Histology of Pulmonary Arterial Supply in Pulmonary Atresia with Ventricular Septal Defect

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SUMMARY  A histologic study was performed on 22 specimens of pulmonary atresia with ventricular septal defect to 1) ascertain the existence of the main pulmonary artery; 2) distinguish the ductus arteriosus from the systemic collateral arteries (SCA); 3) establish the nutritive or functional nature of collateral circulation; and 4) evaluate the morphology of the distal pulmonary bed. Three cases had absent main pulmonary artery, one with and two without signs of infundibular septation. We suggest that absent main pulmonary artery may exist with both infundibular pulmonary atresia and persistent truncus arteriosus. SCAs have been found to have similar histological features as systemic muscular arteries of the same size — their medial muscular layer merges gradually into an elastic one at different depth inside the lungs. Injection of contrast material allowed us to demonstrate that these vessels are functional, since they inosculate into efficient pulmonary arteries ending in the respiratory units. When the distal pulmonary vascular bed is perfused by large SCAs, proliferative lesions like those found in large left-to-right shunts may occur. Early in infancy, banding of large, nonstenotic SCAs could protect the distal pulmonary vasculature. Moreover, total surgical repair should be associated with ligation of the SCA to avoid residual left-to-right shunt, if the pulmonary arteries can carry the full pulmonary blood flow.

A HISTOLOGIC STUDY of the pulmonary arterial supply in pulmonary atresia with ventricular septal defect (VSD) is important for several reasons. First, the macroscopic dissection cannot always reveal the existence of a pulmonary trunk arising from the heart. This is essential in distinguishing cases without from cases with atresia of the main pulmonary artery, and may suggest whether they represent embryologically a form of persistent truncus arteriosus or a pulmonary atresia with VSD. Second, only by histology it is possible to recognize whether a collateral branch that arises from the aortic arch is a ductus arteriosus or a systemic collateral artery. Third, debate exists on whether the collateral arterial supply should be considered functional or nutritive. These vessels are generally reported as a compensatory dilatation or hypertrophy of bronchial arteries. Stenosis of the collateral vessels may be visualized by angiography, but their morphologic substrate is unknown. Finally, some patients with pulmonary atresia actually have an increased pulmonary blood flow and eventually become cyanotic. The question arises whether pulmonary vascular disease occurs in this congenital malformation as much as in other defects with left-to-right shunt.

Definition of Terms

Pulmonary atresia with VSD is the malformation in which both ventricles eject only into the aorta. A pulmonary trunk usually arises from the cardiac base at least as a fibrous stem. The pulmonary circulation is supplied by a patent ductus arteriosus or by systemic collateral arteries originating from the descending aorta.

Truncus type IV is also a cardiac anomaly in which the pulmonary arterial supply comes through systemic collateral arteries or a ductus arteriosus, but in which neither a main pulmonary artery nor an infundibular septum is identifiable.

Material and Methods

Twenty-two hearts were selected from our anatomic collection according to the above mentioned definitions. All specimens had visceroatrial situs solitus, levocardia and atroventricular concordance. The great arteries were normally related when the pulmonary trunk was identifiable. Cases with posterior atretic pulmonary trunk (so-called transposition with pulmonary atresia and VSD) have been excluded from our study.

All patients died within the first year of life. According to the pattern of pulmonary arterial supply, the specimens were divided as follows: 11 cases in which the pulmonary arterial supply was solely ductus-dependent; seven cases without ductus arteriosus in which the pulmonary arterial circulation depended on small systemic collateral arteries arising from the descending aorta; three cases without ductus arteriosus and with large systemic collateral arteries; and one case with a left ductus arteriosus that supplied the left lung and two large systemic collateral arteries that supplied the right lung.

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Segments from the systemic collateral arteries and the ductus arteriosus and blocks from multiple areas of the lungs were embedded in paraffin, sectioned 7μ thick and stained with hematoxylin and eosin and elastic Van Gieson. The great vessels at the cardiac base were examined histologically when the pulmonary trunk was not seen on gross examination. In three patients, postmortem angiography of the pulmonary arterial supply was performed before fixation and histologic examination.

Results

Histology of the Great Vessels at the Cardiac Base

In four specimens a fibrous strand arising from the heart base as a vestige of the pulmonary trunk could not be positively identified by gross examination. In two of these, derivatives of the sixth aortic arches, i.e., ductus arteriosus and pulmonary arteries, were not observed either inside the pericardial cavity or at the pulmonary hila. The pulmonary arterial circulation in these cases was supplied by systemic arteries that arose from the descending aorta; the intracardiac anatomy did not show any signs of infundibular septation. The third heart had a right aortic arch and a left ductus arteriosus connected with two confluent pulmonary arteries; the intracardiac anatomy had an extremely deviated infundibular septum. The fourth heart showed a similar extracardiac anatomy, but we did not see an infundibular septum in the right ventricular outflow tract. On histologic examination the presence of a vessel with an elastic media was demonstrated only in the last case. This vessel, which lay on the left side of the aortic root, was the atretic pulmonary trunk (fig. 1).

Histology of the Ductus Arteriosus and the Systemic Collateral Arteries

The ductus arteriosus had the features of a closing ductus with intimal proliferation, fragmented internal elastic lamina, mucoid lakes and cytolytic necrosis of the media, which appeared musculoelastic.10

The systemic collateral arteries had a muscular media with absent external elastic lamina and a thick adventitia, like any other systemic artery of the same diameter. The media merged gradually into a thin elastic layer; large systemic arteries lost their muscular features near the hilum, while small systemic arteries maintained their muscularity up to the periphery of the lungs (fig. 2). Sections from stenotic segments of systemic collateral arteries disclosed focal fibrous intimal thickenings (fig. 3).

Figure 1. Histology of the root of the great arteries in a case with apparent absence of the main pulmonary artery. A small vascular structure with elastic medial layer is visible aside the aorta. A = aorta; P = pulmonary artery. Elastic-Van Gieson stain; original magnification A) x 12, B) x 48.
Histology of the Lungs

Histologic examination of the lungs was performed in 15 cases. Figure 4 shows the degree of the pulmonary vascular disease plotted against age, according to the pattern of pulmonary arterial supply. Medial hypertrophy, intimal proliferation and even plexiform lesions were observed only in pulmonary segments perfused by large, nonstenotic systemic collateral arteries (fig. 5). Progressive thinning of the media of the small pulmonary arteries and arterioles occurred with age only in those cases with pulmonary arterial supply that depended on a ductus arteriosus and/or small or stenotic systemic collateral arteries. In one patient with multifocal pulmonary arterial supply, different degrees of pulmonary vascular disease were detected. Serial sections, including collaterals and their lung segments, showed that the contrast material injected postmortem passed from systemic arteries with muscular media, through elastic...
arteries, to small arteries, arterioles and capillaries of the respiratory units (fig. 6).

**Discussion**

**Absence of the Main Pulmonary Artery:**

A Form of Persistent Truncus Arteriosus or Pulmonary Atresia with VSD?

Many cardiovascular anomalies cannot be considered either a classic truncus arteriosus communis or a truncus solitarius aorticus or pulmonalis. Whether the single trunk is a persistent truncus or a normal aorta is controversial. This malformation has been considered a pulmonary atresia with VSD16, 17, 19, 26 or a solitary aortic trunk with agenesis of the pulmonary arteries,3, 8 or as a persistent ventral aorta with agenesis of both the sixth aortic arches and the aorto-pulmonary septum.57 Manhoff and Howe26 first recognized the absence of the main pulmonary artery as a separate nosographic entity and described two main forms: 1) single trunk with lungs supplied by arteries arising from the descending aorta or by other anomalous arteries; 2) single trunk with lungs supplied by ductus arteriosus. The first arterial pattern was classified by Collett and Edwards as persistent truncus arteriosus type IV,23 while the latter was described by Edwards’ group as ductal origin of the pulmonary arteries.29, 30 We believe that both intracardiac and extracardiac features are essential in distinguishing these two anomalies. In fact, absence of the main pulmonary artery may be present in pulmonary infundibular atresia (pseudotruncus) as well as in persistent truncus arteriosus (truncus type IV). Among our four cases with absent pulmonary trunk on gross examination, only one was found on histologic examination to have a small elastic vessel next to the aortic root. Among the remaining three, two had an intracardiac anatomy typical of truncus arteriosus and one showed an anteriorly deviated infundibular septum that completely obstructed the intracardiac pulmonary outflow as seen in typical pulmonary atresia with VSD.

**Nature of the Collateral Circulation**

It is generally believed that the development of the collateral circulation takes place after birth, due to hypertrophy and dilatation of the nutritive circulation of the bronchial arteries, while the ductus arteriosus undergoes its natural closure. However, in 1947 Taussig observed that in pulmonary atresia with VSD the ductus arteriosus may often be absent.31 Bharati et al. confirmed this observation in autopsy material.32 We observed collateral arteries even in newborns, suggesting that collateral circulation must be present before birth and may represent the persistence of the primitive arterial connections between the aorta and the pulmonary plexus.6 Absence of the ductus arteriosus has been described in persistent truncus arteriosus type I and II,4 in tetralogy of Fallot with absent pulmonary valve,24 in dogs with pulmonary atresia and VSD,33 and it has been illustrated by Van Mierop et al. in a dog embryo with persistent truncus arteriosus.7 These collateral arteries have the same histologic features as any other systemic muscular artery of the same size. Distally the muscular media merges gradually, at different depth inside the lungs, into an elastic media. The injection of the contrast material allowed us to visualize these vessels insolated into efficient pulmonary arteries, ending at the respiratory units where gas exchange occurs. Since this circulation is functional and not nutritive, the term “bronchial arteries” is inaccurate to describe the collateral vessels.

**Pulmonary Vascular Disease**

A histologic study of the lungs in pulmonary atresia has rarely been performed and no special attention has been paid so far to the pattern of the pulmonary circulation or to the difference between cases with or without VSD.9, 37-39

Despite the complete obstruction of the pulmonary outflow, large systemic collateral arteries may be responsible for increased pulmonary blood flow. In these instances, the pulmonary arterial vascular bed may have pathologic features similar to those in large left-to-right shunts.1, 25 Medial hypertrophy, intimal proliferations and even plexiform lesions were observed in our cases. In such patients, cyanosis may, therefore, worsen as a consequence of pulmonary vascular disease.

We did not perform a quantitative analysis of structural pulmonary features, although such an investigation would be of value also in pulmonary atresia with VSD. There is evidence that the high pulmonary vascular resistance may be due to insufficient develop-
ment of the intra-acinar pulmonary circulation in addition to the hypertensive vascular disease.

**Surgical Considerations**

Our histologic findings show that the peripheral vessels function for gas exchange, regardless of the source of blood supply. If repair is to be attempted, true pulmonary arteries must be demonstrated. Surgical reconstruction can be performed when at least one well-developed true central pulmonary artery can be identified at the pulmonary hilum. Both central pulmonary arteries were absent in only two of our cases. A previously reported gross examination of our specimen disclosed that in 40% of the cases the pulmonary arteries were too diminutive to be used for total repair. Progressive enlargement of hypoplastic pulmonary arteries may be obtained surgically by reconstructing right ventricle-to-pulmonary artery continuity with a pericardial patch graft, leaving the VSD unrepaired.

If no stenoses occur in the systemic collateral arteries before the peripheral distribution, the ultimate pathologic changes will result in severe pulmonary vascular disease. Banding of large, nonstenotic collateral vessels could be indicated early in infancy to protect the lungs. Nevertheless, the obliterative lesions may be unequally distributed, depending on the pattern of pulmonary arterial supply. In one patient in whom the left lung was perfused entirely by the ductus arteriosus and the right lung by...
two large systemic collateral arteries, the pulmonary vascular disease was confined in the right lung; the whole left lung was spared and could be used for surgical reconstruction. This case suggests that very accurate hemodynamic assessment is mandatory before making a decision of inoperability. To avoid residual left-to-right shunt, total surgical repair should be associated with ligation of the collateral vessels if the pulmonary arteries are capable of carrying the full pulmonary blood flow.14

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Effects of Acute Hemodynamic Alterations on Pulmonic Valve Motion

Experimental and Clinical Echocardiographic Studies

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SUMMARY The purpose of this study was to assess the effects of acute alterations of the pulmonary circulation on the pulmonic valve echocardiogram. We measured the pulmonic valve opening velocity (PVOV) and right-sided systolic time intervals (right ventricular preejection period-to-right ventricular ejection time ratio [RPEP/RVET]) in 22 open-chest dogs subjected to acute hemodynamic alterations produced by inferior vena cava constriction, atrial pacing, isoproterenol infusion and microsphere embolization of the pulmonary artery. We found only fair correlations between PVOV and peak pulmonary artery flow (r = 0.56), right ventricular dp/dt (r = 0.43), stroke volume (r = 0.42), pulmonary artery systolic pressure (r = 0.33) and peak pulmonary artery acceleration (r = 0.31). RVET was shortened by reduced venous return (caval constriction) and by increases in heart rate (atrial pacing and isoproterenol), which resulted in increases in RPEP/RVET that did not correspond well to simultaneous changes in pulmonary artery pressure. In seven patients breathing 10% O2 to raise pulmonary artery pressure acutely, we found no change or a fall in PVOV. Thus, the pulmonic valve echocardiogram is influenced by multiple factors relating to parameters of pulmonary flow and right ventricular contractility, and may be of limited clinical usefulness in predicting pulmonary artery pressures.

CHARACTERISTIC ALTERATIONS of echocardiographic pulmonic valve motion in the presence of pulmonary hypertension have been reported.\(^1\)\(^-\)\(^4\) These include rapid pulmonic valve opening velocity (PVOV),\(^2\)\(^-\)\(^4\) attenuation or abolition of the normal pre-systolic pulmonic valve opening ("a" dip),\(^1\)\(^-\)\(^2\) and prolongation of the right ventricular preejection period-to-right ventricular ejection time ratio (RPEP/RVET).\(^3\)\(^-\)\(^4\) Several authors have suggested, on the basis of these studies, that pulmonic valve echocardiography may be useful in the serial assessment of the pulmonary circulation and permit noninvasive detection of developing pulmonary hypertension.\(^1\)\(^-\)\(^3\)\(^-\)\(^4\)

However, all the studies reported have been performed on patients with chronic pulmonary hypertension. Little information is available on the effects of acute changes in pulmonary artery pressure on pulmonic valve motion. In fact, the determinants of pulmonic valve motion in general are not known. Therefore, to evaluate the effects of various acute hemodynamic alterations on the pulmonic valve echocardiogram and to determine what factors influence pulmonic valve motion, we performed experiments in both animals and patients.

Methods

Animal Studies

Twenty-two dogs were anesthetized with intravenous chloralose-urethane, intubated and ventilated with a Harvard respirator. A mid-sternal thoracotomy was performed. The pericardium was incised anteriorly and sutured to the chest wall so that the heart was suspended in a pericardial cradle. A #7F Swan-Ganz catheter was inserted into the right ventri-
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