Pulmonary Vascular Disease in Transposition of the Great Vessels and Intact Ventricular Septum

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SUMMARY Eight of 135 (6%) children with d-transposition of the great vessels and with intact ventricular septum and no patent ductus arteriosus had evidence of progressive pulmonary vascular disease. Seven of 101 (7%) patients for whom histologic data was available, had Heath-Edwards grades IV or V pulmonary vascular disease, six had grade II, and 88 had either normal or grade I findings. One of 34 patients for whom histologic data was not available had hemodynamic evidence of pulmonary vascular disease at cardiac catheterization after the Mustard operation. When infants younger than 3 months old were excluded, eight of 85 (9%) had advanced pulmonary vascular disease. Twenty-three patients had microthrombi in their pulmonary arteries and arterioles, and in one patient thrombi were observed before the development of pulmonary vascular disease. Clinically unrecognized pulmonary microthrombi are suggested as a possible etiologic agent in the development of pulmonary vascular disease in patients with transposition of the great vessels. Progressive pulmonary vascular disease can first be discovered after the Mustard operation, even in patients without preoperative evidence of pulmonary hypertension or elevated pulmonary vascular resistance.

PULMONARY VASCULAR DISEASE is often a complication in patients with complete transposition of the great vessels, particularly when there is a large ventricular septal defect or patent ductus arteriosus. In the absence of these associated defects the incidence is less, but has been reported to occur in 6–40% of cases. This study examines the incidence of progressive pulmonary vascular disease in patients with transposition of the great vessels and intact ventricular septum who were seen at a single institution over a 22-year period, and suggests a possible etiologic factor not previously emphasized by other investigators.

Materials and Methods

The study group (table 1) included 135 patients with transposition of the great vessels and intact ventricular septum or hemodynamically insignificant ventricular septal defect, and no patent ductus arteriosus. All patients were seen at the Willis J. Potts Children's Heart Center, Children's Memorial Hospital, Chicago, between 1956–1977. Lung specimens of 101 patients aged 2 days–12.2 years were examined under light microscopy for evidence of pulmonary vascular disease, and the changes were graded according to the Heath-Edwards classification. We assigned to each patient the highest grade found in the lung sections, even if it was found in only one vessel. This only occurred when the specimen was obtained by open lung biopsy.

We also noted the presence of pulmonary microthrombi. Pulmonary microthrombi cause a variety of lesions distinct from those caused by hypertensive pulmonary vascular disease, including eccentric, noncircular intimal fibrosis, so-called "cushion lesions" (fig. 1, panels A and D), occlusion of vessels with recanalization of nonlaminar intimal fibrosis (fig. 1, panel B), and irregular intraluminal fibrous septa caused by recanalization of organized occlusive thrombi (fig. 1C). The intimal lesions caused by hypertensive pulmonary vascular disease secondary to congenital cardiac defects tend to be laminar and circumferential.

The specimens were obtained at autopsy in 83 patients, and by open lung biopsy in 18 patients, and were stained with hematoxylin and eosin and for elastic tissue. The biopsies were obtained during the Mustard operation, and one child had a repeat open lung biopsy 2 years after surgery. Forty-nine of the patients who were autopsied had no cardiac catheterization and were seen before 1964.

Postoperative hemodynamic assessment was performed on 52 patients age 1.1–13.6 years who underwent cardiac catheterization 1–8 years after a Mustard operation, including 18 patients who had lung biopsies and 34 patients who had no lung specimens available. The postoperative cardiac catheterizations were performed under light sedation with Innovar in room air; oxygen consumption was measured. Pulmonary arterial blood samples and pressure measurements were obtained in all 52 patients. Blood flows and resistances were calculated using the Fick principle. The pulmonary vascular resistance units were calculated by subtracting

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*McNeilab, Inc, dose of 0.3 ml/kg. Each milliliter contained Droperidol 2.5 mg, Fentanyl 0.05 mg.
TABLE 1. Pulmonary Vascular Disease in Transposition of the Great Vessels with Intact Ventricular Septum

<table>
<thead>
<tr>
<th>Method of documentation</th>
<th>N</th>
<th>% of entire group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology only</td>
<td>83</td>
<td>61.4%</td>
</tr>
<tr>
<td>Post-Mustard cardiac catheterization plus histology</td>
<td>18</td>
<td>13.3%</td>
</tr>
<tr>
<td>Post-Mustard cardiac catheterization only</td>
<td>34</td>
<td>25.3%</td>
</tr>
<tr>
<td>Total</td>
<td>135</td>
<td>100%</td>
</tr>
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</table>

pulmonary venous atrium mean blood pressure from pulmonary artery mean blood pressure and dividing by the pulmonary blood flow index.

Results

Histology

Seven patients (7%) had histologic evidence of advanced pulmonary vascular disease, Heath-Edwards grade IV or V (none had grade VI), and all seven were 2 years of age or older (fig. 2) when this was documented. Most patients (88 of 101) had either normal pulmonary vessels, or grade I changes (medial hypertrophy). Twenty-three patients had microthrombi in their pulmonary arteries and arterioles (fig. 1) in various stages of organization. These thrombi were found in four of seven patients with advanced changes (fig. 2, closed circles). In one patient who has been reported previously, thrombi were observed before the development of pulmonary vascular disease. Thrombi were found in 19 patients who had no evidence of progressive pulmonary vascular disease. Cerebrovascular accidents occurred in three of 23 (13%) patients in whom pulmonary thrombi were found, and in two of 78 (2%) patients in whom no pulmonary thrombi were found. We analyzed these differences using the Fisher exact probability test, and found them significant at the 0.076 level.

Hemodynamics

Pulmonary arterial mean blood pressures were measured in all 52 patients who underwent post-Mustard cardiac catheterization (fig. 3). Only four

Figure 1. Pulmonary microthrombi. A) 160-μm vessel, 14-month-old infant, specimen obtained by biopsy, stroke with left hemiparesis at 12 months of age. Arrow indicates intimal "cushion lesion" secondary to organized thrombus. B) 120-μm vessel, 3.5-year-old child who developed pulmonary vascular disease after the Mustard operation. Vessel is occluded with organized thrombus; arrow indicates recanalized lumen. C) 70-μm vessel, same patient as in A. Two channels of recanalization of organized thrombus producing an intraluminal septum. D) 200-μm vessel, same patient as in A. Arrow indicates "cushion lesions."
patients had mean blood pressures greater than 23 mm Hg. Three of them had pulmonary vascular resistances of 12.5, 15, and 33.8 units and grade IV or V histologic changes. The fourth patient, who had a pulmonary artery mean blood pressure of 44 mm Hg and pulmonary vascular resistance of 8.4 units, is alive 9 years after surgery; no lung specimen is available, although previous studies\(^6\) indicate that at least grade IV changes are present. All of the patients with pulmonary arterial mean blood pressures less than 24 mm Hg had normal calculated pulmonary vascular resistances. None of the patients had evidence at cardiac catheterization of pulmonary venous obstruction due to the intraatrial baffle. No significant atrioventricular valve insufficiency was found in any patient.

**Combined Histologic-Hemodynamic Results**

Since pulmonary vascular disease rarely occurs before 3 months of age, a separate analysis was made of patients older than 3 months, using either histologic or hemodynamic findings to demonstrate pulmonary vascular disease (fig. 4). Patients are represented only once in figure 4, based on either histologic or hemodynamic findings; if both sets of data were available, the histologic findings were used. The 85 patients were 3 months–13.6 years old, with a median age of 3 years. Eight of 85 patients (9%) had advanced pulmonary vascular disease — seven had grade IV or V histologic changes and one had severe pulmonary hypertension, but no lung specimen was available. Data from cardiac catheterization were available in six of the eight patients with advanced pulmonary vascular disease.

The earliest age at which advanced pulmonary vascular disease was documented was 2 years (table 2). All eight patients had an adequate interatrial communication, either naturally or created by balloon septostomy or palliative surgery. Two patients never had cardiac catheterization or surgery and the pulmonary vascular disease was discovered at postmortem examination. The discovery of severe pulmonary hypertension and elevated pulmonary vascular resistance in two patients caused the cancellation of planned surgery, and both died several months after cardiac catheterization. Pulmonary vascular disease was first documented in four patients after the Mustard opera-
tion; three of these patients had elevated pulmonary arterial mean blood pressures of 24–33 mm Hg at the time of the preoperative cardiac catheterizations, but the pulmonary vascular resistances were calculated to be within normal limits. Cardiac catheterizations on these last four patients were performed 1–10 months before surgery, and again 2 months, 2.9, 6.2, and 6.5 years after surgery.

Discussion

The early appearance of pulmonary arterial abnormalities in the form of increased medial muscle and intimal proliferation in infants with transposition of the great vessels was noted by Ferguson et al. in 1960. Ferencz² believed that the early appearance and rapid progression of the pulmonary arterial abnormalities in these patients were the result of high blood flow and pressure in the pulmonary circuit, aggravated by arterial vasoconstriction due to hypoxemia and acidosis. Increased pulmonary venous pressure was believed to augment the arterial damage. Wagenvoort et al., in a study based on lung biopsy specimens, noted the presence of microthrombi in 28% of patients studied but ascribed to them no etiologic significance.

Viles et al. emphasized the wide spectrum of pulmonary vascular changes in patients of different ages with different associated defects, and suggested the need for early operations to prevent progression of the vascular disease to irreversible stages. We also found that progression of vascular changes was most rapid when there was an associated large ventricular septal defect or patent ductus arteriosus. However, when there was no significant ventricular or great vessel shunting lesion the incidence of advanced pulmonary vascular changes was less than 10%. Recent studies by Lakier et al. and Clarkson et al. have suggested a higher incidence, estimated at 15–20% in infants 3–11 months old.

Our pathologic and hemodynamic observations indicate that the overall incidence of advanced pulmonary vascular disease in complete transposition of the great vessels with intact ventricular septum is 6%. When patients younger than 3 months of age were excluded, the incidence was 9% in a group of 85 patients with a median age of 3 years. Even in patients without preoperative evidence of pulmonary hypertension or elevated pulmonary vascular resistance, pulmonary vascular disease is known to occur after the Mustard operation.

Table 2. Patients with Advanced Pulmonary Vascular Disease

<table>
<thead>
<tr>
<th>Atrial septum</th>
<th>Age preop cath (years)</th>
<th>PAP (mm Hg)</th>
<th>PVR (units)</th>
<th>Age Mustard operation (years)</th>
<th>Age postop cath (years)</th>
<th>Age death (years)</th>
<th>Postop PAP (mm Hg)</th>
<th>Postop PVR (units)</th>
<th>Grade PVD</th>
</tr>
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<tbody>
<tr>
<td>ASD 2°</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>12.1</td>
<td>—</td>
<td>—</td>
<td>5</td>
</tr>
<tr>
<td>ASD 2°</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>5</td>
</tr>
<tr>
<td>BAS</td>
<td>2</td>
<td>60</td>
<td>12.4</td>
<td>—</td>
<td>—</td>
<td>2.5</td>
<td>—</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>BAS</td>
<td>2</td>
<td>60</td>
<td>11</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>BH</td>
<td>3.2</td>
<td>33</td>
<td>1.8</td>
<td>4</td>
<td>4.2</td>
<td>5.7</td>
<td>65</td>
<td>12.5</td>
<td>5</td>
</tr>
<tr>
<td>BAS</td>
<td>1</td>
<td>15</td>
<td>0.5</td>
<td>1.1</td>
<td>2.3, 3.9</td>
<td>*</td>
<td>45, 58</td>
<td>10, 15</td>
<td>4</td>
</tr>
<tr>
<td>BH</td>
<td>3.9</td>
<td>24</td>
<td>3.3</td>
<td>4.3</td>
<td>10.4</td>
<td>11.8</td>
<td>95</td>
<td>33.8</td>
<td>5</td>
</tr>
<tr>
<td>BAS</td>
<td>1.9</td>
<td>28</td>
<td>3.8</td>
<td>2.2</td>
<td>8.5</td>
<td>—</td>
<td>45</td>
<td>8.4</td>
<td>—</td>
</tr>
</tbody>
</table>

*Patient alive, lung specimen obtained by open lung biopsy age 2.5 years.

Abbreviations: ASD 2° = atrial septal defect, secundum; BAS = balloon atrial septostomy; BH = Blalock-Hanlon; Cath = cardiac catheterization; PAP = pulmonary artery mean blood pressure; Postop = postoperative; Preop = preoperative; PVD = pulmonary vascular disease; PVR = pulmonary vascular resistance; units = dyn-sec-m².
The pathogenesis of progressive pulmonary vascular disease in patients with transposition of the great vessels and intact ventricular septum is more difficult to explain than in patients with an associated ventricular septal defect, since the former patients usually have a normal pulmonary arterial blood pressure during infancy, after the early neonatal period. Several different pathogenetic mechanisms have been suggested by previous investigators. Ferencz suggested increased pulmonary blood flow, pulmonary arterial constriction, and elevated pulmonary venous blood pressure as factors causing vascular injury. Lakier et al. suggested increased pulmonary blood flow and increased blood viscosity leading to increased vessel shear stress as likely etiologic factors. Clarkson et al. thought that increased pulmonary blood flow was the major etiologic factor, and Yamaki and Tezuka thought that the muscular coat of the pulmonary arteries in patients with transposition of the great vessels is inadequate to protect the vessels from the damage which results from increased flow. Aziz et al. suggest pulmonary arterial constriction secondary to local capillary hypoxemia caused by the large broncho-pulmonary collateral vessels and the bronchial arterial vasovasorum as a possible etiologic agent, in addition to those already mentioned by other authors. We suggested in an earlier study that pulmonary microthrombi might also be an etiologic factor, after finding thrombi in a lung biopsy of one patient before the development of pulmonary hypertension and vascular disease, which were subsequently documented by serial cardiac catheterizations and lung biopsies.

Clinically undetected pulmonary microemboli are a recognized cause of pulmonary vascular disease in adults, the source of the emboli being venous thrombosis of the lower extremities or pelvic veins. In 23 of 101 patients in the present study we found histologic evidence of thrombi in the pulmonary resistance vessels with no definite source of emboli. We do not know whether these thrombi were the result of emboli, or whether they occurred in situ. In either case, an ongoing process of thrombosis of the pulmonary arteries could progressively occlude the vascular bed and could contribute to pulmonary vascular disease in these patients. Berman and co-workers recently noted the occurrence of advanced pulmonary vascular disease in a young infant with transposition and intact ventricular septum who had extensive pulmonary microthrombosis.

Other investigators have noted that pulmonary stenosis or pulmonary artery banding was not uniformly protective in preventing pulmonary vascular disease in patients with transposition, but the reasons for this were unclear. We examined (table 3) lung specimens of 95 patients with transposition and large ventricular septal defect — 19 had pulmonic stenosis (left ventricular-to-pulmonary artery gradients ranged from 20–80 mm Hg). Pulmonary microthrombi were found in 23% of patients with intact ventricular septum, 20% with large ventricular defects, and 32% with large ventricular defects and pulmonic stenosis. The incidence of thrombi in the three groups do not differ significantly. We observed hypertensive and thrombotic vascular disease in sections from an open lung biopsy specimen from one patient with pulmonic stenosis. Microthrombi in patients with associated pulmonic stenosis or pulmonary artery banding may be a cause of the pulmonary vascular disease occasionally found.

Some investigators have suggested that patients with transposition and other cyanotic cardiac defects may have a hypercoagulable state, and that intravascular coagulation could be responsible for the apparent increased incidence of thrombotic events in patients with cyanotic congenital heart disease. Waldman et al. did not, however, find evidence for disseminated intravascular coagulation in patients with cyanotic congenital heart disease who were studied under steady-state conditions.

If pulmonary thrombosis is an important factor in the development of progressive pulmonary vascular disease in patients with transposition, some form of treatment or prevention could be considered. Since anticoagulant therapy has its own significant risks, more investigation into the problem is needed before any recommendations regarding this type of treatment can be made. Although pulmonary vascular disease may rarely occur after successful Mustard operations, early operation may prove successful in decreasing the incidence of progressive pulmonary vascular disease, and many centers now routinely operate on patients younger than 1 year old who have transposition complexes.

References

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Pulmonary vascular disease in transposition of the great vessels and intact ventricular septum.

E A Newfeld, M H Paul, A J Muster and F S Idriss

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