Microangiography of the Pulmonary Arterial System in “Hypoplastic Left Heart Syndrome”

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SUMMARY
Microangiographic examination of the pulmonary arterial system in 12 newborn infants with concomitant stenosis or atresia of the aortic and mitral orifices showed that the intrapulmonary arterial pattern is influenced by the state of the foramen ovale. In infants with aortic atresia with a prematurely closed foramen ovale, that is cases in which the left side of the heart is a cul-de-sac, there is moderate or prominent tortuosity of the intralobular pulmonary arteries indicating congenital pulmonary hypertension. This feature is less prominent or absent in infants with valvular insufficiency of the foramen ovale, regardless of the postnatal age of the patient.

Additional Indexing Words:
Congenital pulmonary hypertension Mitral atresia Aortic stenosis Foramen ovale Mitral stenosis Aortic atresia Ductus arteriosus

STRIPPED of its morphogenetic and purely clinical connotations, the term “hypoplastic left heart syndrome” (HLHS) refers to cardiac malformations characterized basically by concomitant atresia or stenosis of the mitral and aortic orifices, with a secondary and explicable relationship of the other anatomic features to these defects. Without compensatory mechanisms, the constellation of mitral and aortic obstruction implies impairment of the pulmonary venous return and the development of congestive pulmonary hypertension. Cardiac catheterization data as well as morphometric observations on muscular pulmonary arteries have suggested pulmonary hypertension even in newborn infants with HLHS.

To complement our morphologic analysis of HLHS, we have applied a microangiographic technic for study of the intrapulmonary arterial system. More specifically, we were interested in finding out whether the microangiographic pattern and, particularly, signs of pulmonary hypertension are influenced by intracardiac shunts potentially capable of improving the drainage of the more or less blind alley formed by the left side of the heart.

Methods
Material
The 12 infants upon whom this report is based form part of a larger consecutive unselected series of 33 cases of HLHS. Material from four of these 12 infants had been collected and frozen some years previously as part of another project unrelated to HLHS. The remaining eight infants were encountered more recently and without selection.

The types of HLHS represented in the case series are listed in table 1. To supplement the information supplied in the table, it can be pointed out that the ductus arteriosus was widely patent throughout the series whereas the state of the foramen ovale differed considerably. Closure of the foramen ovale was noted in four infants and in three of these must be considered to be premature in view of their age. Six infants had
distinct morphologic evidence of valvular insufficiency at the foramen ovale; in three the valve was apparently normally formed but was inadequate to cover the extremely dilated interatrial communication, and in three it was greatly overdimensioned, thickened, and floppy to such an extent that it prolapsed to the right of the interatrial septum (fig. 1). In another infant, the valve of the foramen ovale was greatly thickened but was not overdimensioned or prolapsed. In the remaining infant the foramen ovale was patent and covered from the left by an apparently normal valve. The interventricular septum was intact in all cases. No examples of anomalous pulmonary venous return were encountered in the series.

Technic

The pulmonary arterial tree of one or both lungs was injected with a 7.5 to 10% aqueous suspension of fine barium sulfate (Micropaque) at a pressure of 60 to 80 mm Hg. The injection time was at least 15 min; longer periods of injection do not enhance the contrast filling of the specimen. After injection, the lungs were fixed in 10% neutral formalin. Frontal slices of the lungs, 2 to 3 mm thick, were then cut and radiographed. Representative slices were selected for microangiography, embedded in a 1:4 mixture of yellow beeswax and paraffin (Fibrowax), and cut in 1,000 to 1,500-μ thick blocks which were then stereomicroangiographed with a technic described in detail elsewhere.8

Tortuosity of intralobular pulmonary arteries was taken as angiographic evidence of pulmonary hypertension.7 The degree of arterial tortuosity was expressed in a four-grade scale from 0 to +++ (fig. 2). Previous microangiographic studies8,9 of the intrapulmonary arterial pattern of the normal late fetal, neonatal, and infantile lungs served as a basis for comparison with the present series.

The lungs were also studied histologically in routine paraffin sections, stained with Weigert's elastic tissue stain, and counterstained with van Gieson's stain. In the cases from which non-injected blocks of pulmonary tissue were available for histologic examination, the media index of muscular pulmonary arteries was determined morphometrically according to the principles outlined by Wagenvoorst.10

To avoid bias, grading of arterial tortuosity in the microangiograms and evaluation of the histologic slides were done without access to

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Table 1

Survey of Microangiographic and Histologic Findings in 12 Infants with the Hypoplastic Left Heart Syndrome

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (days)</th>
<th>Sex</th>
<th>Birth weight (g)</th>
<th>Mitral orifice</th>
<th>Aortic orifice</th>
<th>Foramen ovale</th>
<th>Intralobular pulmonary arteries</th>
<th>Tortuosity</th>
<th>Media index</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 57</td>
<td>1</td>
<td>M</td>
<td>3890</td>
<td>Stenosis</td>
<td>Atresia</td>
<td>Patent</td>
<td>+</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>A 169</td>
<td>1</td>
<td>F</td>
<td>3770</td>
<td>Stenosis</td>
<td>Atresia</td>
<td>Closed</td>
<td>+</td>
<td>0.19</td>
<td>+</td>
</tr>
<tr>
<td>A 174</td>
<td>2</td>
<td>M</td>
<td>3080</td>
<td>Stenosis</td>
<td>Atresia</td>
<td>Incomplete</td>
<td>valve</td>
<td>0</td>
<td>0.19</td>
</tr>
<tr>
<td>A 175</td>
<td>2</td>
<td>M</td>
<td>3160</td>
<td>Stenosis</td>
<td>Stenosis</td>
<td>Practically</td>
<td>closed</td>
<td>+</td>
<td>0.23</td>
</tr>
<tr>
<td>A 39</td>
<td>3</td>
<td>F</td>
<td>3275</td>
<td>Atresia</td>
<td>Atresia</td>
<td>Floppy valve</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>A 147</td>
<td>3</td>
<td>M</td>
<td>3500</td>
<td>Stenosis</td>
<td>Atresia</td>
<td>Floppy valve</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>A 172</td>
<td>3</td>
<td>F</td>
<td>3300</td>
<td>Atresia</td>
<td>Atresia</td>
<td>Incomplete</td>
<td>valve</td>
<td>0</td>
<td>0.15</td>
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<tr>
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<td>6</td>
<td>F</td>
<td>4210</td>
<td>Stenosis</td>
<td>Atresia</td>
<td>Patent</td>
<td>+</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>A 181</td>
<td>6</td>
<td>F</td>
<td>2340</td>
<td>Stenosis</td>
<td>Atresia*</td>
<td>Practically</td>
<td>closed</td>
<td>+</td>
<td>0.19</td>
</tr>
<tr>
<td>A 191</td>
<td>7</td>
<td>M</td>
<td>3840</td>
<td>Stenosis</td>
<td>Atresia</td>
<td>Patent,</td>
<td>thickened valve</td>
<td>+</td>
<td>0.17</td>
</tr>
<tr>
<td>A 5</td>
<td>10</td>
<td>M</td>
<td>3710</td>
<td>Stenosis</td>
<td>Atresia</td>
<td>Incomplete</td>
<td>valve</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>A 171</td>
<td>40</td>
<td>M</td>
<td>2910</td>
<td>Stenosis</td>
<td>Atresia</td>
<td>Closed,</td>
<td>minor fenestrations</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

*Surgery at the age of 5 days with aortic valvulotomy and atrial septostomy.
Case A 147. Floppy valve of the foramen ovale. Seen from the right atrium (A), the excessive and thickened valvular tissue has prolapsed toward the observer. The interatrial communication formed in this manner can be better appreciated in B which displays the same valve from the left atrium. Note the stenotic mitral orifice (arrow).

Figure 1

Details of cardiac morphology and age of the patient.

Results

Microangiographic Findings

Some degree of tortuosity characterized the intralobular pulmonary arteries in nine infants with HLHS. This feature was particularly prominent (+++) in the oldest infant of the series (age, 40 days) in whom at autopsy the foramen ovale was closed except for minor fenestrations. Tortuosity of intrapulmonary arteries was moderately prominent (+) in two infants in whom the foramen ovale was prematurely closed, and in one infant in whom the patent foramen ovale was covered with a thickened but seemingly competent valve. Slight (+) tortuosity of intralobular pulmonary arteries was recorded in one infant in whom the foramen ovale was practically completely closed at 2 days of age and in four infants with patency or valvular insufficiency of the foramen ovale. In the remaining three infants in the series, all with valvular insufficiency of the foramen ovale, the microangiographic pattern of the pulmonary arterial system was interpreted as normal (table 1; fig. 2).

In one case (A 5), the number of bronchopulmonary arteries in the circumhilar portion of the lung was slightly increased. There was no evidence of abnormal arterial bronchopulmonary anastomoses in the case series.

Histologic Findings

Routine sections from the lungs showed no parenchymatous lesions except congestion and, in some cases, intraalveolar edema and hemorrhage. Muscular and transitional pulmonary arteries, as well as pulmonary arterioles were primarily interpreted as normal in five and as unduly thick-walled in seven cases. However, in only one instance (A 175) was this latter impression corroborated by an abnormally high media index (0.23). In the other cases in which morphometry of the muscular pulmonary arteries was done, the media index ranged between 0.15 and 0.19, that is, within normal limits for the perinatal lung.11 Intimal fibrosis and thrombotic or plexiform lesions were not observed.
Microangiographic pattern of the intrapulmonary arterial system in HLHS. (A) Case A 39. Normal intrapulmonary arterial pattern scaling down from elastic-transitional branches at upper left to muscular intralobular branches. No appreciable arterial tortuosity. Moderate degree of alveolar capillary filling; \( \times 13 \).

(B) Case A 171. Corresponding segment of the intrapulmonary arterial tree with prominent tortuosity (+++ ) of the peripheral muscular branches. In this field there is virtually no filling of alveolar capillaries (an inconstant finding in pulmonary-artery-injected specimens from cases of pulmonary hypertension); \( \times 13 \).

The normal pattern in A was found in a 4-day-old infant with mitral and aortic atresia but with an incompetent floppy valve of the foramen ovale which could permit a decompressive left-to-right shunt. The hypertensive pattern in B was obtained from a 40-day-old infant with mitral stenosis, aortic atresia, and a closed foramen ovale.

In three cases the intrapulmonary veins had elastic hyperplasia with arterialization as defined by Wagenvoort,\(^2\) that is, condensation of medial elastic fibers into distinct internal and external elastic laminae. No changes of this type were noted in the pulmonary veins in the other nine infants (table 1; fig. 3).

Discussion

The HLHS, in our view, is basically a defect involving the mitral and aortic orifices. In these cases the right heart is invariably dilated and hypertrophied, the ductus arteriosus is patent and wide and the ascending aorta very narrow. The thickness and the degree of fibroelastosis of the left ventricle depend upon
Figure 3

Histologic appearance of pulmonary vascular changes in HLHS. (A) Case A 175. Unduly thick-walled muscular pulmonary artery in infant with mitral stenosis, aortic stenosis, and closed foramen ovale. Media index of muscular pulmonary arteries = 0.23. Age 2 days. Elastin-van Gieson; × 550. (B) Case A181. Elastic hyperplasia in small septal pulmonary vein. The vein is “arterialized,” that is, there are well-differentiated internal and external elastic laminae enclosing the media. Case of mitral stenosis, aortic atresia, and closed foramen ovale. Age, 5 days. Elastin-van Gieson; × 210.

whether this ventricle is a cul-de-sac or has another outlet, that is, has a ventricular septal defect, in addition to the partially or wholly closed valvular orifices. The same conditions apply to the left atrium; here the volume and wall thickness depend upon the flow through the gaping open or closing foramen ovale.  

In the present series, the interventricular septum was consistently intact, and the only visible potential intracardiac shunt was provided at the atrial level, by valvular insufficiency of the foramen ovale. The morphologic prerequisite for an interatrial shunt is easily recognized when there is incomplete covering of the foramen ovale, due to either underdevelopment of the valve or dilatation of the foramen. The pathway is less obvious when there is an overdimensioned, floppy valve. In the latter condition, the interatrial left-to-right shunt seems to be facilitated by herniation of the abnormal valve through the foramen ovale as noted by Kanjuh and associates.  

The presence of a cardiac septal defect does not necessarily imply a shunt mechanism. However, in view of the hemodynamic situation in HLHS, an interatrial left-to-right shunt seems highly probable in infants with valvular insufficiency of the foramen ovale. Such a shunt would no doubt enhance the pulmonary venous drainage and hence reduce the risk of pulmonary hypertension. Our microangiographic findings suggest that this in fact is the case; tortuosity of intralobular pulmonary arteries was absent or only slightly developed in those infants in whom an
interatrial shunt could be assumed on morphologic grounds. Conversely, infants in whom the foramen ovale had closed or had a seemingly competent valve had moderate or prominent tortuosity of intralobular pulmonary arteries, an indication of more advanced pulmonary hypertension. Arterial tortuosity was particularly prominent in the oldest infant in the series, but was otherwise unrelated to the age of the patients.

Practically complete closure of the foramen ovale by 2 days of age also characterized our single case of mitral and aortic stenosis (A 175). In this infant, drainage of the small but hypertrophied and fibroelastic left atrium through the stenotic valvular orifices was obviously sufficient to prevent the development of even moderate tortuosity of intralobular pulmonary arteries. However, the media index of muscular pulmonary arteries was increased in the noninjected lobe of the same specimen, a finding suggesting pulmonary hypertension. The microangiographic and morphometric findings are thus contradictory in this particular infant for unknown reasons.

In this study we were primarily concerned with the pulmonary arterial pattern but the elastic hyperplasia with arteriolarization of pulmonary veins seen in the histologic sections provides a further morphologic hint of congestive pulmonary hypertension, at least in infants with a foramen ovale which had closed or had a competent valve.

To judge from our microangiographic findings, then, pulmonary hypertension is a dependent phenomenon within the framework of HLHS and is associated with sealing off of the left heart by closure of the foramen ovale. This concept has not clearly emerged from previous functional and morphologic studies of the HLHS. For example, Sinha and associates specifically mentioned the state of the foramen ovale—"practically closed"—for only one of the three infants in whom they obtained a significant left-to-right pressure gradient between the atria. Moreover, the clinical data of Krovetz and associates for infants with aortic atresia and mitral stenosis indicated a pulmonary artery mean pressure equal to, or exceeding, systemic artery mean pressure regardless of whether the foramen ovale was described as being closed, probe patent, or having a large opening. Wagenvoort and Edwards, in reporting an increase of medial thickness in muscular pulmonary arteries in some perinatal cases of HLHS, do not consider the state of the foramen ovale. Naeye, even for newborn infants, as indicated-infants in his HLHS series as having "a patent foramen ovale or other type of interatrial defect which permitted the shunt of pulmonary venous flow into the right atrium." It is difficult to reconcile this ease of outflow from the left atrium with the uniform increase in relative pulmonary arterial mass reported by Naeye, even for newborn infants, as indicating congenital pulmonary hypertension.

Intracardiac left-to-right shunt is not the only possible egress from the pulmonary venous system in mitral or aortic atresia. Pulmonary venous drainage to the superior vena cava by means of a levoatrio caval vein has been recognized in a few cases of HLHS, as well as myocardial sinusoids serving as a shunt between the left ventricle and the sinus coronary. Bronchial veins emptying into the azygos system could provide an additional route for the pulmonary veins emptying into the azygos system could. The angiographic methods used in the present study do not, however, permit the analysis of collateral venous pathways. Therefore, a microphlebographic study of the lungs in HLHS has been initiated; preliminary results suggest an increase of pulmonary systemic venous collaterals in cases with prematurely closed foramen ovale.

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