experimental and Anatomic Pathology, and the Mayo Graduate School of Medicine (University of Minnesota), Rochester, Minnesota.

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Grade of obstructive pulmonary vascular disease (PVD) in transposition of the great arteries plotted on abscissa according to age and associated lesions. Left, Patients with intact ventricular septum. Right, Patients with ventricular septal defect. Note that age scale is not continuous.

Figure 2

Pulmonary vessels from neonates without ventricular septal defect. ELVG; ×350. (A) Thin vessels from 12-day-old child (normal for older infants). (B) Grade 1 changes (medial thickening) from 11-day-old child (normal for age).
Blocks of formalin-fixed pulmonary tissue were cut from the periphery and hilus of the upper and lower lobes of each lung so that a total of eight blocks was taken in each case. At least two adjacent sections 7 μ thick were cut from each block and stained with either hematoxylin and eosin or Lawson's elastic tissue stain with van Gieson's counterstain (ELVG).

Each section was examined only with the knowledge that transposition of the great arteries was present. Structural changes in the small pulmonary arteries were graded according to the Heath-Edwards criteria. Each section was examined by two of the authors, and an independent assessment of the degree of PVD was made. When assessments were in conflict, the sections were reviewed and a consensus reached, usually in favor of the lower grading of PVD. After the histologic findings were graded, they were correlated with age and gross anatomic diagnosis.

Results

Patients were classified into two major groups: those with intact ventricular septum and those with ventricular septal defect. Each group was subdivided by age into neonates (age, 4 weeks or less), infants (age, 1 to 6 months), and older children (age, more than 6 months). The presence of pulmonic stenosis (either natural or from pulmonary artery banding), of a large patent ductus arteriosus (3 mm or more in diameter), and of a small ventricular septal defect (less than 5 mm in diameter) was considered. Small ductus arteriosus and small ventricular septal defect were considered likely not to have had hemodynamic significance. All results are summarized in figure 1.

Intact Ventricular Septum (23 Patients)

Ten patients were 4 weeks of age or less at death. Grade 1 changes (fig. 2), normal for this age, were present in eight, of whom two had a large patent ductus arteriosus and one had pulmonic stenosis. In two neonates the media was thin as in older, normal infants.
Figure 4

Case 1. Pulmonary vessels from a 16 11/12-year-old boy without ventricular septal defect. Plexiform lesion of grade 4 PVD below. Parent vessel (above) at this level shows medial hypertrophy and fibrous intimal proliferation. ELVG; × 350.

Neither had significant pulmonic stenosis and one had a large patent ductus arteriosus.

Infants, 1 to 6 months old at death, presented a wider range of morphologic pulmonic vascular disease (fig. 3). Of the eight in this age group, three were judged to have grade 2 or 3 changes, which were associated with a large patent ductus arteriosus in two. A 6-month-old infant without a patent ductus had grade 3 PVD (fig. 3B). Pulmonic stenosis was present in one infant with grade 1 PVD. The pulmonary vessels of the other four were considered to be normal.

Of the five children older than 6 months without ventricular septal defect, only one, aged 8 months, had normal pulmonary vessels. The oldest patient in this series, age 16 years (case 1), and a 2 8/12-year-old child, who died in 1967 6½ months after a Mustard operation (case 2), had grade 4 pulmonary vascular changes (figs. 4 and 5A).

**Ventricular Septal Defect (30 Patients)**

Only one neonate with a ventricular septal defect is represented in this series. The defect was small and grade 1 PVD changes were present.

Eleven patients with ventricular septal defect were 1 to 6 months of age at death. The condition of the pulmonary vessels in these varied from normal (in two with a small ventricular septal defect) to that characteristic of grade 2 to 3 PVD (four cases) (fig. 6). In four of the 11 the ventricular septal defect was small and in three other infants there was associated pulmonic stenosis. Neither of these situations guaranteed protection from PVD, as one patient with a small ventricular septal defect and another with pulmonic stenosis had acquired grade 2 changes by ages 2 and 4 months, respectively.

Eighteen patients with transposition of the great arteries and ventricular septal defect lived more than 6 months. The majority died after attempted surgical repair of their defects. Most had large ventricular septal defects, although one child, 1 10/12 years old, had a 3-mm ventricular septal defect and a grade 4 pulmonary vascular disease (fig. 7A). In the absence of pulmonic stenosis, severe PVD was the rule in these older patients (fig. 7B).

Five older patients had significant pulmonic stenosis and large ventricular septal defects. In two (cases 3 and 4), pulmonic obstruction was congenital; one had normal pulmonary vessels while the other had grade 3 changes (fig. 8). The other three patients had pulmonary artery stenosis created as part of a palliative procedure in infancy. Pulmonary vascular changes were present in all three (fig. 9). They were grade 2 in one (case 5) and grade 4 in the other two (including case 6). Hemodynamic and angiocardiographic data indicated the presence of severe pulmonic stenosis in all.

One child died at 11 months of age of a hyperthermic reaction following an orthopedic procedure for a hypoplastic radius. A Senning procedure with closure of a ventricular septal...
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Figure 5

Pulmonary vessels from cases of late death following complete repair. ELVG; ×200. (A) Grade 4 PVD in pulmonary vessels from a 2 8/12-year-old boy dying 6½ months after Mustard operation (case 2). (B) Minimal medial thickening in pulmonary vessels from 11-month-old boy dying 8 months after Senning operation.

defect measuring 5 by 9 mm had been performed at 3 months of age with an excellent functional result. Autopsy showed a 3-mm defect at the posteroinferior border of the reconstructed atrial septum. The repair of the ventricular septal defect was intact. Minimal medial thickening was seen on microscopic examination of the pulmonary vessels (fig. 5B).

In three of the 11 children more than 6 months of age with ventricular septal defect and grade 4 PVD the atrial septum was intact. A valve-incompetent foramen ovale was present in four. The remaining four had large atrial septal defects; in three these had been created as part of palliative procedures in infancy.

Discussion

The material presented may not reflect the natural history of the pulmonary vasculature in complete transposition of the great arteries since the majority of the patients represented herein who were more than 6 months of age had died after attempted repair of their defects. During the same 5-year period covered by this study, 15 children with transposition of the great arteries and ventricular septal defect survived repair by either the Senning or the Mustard technic. The status of their pulmonary vascular bed is unknown; they may represent a group without severe PVD which did not have a counterpart in this autopsy series. Nonetheless, certain features of PVD in transposition of the great arteries are apparent from this study.

Like Ferguson and co-workers, Ferencz, and Wagenvoort and associates, we found that PVD may occur at an early age in children with transposition of the great arteries. Pulmonary vascular disease was the rule in patients with transposition and ventricular
Pulmonary vessels from infants with ventricular septal defect. ELVG; ×350. (A) Medial thickening in pulmonary vessel from 4-month-old child. (B) Grade 3 PVD (fibrous intimal proliferation) in 3-month-old child.

Figure 6

Septal defect after 6 months of age, even though pathologic changes in pulmonary vessels in patients with ventricular septal defect and normally oriented great arteries are rare before 2 years of age.

While the presence of a ventricular septal defect apparently leads to longer survival, a high incidence of PVD occurs at a young age in such patients. The presence of a ventricular septal defect, however, is not necessary for the development of PVD, as pathologic changes of grade 2 or higher were seen in six of the 12 infants and children without a ventricular septal defect (associated with a large patent ductus arteriosus in three). In addition, two children with only small ventricular septal defects had grade 2 and 4 PVD at age 2 years and 22 months, respectively.

The presence of pulmonic stenosis was not a guarantee against the development of PVD. Both children without a ventricular septal defect in whom significant pulmonic stenosis was evident at autopsy were free of PVD (grade 1 changes in both at ages 1 week and 5 months, respectively). Two of five children with significant pulmonic stenosis and ventricular septal defect, however, had grade 2 or 3 changes at ages 4 months and 8 years, respectively. In addition, two of the three children in whom pulmonary artery banding had been performed as part of a palliative procedure in infancy had severe PVD (grade 4) at ages 3 and 4 years despite creation of a peak systolic gradient of 20 to 50 mm Hg across the area of narrowing of the pulmonary artery (measured at the time of the palliative operations performed at 2 and 5 months of age). Angiocardiography demonstrated significant narrowing of the main pulmonary artery in these two patients just prior to attempted repair.
It is apparent, therefore, that children of similar age with transposition of the great arteries and similar intracardiac defects present a spectrum of PVD. Neither pulmonic stenosis, natural or acquired, nor the absence of free communication between the two circulations at ventricular level is necessarily protective against the development of PVD although in most patients such protection is apparent. Whether this spectrum of PVD in transposition of the great arteries will be altered by vigorous attempts at palliation in neonates and infants is unknown. The creation of atrial septal defects to allow better mixing between the pulmonary and systemic circulations and to relieve left atrial hypertension and, in addition, the creation of pulmonary artery stenosis in selected cases may slow the development of PVD. Our observations indicate the PVD still may be present, however, despite these attempts to prevent or slow its development.

The findings in this study indicate that measurement of pulmonary artery pressure and estimation of systemic and pulmonary blood flows are necessary in patients with transposition of the great arteries in whom correction by present surgical technics is contemplated. Such measurements are necessary in all patients regardless of the presence or absence of ventricular septal defect or pulmonic stenosis. Furthermore, operation probably should be performed as soon as technically feasible since a number of children will have severe and presumably irreversible PVD by the age of 2 years.

Illustrative Cases

Case 1 PVD with Intact Ventricular Septum

A 16-year-old boy had been cyanotic since birth. Cardiac evaluation at age 7 years had indi-
cated transposition of the great arteries with intact ventricular septum. Pulmonary artery pressure was 23/7 mm Hg. At age 15 years, left ventricular pressure was 50/0-10 mm Hg and pulmonary blood flow was estimated to be 1.5 times systemic blood flow. Atrial pressures were slightly elevated. The pulmonary artery was not entered. Mild coarctation of the aorta existed. Repair by the Senning technic was performed. Before correction the pressure in the left ventricle was three fourths that of the systemic pressure. The atrial septal defect measured 2.5 by 1.5 cm. No ventricular septal defect or pulmonary stenosis was identified. Postoperative pressures were not obtained. The patient died of respiratory insufficiency and low cardiac output on the third postoperative day. Autopsy showed the ventricular septum to be intact and pulmonic stenosis to be absent. Atrial reconstruction appeared adequate without pulmon- ary or systemic venous obstruction. Mild coarctation of the aorta (8-mm lumen) was present, and the ductus arteriosus was obliterated. Pulmonary vessels had grade 4 changes (fig. 4).

Severe PVD was present in this case despite the absence of severe left ventricular and (presumably) pulmonary artery hypertension. In addition, hemodynamic evidence suggested that pulmonary blood flow exceeded systemic blood flow.

**Case 2 PVD after Complete Repair, with Intact Ventricular Septum**

A 2 8/12-year-old boy had cyanosis at birth. Cardiac evaluation at 1 month of age indicated transposition of the great arteries without ventricular septal defect. A Blalock-Hanlon procedure was performed with improvement. At age 1 9/12 years, repeat cardiac catheterization and angiography confirmed the diagnosis. Left ventricular (pulmonary) pressure was 40/0 mm Hg, while right ventricular (systemic) pressure was 85/0. Repair by the Mustard technic was performed at age 2 2/12 years, at which time the pressures in the two ventricles were the same as measured at catheterization. Pressures were not measured after operation. The atrial septal defect measured 2 cm in diameter, the ductus arteriosus was not patent, and the ventricular septum was intact. At examination 6 weeks after operation the patient

**Figure 8**

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was in satisfactory condition but had mild hepatomegaly. He returned 6 months after operation with dyspnea, cyanosis when crying, and cough of 1 month's duration. Congestive heart failure with peripheral edema was present. Cardiac catheterization (while he was breathing 100% oxygen) revealed marked elevation of pulmonary arterial pressure (113/64 mm Hg when the aortic pressure was 99/68 mm Hg) and pulmonary venous hypertension (17/14 mm Hg). No intracardiac shunts were identified. Pulmonary vascular resistance exceeded systemic vascular resistance. Arterial desaturation (33%) while he was breathing room air also was demonstrated. The patient died suddenly at home 6½ months after complete repair. At autopsy the anatomic repair of the heart was intact. The pulmonary vessels had marked medial thickening, intimal fibrosis, and dilatation—the lesions of grade 4 PVD (fig. 5A).

In this child PVD may have developed after operation, as suggested by the fact that pulmonary hypertension was not present preoperatively and the immediate postoperative convalescence was uncomplicated. The possibility that pulmonary venous obstruction was present after operation, although not identified at autopsy, cannot be completely excluded.

Case 3 Apparent Protective Effect of Pulmonary Stenosis

An 11 11/12-year-old boy had been cyanotic since birth. A left subclavian-to-pulmonary artery anastomosis had been performed at 3 years of age because of reduced pulmonary blood flow. Clinical evaluation suggested tetralogy of Fallot with a functioning systemic-to-pulmonary artery shunt and was supported by cardiac catheterization performed at another institution at 3 years of age. Catheterization and angiography were not repeated. At operation transposition of the great arteries, a large ventricular septal defect (2.5 by 3.0 cm), and valvular and subvalvular pulmonic stenosis were present. No atrial septal defect was identified. Repair by the Mustard technic was attempted, but the subpulmonary stenosis could not be relieved adequately and the boy died 10 months later.
Case 4 Failure of Pulmonary Stenosis to Protect from PVD

An 8 5/12-year-old boy had been cyanotic since birth, with slow growth and development. Cardiac catheterization demonstrated transposition of the great arteries, a ventricular septal defect, and pulmonary valvular stenosis. Pressures in the left ventricle and pulmonary artery were 130/0-4 and 22/12 mm Hg, respectively. Repair was performed by the Senning technic. The foramen ovale was patent and the ventricular septal defect measured 5 by 12 mm. The ventricular septal defect was closed, and the pulmonary valvular stenosis was relieved. Pressures were not obtained after operation. Postoperative convalescence was slow. The patient died suddenly and unexpectedly 5 weeks after operation. At autopsy the repair was complete except for a residual ventricular septal defect, 3 mm in diameter. The pulmonary valve was bicuspid, but not stenotic. PVD, grade 3, was present. Medial thickening of small pulmonary arteries with intimal fibrosis was present, but no dilatation was seen (fig. 8B). Large pulmonary arteries and pulmonary veins showed intimal fibrosis as well.

Severe pulmonic stenosis did not prevent PVD in this child. Preoperative hemodynamic evaluation was misleading and indicated normal pulmonary blood flow and pressure.

Case 5 Apparent Protection from PVD Afforded by Palliative Procedure

A 5 8/12-year-old girl with transposition of the great arteries and a ventricular septal defect had had pulmonary artery banding performed at age 6 months. The distal pulmonary artery pressure fell from 80/50 to 36/25 mm Hg. At age 2½ years, because of persistent slow growth and development, an atrial septal defect was created. Findings on cardiac catheterization at age 5 7/12 years were those of transposition of the great arteries with a ventricular septal defect. Pressures in the left ventricle and distal pulmonary artery beyond the area of narrowing were 94/11 and 25/17 mm Hg, respectively. The site of the pulmonary artery band was heavily calcified, with a lumen of 5 mm. Large systemic-to-pulmonary collateral vessels were identified. Repair by the Mustard technic was performed. Pressures measured at operation following repair were 100 mm Hg in the right (systemic) ventricle, 50 mm Hg in the left (pulmonary) ventricle, and 25 to 30 mm Hg in the distal pulmonary artery. The postoperative course was marked by hypotension and respiratory difficulty, and death occurred on the fourth postoperative day. Autopsy showed widespread sepsis due to Staphylococcus aureus, with septic thrombi in the lungs, adrenals, ovaries, and kidneys. The repair was complete. The closed ventricular septal defect measured 8 by 10 mm. The lumen of the narrowed portion of the main pulmonary artery measured 8 mm in diameter after repair. The ductus arteriosus was obliterated. Microscopic examination of the sections of lung showed that the small pulmonary arteries had intimal cellular proliferation with early fibrosis representing late grade 2 PVD (fig. 9A).

This patient died of infection with generalized sepsis. The appearance of the pulmonary vasculature suggested that a good postoperative result could have been expected. The palliative procedures performed in infancy may have protected the pulmonary vascular bed.

Case 6 Failure of Palliative Procedure to Protect from PVD

A 4 9/12-year-old girl had been cyanotic since birth. Congestive heart failure was present at 3 months of age. Transposition of the great arteries with a ventricular septal defect was diagnosed in infancy. Pulmonary artery banding was performed at 5 months of age with decrease in the distal pulmonary artery pressure from 80/40 to 50/20 mm Hg. Cardiac catheterization repeated at age 4 years, prior to corrective surgery, confirmed the anatomic defects. The gradient across the site of pulmonary artery narrowing was 26 mm Hg (from 80/37 to 54/37 mm Hg). Pulmonary flow was estimated to exceed systemic flow. Angiocardiography showed that the degree of pulmonary artery obstruction was severe. Repair by the Mustard technic was performed. The atrial septum was intact and the ventricular septal defect measured 1.5 by 2.5 cm. Postoperative convalescence was slow and complicated by complete heart block and congestive heart failure. Despite the insertion of a permanent cardiac pacemaker and vigorous anticongestive therapy, the patient died 1 month after operation. At autopsy there was a residual ventricular septal defect measuring 3 by 7 mm at the inferior margin of the patch. A 5-mm defect also was present along the inferior
margin of the atrial baffle, but the atrial reconstruction seemed otherwise adequate. The pulmonary artery was narrowed in the region of the band (lumen of 7 mm). The ductus arteriosus was obliterated. The small pulmonary arteries showed medial thinning and intimal fibrosis with angiomatoid and plexiform lesions of grade 4 PVD (fig. 9B). Focal areas of hemosiderin deposition were also present.

Pulmonary artery banding failed to protect this child from PVD even though the banding appeared to be adequate as judged from the pressure gradient developed at the time of palliation, the gradient at preoperative catheterization, and the angiographic appearance. No atrial septal defect was present.

Concluding Comment

Obstructive pulmonary vascular disease (PVD) occurs at an early age in patients with complete (dextro) transposition of the great arteries. Sections of lung taken at autopsy in 53 patients with transposition of the great arteries were examined for PVD according to the Heath-Edwards criteria. Patients were grouped according to the presence or absence of a ventricular septal defect, with subgrouping by age into neonates (birth to 4 weeks), infants (age 1 to 6 months), and older children (age more than 6 months). The presence of a large patent ductus arteriosus (more than 3 mm), of a small ventricular septal defect (less than 5 mm), and of pulmonic stenosis as well as the size of atrial septal defect was noted. Small ductus arteriosus and small ventricular septal defect were considered likely not to have had hemodynamic significance. Twenty-three patients had an intact ventricular septum: 10 neonates had normal vessels or grade 1 PVD; two of eight infants had grade 3 PVD, one in the absence of patent ductus arteriosus; four of five older children had severe PVD. Thirty patients had ventricular septal defect: The one neonate (with a small ventricular septal defect) had grade 1 changes; four of 11 infants had grade 2 or 3 PVD even in the presence of pulmonic stenosis or with only a small ventricular septal defect; severe PVD was the rule in older children with transposition of the great arteries and ventricular septal defect.

Children of similar age and associated defects had widely differing degrees of PVD and presented a spectrum of disease. The presence of pulmonic stenosis (congenital or acquired by pulmonary artery banding in infancy), a small ventricular septal defect, or a large atrial septal defect did not always protect against development of severe PVD. The findings of this study demonstrate the need for thorough hemodynamic evaluation of patients with complete transposition of the great arteries prior to repair by present techniques. In addition, operation should probably be performed as soon as technically feasible.

References

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