The Hypoplastic Left Heart Syndrome With Intact Atrial Septum: Atrial Morphology, Pulmonary Vascular Histopathology and Outcome

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OBJECTIVES
The purpose of this study was to investigate the outcome in infants with hypoplastic left heart syndrome and intact atrial septum and to evaluate the relationship of atrial morphology, left atrial decompression pathway and lung histopathology to outcome.

BACKGROUND
In the hypoplastic left heart syndrome, severe restriction at the atrial level results in marked systemic hypoxemia after birth. Infants with intact atrial septum may be at high risk for mortality after Norwood operation.

METHODS
Of 316 infants with hypoplastic left heart syndrome seen at our center over a 6.5-year period, 18 (5.7%) had intact atrial septum. Medical records and echocardiograms were reviewed.

RESULTS
On echocardiography, three types of intact atrial septal morphology were identified: 1) large left atrium, thick prominent septum 2° with thin septum 1° adherent (type A, n = 12); 2) small left atrium with thick, muscular atrial septum (type B, n = 4), and 3) giant left atrium, thin atrial septum with severe mitral regurgitation (type C, n = 2). Seven infants had left atrial decompression pathways that were severely obstructed (3/12 type A, 4/4 type B). Norwood operation was performed in 17 infants; one underwent emergency balloon atrial septostomy and died. Of six early survivors, all with type A atrial morphology and unobstructed decompression pathway; three died after subsequent cavopulmonary surgery. Lung histopathology revealed severely dilated lymphatics and "arterialization" of the pulmonary veins in those with the severest degree of obstruction to left atrial egress (type B atrial morphology).

CONCLUSIONS
Despite aggressive intervention, outcome for infants born with hypoplastic left heart syndrome and intact atrial septum is poor. Maldevelopment of the pulmonary vasculature contributes to the high mortality seen. Atrial morphology can be used as a marker for the severity of pulmonary vascular disease. (J Am Coll Cardiol 1999;34:554–60) © 1999 by the American College of Cardiology

In the normal heart before birth, the left-sided structures fill primarily from the right atrium via the foramen ovale. With prenatal restriction, or complete premature closure of the foramen ovale (i.e., intact atrial septum), flow is diverted away from the left atrium and left ventricle. This has little effect on systemic perfusion in utero, because the right ventricle continues to eject the systemic circulation via the ductus arteriosus, and pulmonary blood flow is relatively minimal. However, once separation from placental circulation takes place at birth, pulmonary blood flow increases substantially, as does pulmonary venous return to the left atrium. If left ventricular hypoplasia and an intact atrial septum (IAS) are present, effective egress from the left atrium is impeded, resulting in marked elevation of pulmonary venous pressure. Because the systemic and pulmonary circulations are perfused in parallel by the right ventricle, elevation of pulmonary venous pressure due to an intact atrial septum causes a shift in the distribution of blood flow away from the pulmonary vascular bed. The combination of single-ventricle physiology and impediment to pulmonary venous egress can result in postnatal hypoxemia to a degree which may be incompatible with life.

Survival of infants with left ventricular hypoplasia is presently possible with early identification of the anomaly and application of a strategy consisting of either heart transplantation or staged surgical reconstruction starting...
with the Norwood operation (1–9). Infants with IAS, however, may be at risk for poor outcome. The purpose of our study was to determine the outcome of infants born with an IAS in the present era of aggressive surgical management for the hypoplastic left heart syndrome (HLHS). In addition, the structural makeup of the atrial septum can vary, and other potential sites for left atrial egress such as a levoatrial cardinal vein may exist (10,11). We investigated whether the anatomic variability in atrial septal morphology and alternate left atrial decompression pathways relate to outcome. Furthermore, it has been suggested that pulmonary vascular disease may be present in infants with IAS (12). We therefore evaluated our patients for histologic evidence of pulmonary vascular pathology and correlated these findings with atrial morphology, decompression pathway obstruction and outcome.

METHODS

We searched the surgical and echocardiographic databases at The Children’s Hospital of Philadelphia. Between January 1990 and June 1997, 316 infants were diagnosed with HLHS (mitral stenosis or atresia, aortic stenosis or atresia, and D-looped hypoplastic left ventricle). Of these, 18 (5.7%) were identified as having IAS defined as: 1) absence of any visible deficiency in the atrial septum on two-dimensional echocardiography; and 2) absence of color flow crossing any portion of the atrial septum on Doppler color flow mapping. Patients described as having a very restrictive, or nearly intact, atrial septum, although possibly manifesting similar physiology, were excluded from this study to study the extreme spectrum of the disease. All patients had situs solitus and normal connection of all four pulmonary veins to the left atrium.

We retrospectively reviewed the echocardiograms and medical records of these 18 cases. To characterize atrial morphology, notation was made of the appearance of the atrial septum and left atrium when imaged from the subcostal views in the frontal, left anterior oblique and sagittal sweeps. In addition, we identified the nature of any anatomic structures providing for alternate pathways for left atrial decompression imaged from the subcostal as well as suprasternal windows. The presence of obstruction in these pathways was assessed. Left atrial decompression pathways were defined as severely obstructed in the presence of: 1) luminal narrowing at any point along the pathway course measuring ≤2 mm on Doppler color flow mapping; and 2) continuous nonphasic flow with velocity ≤1.2 m/s on pulsed Doppler echocardiographic sampling performed within the pathway.

Fetal echocardiography was performed in four patients and the prenatal diagnosis of IAS was made at 22 to 28 weeks gestation. Prenatal imaging studies in these four were compared with the postnatal studies for presence of decompression pathways and for atrial morphology.

Histopathologic evaluation of the pulmonary vasculature was performed on the lungs removed at autopsy from six patients with intact atrial septum (33%). Findings were compared with three control infants with HLHS and an atrial septal defect (at least 3 to 4 mm in diameter) who died after Norwood operation for reasons other than a restrictive interatrial communication. Specimens from lung tissue were examined microscopically and notation made on hematoxylin and eosin and elastin tissue stained slides of the appearance of the pulmonary arteries, lymphatics and veins. Slides were reviewed without knowledge of obstruction to left atrial egress or atrial septal anatomy. Findings were subsequently correlated with atrial morphology and the presence of decompression pathway obstruction.

RESULTS

Echocardiography. Review of the echocardiograms obtained before intervention in the 18 infants with IAS revealed three distinct types of atrial morphology:

1. Type A atrial morphology (n = 12). A relatively large left atrium with a thick septum secundum and a thin septum primum adherent to each other (Fig. 1). Of these, five had a leftward and posteriorly deviated septum primum, which attached to the roof of the left atrium.

2. Type B atrial morphology (n = 4). A small, muscular left atrium with circumferential thickening of the atrial walls and a thick “spongy” muscular atrial septum without ostensible distinction between septum primum and septum secundum (Fig. 2).

3. Type C atrial morphology (n = 2). A giant left atrium with a thin, rightward bulging, septum primum and secundum, this in the setting of severe mitral regurgitation (Fig. 3).

Alternate pathways for decompression of the left atrium were identified in 15 of the 18 patients (Table 1). No patient had more than one decompression pathway identified. One patient (type B) had no evidence for any pathway of egress from the left atrium; two patients (type C) had mitral stenosis and limited antegrade flow across a hypoplastic and severely stenotic aortic valve.

Of the patients with type A atrial morphology, three of 12 (25%) had a severely obstructed decompression pathway. Of note, all four infants with type B atrial morphology had either severe obstruction or complete absence of a decompression pathway. Hence the 18 patients, seven (39%) had severe obstruction to left atrial egress by virtue of an IAS and a severely obstructed decompression pathway.

Characterization of atrial morphology on fetal echocardiography was identical to that at initial postnatal echocar-
diographic study in the four patients diagnosed in utero (two patients with type A, one type B, one type C atrial morphology). Identification of alternate decompression pathways on fetal echocardiography was difficult. A left atrial cardinal vein connecting to the innominate vein was present in two of these infants; however, it was identified in only one on fetal echocardiography. The prenatal presence or absence of obstruction in this patient could not be determined reliably.

Management and outcome. All 18 patients presented to our center and had intervention within the first 36 h of life. Patient #17 had emergency cardiac catheterization and an attempt at balloon atrial septotomy; however, left atrial rupture and cardiac tamponade occurred, and the patient died. Seventeen patients underwent Norwood procedure with 11 in-hospital deaths (65% mortality). Death after Norwood procedure was commonly related to severe hypoxemia, with radiographic evidence of lung parenchymal disease and an inability to wean from positive pressure ventilation. Of the nonsurvivors, two patients underwent further surgery due to severe hypoxemia: one patient underwent placement of a second aortopulmonary shunt at two days after surgery, and one patient underwent reoperation for residual atrial level obstruction at 10 weeks after surgery.

Two patients diagnosed prenatally were treated at birth in a unique manner utilizing strategies which were thought to offer the best opportunity for survival:

1. Patient #16 (type B atrial morphology) had scheduled induction of labor at an adjacent hospital with the cardiac team present at delivery. Immediate postnatal arterial PO2 in 100% inspired oxygen was 9 torr. To allow for a period of unobstructed left atrial and pulmonary venous drainage, which might improve subsequent lung function and systemic oxygenation, an open surgical atrial septectomy was performed as an initial procedure.
at 1 h of life. At surgery a very thick muscular atrial septum was noted. At day 3 of life, the atrial septum was observed by echocardiography to be restrictive, and a stent was successfully placed via cardiac catheter relieving the obstruction. Although adequate left atrial decompression was achieved, difficulty was present in maintaining arterial PO2 > 30 torr without the use of inhaled nitric oxide and high levels of positive pressure ventilation. A Norwood procedure was performed at 2 weeks of age; however, pulmonary interstitial emphysema developed, and the infant died at day 32 of life.

2. Patient #18 (type C atrial morphology) was delivered via scheduled cesarean section at The Children’s Hospital of Philadelphia to minimize the duration of anticipated hypoxemia before intervention. Confirmation of the anatomy was made in the operating room immediately after birth, and the infant was placed on cardiopulmonary bypass within 30 min of life. Arterial blood gas just before surgery in 100% inspired oxygen revealed a PO2 of 14 torr. In addition to a Norwood procedure, the infant had suture closure of the mitral valve to reduce the degree of regurgitation. Despite these attempts, progressive left ventricular dilation and right ventricular failure ensued. After a period of extracorporeal support, the infant died at three weeks of age.

No infant with an obstructed decompression pathway (three type A morphology, all four type B morphology) survived initial intervention, and in addition there were no survivors of type C atrial morphology. The six survivors of initial intervention all had type A atrial morphology with an unobstructed decompression pathway. Of these six, three died after subsequent cavopulmonary surgery. One patient died after hemi-Fontan operation with marked hypoxemia and chronic effusions, one died suddenly at home after hemi-Fontan and one died after Fontan operation with low cardiac output. At present one patient is awaiting Fontan operation, and two patients are alive after completion of the Fontan operation.

### Pulmonary vascular histopathology

Lung tissue specimens were obtained from six patients: 1) two type A without decompression pathway obstruction (Patients #2, #17, and #18)
#6); 2) three type B all with severe obstruction (Patients #13, #14, #16), and 3) one type C (Patient #18). Findings were compared with these in three control subjects (Table 2). No significant difference was noted in appearance of the arteries between the groups. Venous structures were slightly more dilated in the type C infant than in the others. Most striking were the findings in the type B patients. The lymphatics were severely dilated and the pulmonary veins were thick, dilated and “arterialized” with multiple elastic laminae noted (Fig. 4).

**DISCUSSION**

Hypoplastic left heart syndrome with IAS is a rare finding, reported in only 1% of pathologic specimens with hypoplasia of the aortic tract complex (13). It is associated with nonimmune fetal hydrops (14) and congenital pulmonary cystic lymphangiectasis (15), indicating that impediment to pulmonary venous drainage in utero may result in prenatal morbidity or mortality in some. Of those surviving to term, death ensues rapidly during infancy (16–18). In the current era of success with staged surgical reconstruction for HLHS, infants with IAS are presenting for intervention with increasing frequency. An IAS was present in 5.7% of the population of infants presenting to us with the diagnosis of HLHS. The number of infants with a patent, but very restrictive atrial septum exhibiting the deleterious physiology of obstruction to left atrial egress may in fact be greater. Although outcome for infants with HLHS continues to improve (19), it is unclear if the growing experience with treatment strategies for HLHS have had an influence on survival in the subset of infants with IAS.

We found that despite early and aggressive intervention, survival of infants with HLHS and IAS is poor. In a multi-institutional study, 1-month survival was recently reported to be 74% after the first stage of the Norwood operation (19). Overall survival for the Norwood operation in our institution is similar, yet early survival in the subset of infants with intact atrial septum is only 33%. It is interesting to note that survival was related to the presence of an adequate natural decompression pathway for left atrial egress. Surgical creation of an adequate pathway for pulmonary venous egress in those with a very restrictive natural pathway at the time of Norwood operation did not influence the outcome positively.

The reason for poor outcome in infants with IAS may be related to the presence of a unique structural abnormality of the pulmonary vasculature. In general, pulmonary arterial abnormalities such as increased tortuosity, muscular extension and arterial wall medial hypertrophy have been previously reported in HLHS (20–22). This may explain why

<table>
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<tr>
<th>Arteries</th>
<th>Moderate degree of muscular extension into intra-acinar arteries</th>
<th>Same as control</th>
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<tr>
<td>Veins</td>
<td>Normal, or mildly dilated</td>
<td>Same as control</td>
<td>Thick and dilated with “arterialization,” ≥2 elastic laminae</td>
<td>More dilated than control</td>
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<td>Lymphatics</td>
<td>Normal, or mildly dilated</td>
<td>Same as control</td>
<td>Severely dilated</td>
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Table 2. Pulmonary Vascular Histopathology

Figure 4. Elastin stain of pulmonary veins (×400 reduced by 50%). (A) Control patient with hypoplastic left heart syndrome and an atrial septal defect measuring 3 to 4 mm. The pulmonary vein is thin. There is little elastin staining within the wall and no distinct elastic lamina noted. (B) Infant with type B atrial morphology and obstructed decompression pathway. The pulmonary vein is thick walled with multiple elastic laminae noted (“arterialization” of the pulmonary vein).
infants with HLHS exhibit an exquisite sensitivity to various pulmonary vasoactive agents (23). Pulmonary venous abnormalities, however, have not been as commonly appreciated. Condensation of the medial elastic fibers into distinct internal and external elastic laminae, so-called “arterialization” of the pulmonary vein, was first described by Samuelson et al. (24) in some infants with congenital mitral stenosis; however, no mention was made of the state of the interatrial communication or the degree of left atrial hypertension in these patients. In addition, Collins et al. noted an association between the presence of pulmonary venous vasculopathy and the severity of preoperative left-sided obstruction in children after heart transplantation for HLHS (25). In our series, we found distinct “arterialization” of the pulmonary veins and marked dilation of lymphatics in those with the severest degree of restriction to pulmonary venous egress (i.e., IAS and obstructed decompression pathway). LaBourne et al. (26) demonstrated that by banding the pulmonary veins of piglets, ultrastructural remodeling consisting of increased elastin and collagen content could be seen in the walls of the proximal pulmonary veins within one week of operation. Our data support the view that a similar process likely takes place in utero in the presence of pulmonary venous hypertension secondary to an IAS. Those with the severest degree of obstruction in utero, that is, IAS and obstructed decompression pathway, develop a fixed structural abnormality of the pulmonary veins.

Abnormality of the pulmonary vascular bed may further explain the relatively high mortality seen after cavopulmonary surgery in our small group of survivors after Norwood operation. The findings of hypoxemia after hemi-Fontan, and low cardiac output after Fontan operation as seen in two of our late deaths, suggest the presence of an abnormally elevated pulmonary vascular resistance. Although the precise cause of death in the child who died suddenly at home after hemi-Fontan is not known, it is plausible that a sudden pulmonary vasospasm may have taken place. Long-standing pulmonary venous hypertension during in utero development may result in an abnormally hyperreactive pulmonary arteriolar bed with the potential for late vasospasm (27). Of note, none of our survivors of initial palliation exhibited hypoxemia, elevated pulmonary artery pressures or obstruction to left atrial egress on cardiac catheterization before their cavopulmonary surgery, suggesting the absence of any fixed obstruction. The propensity for pulmonary vascular lability, however, may not be easily recognizable by conventional means of preoperative hemodynamic evaluation. A predilection for abnormal pulmonary vasospasm may be present in the patients with IAS who do not have a severely obstructed decompression pathway at birth and survive initial palliation.

Variability in atrial septal morphology is present among infants with HLHS and IAS. These differences suggest that a variety of different embryological mechanisms may result in the development of an IAS. Type A atrial morphology may in part be related to malposition of the septum primum in relation to septum secundum leading to occlusion of the foramen ovale. Nearly half of our infants with type A morphology had posterior and leftward deviation of the superior attachment of septum primum (28). Type B atrial morphology may be due to complete absence of formation of the ostium secundum, because there is no detectable anatomic distinction between septum primum and secundum in this subset. Type C atrial morphology is likely related to primary mitral valve disease. Dysplasia and insufficiency of the mitral valve early in gestation can lead to left atrial hypertension, resulting in adherence of the septum primum to septum secundum, preventing normal right-to-left flow at the atrial level (14,29).

Most infants with type A atrial morphology had alternate pathways of pulmonary venous egress that were not severely obstructed (nine of 12); all six early survivors were of this category. In contrast, all four with type B atrial morphology had severely obstructed or absent decompression pathways, and none survived. Pulmonary vascular histopathologic abnormalities were of greatest severity in this group. Hence, atrial septal morphology appears to be a marker for the degree of severity of pulmonary venous egress. This can be helpful, because evaluating directly for venous anomalies can be difficult with fetal echocardiography (30). Because there was no change in morphologic appearance of the atria between the prenatal and postnatal studies in our series, prenatal characterization of atrial morphology may reliably allow for detection of patients at high risk for severe obstruction and poor prognosis.

On the basis of our findings, alternate strategies to conventional staged surgical reconstruction should be considered for patients with HLHS, IAS and severe left atrial obstruction. Early identification of the anomaly with an intervention aimed at opening the atrial septum and allowing for a period of adequate left atrial decompression before the Norwood operation may improve outcome. From the time of the initial compilation of this article, we have had one patient with type B atrial morphology diagnosed prenatally who underwent surgical atrial septectomy alone in the first hours of life. Lung biopsy at the time revealed findings of severe pulmonary venous “arterialization.” After three days, the infant underwent successful Norwood operation and was discharged to home on oxygen at 11 days of age. These results are preliminary, and uncertainty exists as to the potential candidacy of this child for a future cavopulmonary connection. Although we have not had success using a standard blade and balloon technique, a more aggressive approach such as using a biotome to cut through the thick atrial septum may achieve a similar result to surgical septectomy and allow for adequate left atrial decompression (E. Bove, T. Lloyd, personal communication, December 1998). Alternatively, prenatal identification of HLHS with type B intact atrial septum may be an indication for listing the fetus for organ transplant. Lung transplantation may be indicated due to the pathology present in the pulmonary vasculature; however, heart transplantation
alone may suffice, because the presence of two well functioning ventricles may improve forward pulmonary blood flow to the extent of possibly overcoming the pulmonary vasculopathy present. Theoretically, prenatal intervention with opening of the atrial septum and relief of obstruction may be beneficial and allow for in utero remodeling of the pulmonary venous architecture toward normal with an improved course after birth. The most effective timing for intervention and the logistical feasibility of such a maneuver in the human fetus is speculative at this time.

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