Hypoplastic left heart syndrome (HLHS) is the most common congenital heart lesion resulting in death during the first year of life (1). The development of staged reconstructive surgery in the early 1980s and the subsequent introduction of heart transplantation for neonates with HLHS, however, have radically improved the prognosis of this condition (2–8). Nevertheless, a considerable number of infants with HLHS remain at high risk of mortality. Aortic valve dysplasia (LA) hypertension is one of the most critical risk factors that has an impact on the outcome of HLHS for both prenatally diagnosed and postnatally diagnosed infants (9–14). Affected neonates present with profound hypoxemia immediately after birth and may die or sustain a significant insult before medical or surgical intervention (9–11,14). Furthermore, restrictive FO places the infant at risk of severe pulmonary hypertension, which complicates the perioperative course (11) and may jeopardize successful long-term, single-ventricle palliation.

Prenatal recognition of restrictive FO in fetuses with HLHS, in providing an opportunity to plan the delivery and immediate postnatal intervention, has the potential to improve the outcome of this group of patients. It is also crucial for accurate prenatal counseling regarding the prognosis of the affected fetus. However, direct evaluation of the aortic valve in the fetus with HLHS may be difficult because of a high and posterior position of the interatrial communication, which is common in this condition (15), a very diminutive LA often observed in mitral atresia, or difficult fetal position, particularly late in gestation.

Doppler assessment of venous flow patterns has been shown to indirectly reflect downstream atrial filling pressures. Altered systemic venous flow patterns with increasing a-wave reversal have been shown to correlate with increased right atrial pressures in adults (16) and fetuses (17). Increased a-wave reversal in the pulmonary veins (PVs) has been shown to reflect LA hypertension in adults (18–24), and preliminary work suggests that it may also reflect LA hypertension in fetal HLHS (15,25). In the present study, we sought to determine whether direct FO measurements and PV patterns correlate with postnatal FO restriction, clinical evidence of LA hypertension, and outcome after birth. We hypothesized that fetal PV flow patterns, in reflecting LA pressure before birth, best predict postnatal clinical presentation and outcome.

METHODS

We retrospectively identified all fetuses diagnosed with HLHS or a variant of HLHS at The Hospital for Sick Children who underwent a prenatal echocardiography evaluation and, at the discretion of the attending physicians, received postnatal FO assessment following birth. Our analysis focused on fetuses who had both prenatal and postnatal echocardiograms, and who had no other associated congenital anomalies that would affect the formation of the atrial septum. We reviewed all prenatal and postnatal echocardiograms and clinical outcomes from May 1999 to May 2001.

BIBLIOGRAPHY

Abbreviations and Acronyms

FO = foramen ovale
HLHS = hypoplastic left heart syndrome
LA = left atrial/atrium
PA = pulmonary artery
PV = pulmonary vein/venous
VTI = velocity-time integral

Children, Toronto, between May 1999 and January 2002. Only fetuses with anatomic pathology at risk for LA hypertension were included. Fetuses with an atrioventricular septal defect or anomalous PV drainage with a small left heart were excluded.

Echocardiographic examinations and measurements.

Fetal echocardiograms were obtained with a 7-4 or a 5-3 MHz curved array transducer on a Philips Medical HDI 5000 (Andover, Massachusetts) high-density imaging system. Postnatal echocardiograms were obtained with an 8-5 or 12-5 phased array transducer (Philips Medical HDI 5000) or S12 or S8 phased array transducer on a Philips Medical Sonos 5500 system. All prenatal and initial postnatal echocardiograms were retrospectively reviewed from videotape recordings to determine the fetal and neonatal FO size, the diameters of pulmonary artery (PA) and PV branches, and, if available, the pattern and velocity of flow across the FO. The diameter of FO was measured between the superior and inferior limbs of the FO, where the FO flap was at its maximum leftward excursion during the cardiac cycle, from a four-chamber orientation of the fetal heart, with the plane of imaging perpendicular to the plane of the atrial septum, as previously described (26). Similar measurements were obtained from the initial neonatal echocardiogram. The FO was considered to be restrictive in utero when the maximum diameter measured in a four-chamber view was ≤ 2.5 mm (≤ 5th percentile for gestational age ≥ 20 weeks [27, 28]), with continuous high-velocity flow (> 60 cm/s; abnormally high peak FO velocity in the mid and third trimesters [28]). Color flow mapping was used to confirm the FO location.

To obtain the PV flow spectrum, the Doppler sample volume was placed over a PV in the lung parenchyma or at its LA junction, using color flow mapping to guide positioning (27, 28). Tracings were obtained with the sample volume as parallel to the direction of blood flow as possible.

As shown in Figure 1a, the normal fetal PV flow pattern is composed of forward flow in ventricular systole and diastole, with cessation of flow or small a-wave reversal during atrial systole (29, 30). Reversal of the a-wave is not a systematic finding, occurring in only 18% of normal fetuses (30). We measured and averaged three sequential peak systolic and diastolic and a-wave reversal velocities and velocity-time integrals (VTIs) for forward and reverse PV flow and calculated the ratio of averaged reverse (R) and forward (F) flow VTI (VTIR/VTIF) (Fig. 1b).

Postnatal records were reviewed for the first neonatal arterial blood gas, oxygen saturation, need for ventilation or inotropic support immediately after birth, need for emergent atrial septoplasty, and clinical outcome.

Statistical analysis. Patients were grouped according to: 1) the severity of FO restriction, as determined by direct fetal FO assessment; and 2) the pattern of fetal PV spectra. Neonatal FO size and clinical indexes of LA hypertension severity were compared between groups by using the Mann-Whitney U (two-group comparisons) and Kruskal-Wallis (three-group comparisons) tests for continuous variables and the Fisher exact test for categorical variables. Data were entered into a computerized data base and analyzed with StatView-J Version 5.0 software (SAS Institute Inc., Cary, North Carolina). A value p < 0.05 was considered statistically significant.

RESULTS

Forty-five fetuses with HLHS or a variant of HLHS were identified during the study period, including 27 with mitral and aortic atresia, 9 with critical aortic stenosis and mitral hypoplasia, 7 with a double-outlet right ventricle with mitral atresia or severe stenosis, and 2 with a ventricular septal defect and severe mitral and aortic stenosis. The mean gestational age at cardiac diagnosis was 24.6 ± 6.3 weeks. A total of 71 echocardiograms obtained in these fetuses were reviewed. There were 24 pregnancy terminations and 21 live births, of whom 20 had postnatal follow-up. One fetus with a diagnosis of trisomy 18 was not transferred to our
institution after birth. No other live births had associated chromosomal abnormalities.

**Assessment of FO in fetal HLHS.** The FO could be visualized in 39 (87%) of 45 fetuses and in 60 (85%) of 71 examinations, despite attempted direct FO evaluation in all during the actual study. Twenty-six were believed to have an unrestricted FO at first assessment, 12 had a restrictive FO, and one had an intact atrial septum. Among the 39 in whom the FO was visualized, 19 were continued pregnancies, and all had postnatal follow-up at our institution. Significant progression of FO restriction, based on anatomic and direct Doppler assessment, was not found prenatally in any of the fetuses assessed serially.

The FO size measured on the first and last fetal echocardiograms did not correlate well with neonatal FO size (r = 0.42 and 0.62, respectively). To determine whether fetal FO assessment would help to identify neonates at high risk because of restrictive FO and LA hypertension, we compared the neonatal FO size and clinical condition of fetuses with an unrestricted FO (n = 13) with those with a restrictive FO or intact atrial septum (n = 6), based on direct FO assessment (Table 1). Patients with suspected FO restriction, based on direct FO assessment before birth, tended to have a smaller FO postnatally and required more ventilation and inotropic support, but this did not reach statistical significance. It is noteworthy that one fetus was diagnosed only after birth with an intact atrial septum and severe LA hypertension. Direct prenatal assessment of the FO in this fetus had been difficult, despite repeated examinations.

**Fetal PV flow in HLHS.** Pulmonary venous flow could be interrogated in 40 (89%) of 45 fetuses and 62 (87%) of 71 examinations. Of the nine examinations in which we were not able to document PV flow patterns, no attempt was made to interrogate PV flow in six examinations. We identified three PV flow patterns in the fetuses with HLHS (Fig. 2). Type A flow was defined as continuous forward flow during ventricular systole and early diastole with a normally limited a-wave reversal (VTIR/VTIF ratio < 0.18) during atrial contraction. Type B was defined as continuous forward flow with an increased a-wave reversal (VTIR/VTIF ratio ≥ 0.18), and type C was defined as brief to-and-fro flow with minimal or no early ventricular diastolic flow. Of these, 27 had a type A pattern at first PV assessment, 7 had type B, and 6 had type C. All fetuses with type C flow had dilated PVs with a significantly increased PV/PA diameter ratio, as compared with those with type A or B flow (Fig. 3).

Nineteen of the fetuses with PV assessment were live-born and had postnatal follow-up. Of these, one with type A flow at first examination developed type C in advanced gestation. On the last fetal echocardiogram, 12 had type A spectra, 4 had type B, and 3 had type C. The neonatal FO size in fetuses with type B flow was significantly smaller than that of fetuses with type A flow, and all fetuses with type C flow had an intact atrial septum postnatally, including one whose FO could not be evaluated directly before birth (Table 2). One patient with a type B spectrum prenatally also had an intact atrial septum, but there was a large systemic vein identified only after birth that decompressed the LA.
To determine whether fetal PV flow patterns correlated with clinical evidence of severe LA hypertension after birth due to restrictive FO, the neonatal clinical variables were compared between the fetuses with the three PV flow patterns (Table 2). Patients with type C spectra had a significantly lower PaO₂ and lower base excess than did patients with type A or B, and all patients with type C spectra needed respiratory support immediately after birth and required emergent atrial septoplasty within 3 h after birth. Two patients had critical aortic and mitral stenosis, and both presented with severe hypoxemia and acidosis. The third patient had severe subaortic obstruction and a hypoplastic mitral valve with anterograde flow. She presented with moderate hypoxemia and severe metabolic acidosis with a low cardiac output. None of the three patients had direct assessment of LA pressures before the intervention, although two had pullback gradients of 24 and 14 mm Hg, respectively, after initial septoplasty. The neonates with type A or B PV flow before birth were more stable at delivery, and none required atrial septoplasty.

The outcomes of all fetuses with neonatal surgical intervention are shown in Figure 4. One patient with type A flow was not offered any intervention because of severe prematurity. Two of three patients with type C flow in utero died after neonatal heart transplantation, whereas only one with type A or B PV flow died postoperatively as a result of sepsis. At postmortem analysis, neonates with type C flow patterns before birth had pathologic hypertensive changes (Fig. 5), whereas the lung tissue in one patient with type A flow pattern before birth did not show any hypertensive changes. The only survivor with type C flow was the infant in whom the flow pattern changed from type A to C later in gestation.

**DISCUSSION**

Technologic advances and increased experience in the prenatal diagnosis and perinatal outcome of many conditions have resulted in a rigorous quest to fine-tune the anatomic and functional diagnoses in order to provide more accurate prenatal counseling and improve the perinatal management and thus outcome of affected fetuses. Hypoplastic left heart syndrome is one of the most commonly encountered forms of structural heart defects diagnosed in the fetus, and in many pediatric cardiology programs, many affected pregnancies are identified before birth. Although the majority of affected fetuses, when managed appropriately, have a similar, usually uncomplicated perinatal and preoperative course, those with a truly restrictive FO with severe LA hypertension are at very high perioperative risk, with an associated mortality of 52% to 65% (9–14). As such, identification of this pathology in fetal HLHS is crucial for both accurate

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**Figure 3.** The ratio of pulmonary vein (PV) to pulmonary artery (PA) diameter compared between the three PV flow pattern groups. The PV/PA ratio in fetuses with type C flow was significantly increased compared with that in fetuses with type A or B flow. The mean PV/PA ratios were 0.76 ± 0.19 in type A, 0.73 ± 0.23 in type B, and 1.53 ± 0.24 in type C flow.

**Figure 4.** Outcome of patients with perinatal surgical intervention. Perioperative survival was 91% in patients with type A, 100% with type B, and 33% with type C pulmonary vein flow. HTX = heart transplant.

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**Table 2.** Comparison of Neonatal FO Size and Clinical Condition Between Fetuses With Different Pulmonary Venous Flow Patterns Identified in Utero

<table>
<thead>
<tr>
<th></th>
<th>Type A Flow (n = 12)</th>
<th>Type B Flow (n = 4)</th>
<th>Type C Flow (n = 3)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal FO (mm)</td>
<td>4.5 ± 2.1</td>
<td>1.6 ± 1.6</td>
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<td>PaO₂ (mm Hg)</td>
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<td>61.7 ± 25.9</td>
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<tr>
<td>BE (mmol/l)</td>
<td>−2.6 ± 3.6</td>
<td>−4.3 ± 1.4</td>
<td>−12.2 ± 11.1</td>
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<td>Inotropic support</td>
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<td>Emergent septoplasty</td>
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<td>0</td>
<td>3</td>
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</tr>
</tbody>
</table>

*The Kruskal-Wallis test was used to compare continuous variables and the Fisher exact test for categorical variable. Data are presented as the mean value ± SD or number of patients.

FO = size of foramen ovale; other abbreviations as in Table 1.
counseling and planning of a timely delivery, with availability of interventional cardiology and cardiovascular surgical staff.

Although the FO can be visualized in most fetuses, we have demonstrated that direct anatomic and Doppler observations are not consistently predictive of clinical indices of severe LA hypertension after birth. In many, accurate measurement of the FO may be difficult given an inability to image the FO in a plane that is perpendicular to the atrial septum. Even though color flow mapping provides further confirmation of the presence and size of the FO, such observations may still not truly reflect the degree of LA hypertension, particularly when systemic veins decompress the LA (11).

In contrast to our experience with direct FO assessment, PV flow patterns provide a more consistent and accurate means of predicting FO restriction and severe LA hypertension after birth. We and others (15) have shown that fetal HLHS is often associated with abnormal PV Doppler observations. This pattern consists of continuous flow in ventricular systole and early diastole, with a short a-wave reversal during atrial contraction. Our three types of PV flow patterns likely represent a continuum in the degree of LA hypertension, with progressively decreasing early diastolic forward flow and increasing a-wave reversal with worsening LA hypertension. The short, very pulsatile, to-and-fro flow PV flow pattern has only been previously demonstrated in an isolated case report of fetal HLHS with an intact atrial septum (25). The fact that differences in the degree of a-wave reversal observed in type A and B flow patterns did not result in significant clinical differences may reflect only more subtle but not clinically relevant differences in LA pressure, as well as the influence of other variables on PV flow patterns (18,21–24).

Given the progressive nature of left heart obstruction (31,32), progressive restriction of the FO may occur in some fetuses with HLHS. In the present study, although there was no obvious case of progressive FO restriction based on direct assessment of the FO, we did find one fetus with a change in the PV flow pattern from type A in the mid-trimester to type C just before delivery, suggesting the potential for worsening LA hypertension before birth.

One other study has documented a correlation between PV flow and restrictive FO in fetal HLHS (15). Our study differs from that of Better et al., in that we chose to use the neonatal FO gradient to define FO restriction. Doppler flow through the FO may be increased in the presence of excessive pulmonary blood flow, as well as an anatomically restrictive FO and LA hypertension. We chose to correlate our prenatal PV flow patterns and FO assessment with other variables that better reflect clinical LA hypertension severity after birth.

Even with aggressive early neonatal intervention, patients with the most severe LA hypertension have a poor prognosis. In those with type C PV flow, pulmonary hypertension clearly complicated the postoperative course and ultimately contributed to the demise of two patients. We suspect that pathologic hypertensive PV changes develop during fetal life and may be more severe if LA hypertension develops earlier in gestation. That the only survivor with type C flow documented before birth initially had type A flow could suggest a better prognosis in fetuses with late development of FO restriction, but this requires further prospective experience. The pathologic changes we found in type C PV flow were similar to the observations reported by Rychik et al. (11). In their study, the most severe atrial morphology in patients with HLHS and an intact atrial septum was a small muscular LA with circumferential thickening of the atrial

Figure 5. Histologic findings of the lung tissue in one patient with a prenatal diagnosis of hypoplastic left heart syndrome and a type C pulmonary vein (PV) flow pattern, who died at seven weeks of age. (a) There were dilated lymphatic vessels (L) and PVs with internal and external elastic lamellae, consistent with early stage arterialization. (Movat's stain, ×100 magnification.) (b) Muscular pulmonary artery with medial (M) thickening and neointimal (N) hyperplasia, indicators of pulmonary hypertension, Heath-Edwards grade II, in the same infant. (Movat's stain, ×400 magnification.)
walls associated with severely dilated lymphatic vessels and PV “arterialization.” Even with adequate early decompression of the LA after birth, the PV morphology may take time to or may never normalize in the majority. The poor outcome in this subset of fetuses with HLHS should be taken into consideration not only for prenatal counseling but also in the planning of delivery and neonatal management. Given the need for immediate medical or surgical intervention, caesarean section would make certain a timely delivery; however, the risk of a caesarean section to the woman and her future reproductive health should be weighed against the likelihood of survival of her baby.

**Study limitations.** This study was primarily limited by the small number of fetuses with HLHS assessed, as well as its retrospective nature.

**Conclusions.** Attempts at direct fetal FO observation during fetal echocardiography in HLHS do not consistently correlate with neonatal FO size or the clinical degree of LA hypertension after birth. The fetal PV flow pattern may be a more useful predictor of the degree of LA hypertension and outcome and may provide insights into the pathogenesis of PV pathology observed in affected neonates. This information is crucial for prenatal counseling and planning of perinatal management.

**REFERENCES**