Predictive Value of Fetal Pulmonary Venous Flow Patterns in Identifying the Need for Atrial Septoplasty in the Newborn With Hypoplastic Left Ventricle

Erik Michelfelder, MD; Carlen Gomez, MD; William Border, MBChB; William Gottliebson, MD; Cheri Franklin, CNP

Background—Pulmonary venous Doppler (PVD) flow patterns in the fetus with hypoplastic left heart syndrome (HLHS) have been correlated with restrictive interatrial communication or intact atrial septum (RAS) postnatally; however, the ability of PVD to identify the neonate requiring emergent atrial septoplasty (EAS) for severe left atrial hypertension and hypoxemia has not been critically evaluated. It was the purpose of this study to determine the predictive power of fetal PVD in identifying the need for EAS in newborns with HLHS and RAS.

Methods and Results—Forty-one patients with fetal PVD flow analysis and postnatally confirmed HLHS were studied. Pulsed-wave assessment of PVD flow included S-, D-, and A-wave velocity, time-velocity integral (VTI) of forward and reverse flow, and S/D velocity and forward/reverse VTI ratio. Neonatal EAS was used as the primary clinical outcome variable. Receiver operating characteristic curves were used to determine cutpoints at which PVD indices best predicted EAS. Cutpoints were evaluated for clinical accuracy and usefulness by use of Bayesian analysis. Eight of 41 subjects underwent EAS. Need for EAS was most accurately predicted by forward/reverse VTI ratio \( \frac{5}{1} \) (sensitivity, 0.88, 95% CI, 0.49 to 0.99; specificity, 0.97, 95% CI, 0.82 to 0.99), which, when present, increases the posttest likelihood of EAS to 74%, assuming a pretest prevalence of 10%. Accuracy and usefulness of other PVD indices were affected by false-positive results.

Conclusions—In the fetus with HLHS, a PVD forward/reverse VTI ratio of \( \frac{5}{1} \) is the strongest predictor of the need for EAS in the newborn period. These observations should improve our ability to identify and expectantly manage the fetus with HLHS and RAS. (Circulation. 2005;112:2974-2979.)

Key Words: heart defects, congenital ■ echocardiography ■ diagnosis ■ hypoplastic left heart syndrome
immediately proximal to its entry into the left atrium, as previously possible, with the sample volume placed in the pulmonary vein with the angle of insonation as parallel to the direction of flow as Doppler in the transverse plane. Doppler recordings were obtained significant in the fetus. Pulmonary veins were imaged by color flow either the right or left vein, because differences between right and

become most predictable? Thus, the purpose of this study is to rigorously evaluate the clinical accuracy of pulmonary venous Doppler flow indices in predicting the need for urgent atrial septoplasty in the fetus with HLHS and to attempt to identify the clinical “cutpoints” that are most predictive of the need for atrial septoplasty in this population.

Fetal Venous Flow Analysis
Pulsed Doppler evaluation of pulmonary vein flow was performed in either the right or left vein, because differences between right and left pulmonary vein flow have previously been shown to be insignificant in the fetus.16 Pulmonary veins were imaged by color flow Doppler in the transverse plane. Doppler recordings were obtained with the angle of insonation as parallel to the direction of flow as possible, with the sample volume placed in the pulmonary vein immediately proximal to its entry into the left atrium, as previously described. Low-pass filters were adjusted to ensure recording of lower-velocity signals.

Methods
Study Population
We conducted a multicenter, retrospective review of fetuses with left heart obstructive lesions and at risk for left atrial hypertension. All data collection and storage was performed under approval of the Institutional Review Board for each center to ensure proper handling of protected health information under the Health Information Portability and Accountability Act. The study population included fetuses, studied between January 2001 and June 2004, with HLHS consisting of aortic and mitral valve atresia and/or stenosis, as well as fetuses with mitral atresia and hypoplastic left ventricle in the setting of double-outlet right ventricle. Fetuses with unbalanced atroventricular septal defects were not included in the analysis. In fetuses with serial fetal echocardiograms, only the most recent study was used for analysis. Patient medical records were reviewed to identify patients who underwent EAS in the newborn period. All fetuses ultimately requiring EAS and with PVD were compared with a randomly selected cohort of fetuses with PVD who did not require EAS in the newborn period.

Fetal Echocardiography
Fetal echocardiograms were performed at each center on commercially available machines under direct supervision of a cardiologist experienced in fetal echocardiography. Complete 2D, color flow, and spectral Doppler studies were performed by use of accepted standards to establish the anatomic diagnosis.

Statistical Analysis
Statistical analyses were performed using either StatView (SAS Inc) or SPSS 11.5 (SPSS, Inc) software. Continuous, descriptive data are expressed as mean ±SD. PVD data are expressed as median with ranges, because the distribution of these data is nonnormal. Inter-group comparisons of PVD indices were performed by use of the Mann-Whitney U test. The receiver operating characteristic (ROC) curves for PVD indices in predicting need for EAS were plotted; the data were subsequently used to identify cutpoints for each index that predicted need for EAS with the greatest sensitivity and specificity. Positive and negative predictive values and positive and negative

Reproducibility
Intraobserver and interobserver variability of PVD indices was assessed using a subset of 20 patients. One reader (E.M.) repeated measurements at a time temporally remote from initial assessment. To assess interobserver variability, a second reader (W.G.), blinded to the original data, repeated PVD measurements. Intraobserver and interobserver variability was assessed by calculation of mean percent error, defined as the absolute difference between observations divided by the mean of observations.

Clinical Data
For the purposes of analysis, performance of EAS in the newborn period was used as the primary clinical outcome variable. In all cases, EAS was performed at the discretion of the clinician, on the basis of the degree of hypoxemia, acidosis, postnatal echo findings, and suspicion of significant left atrial hypertension. Findings on fetal echocardiography were not used as a criterion to intervene.
Results

A total of 41 subjects with PVD examinations adequate for analysis were identified for review. All fetuses were in a normal cardiac rhythm with 1:1 atrioventricular conduction at the time of PVD study. The anatomic diagnoses of study subjects are shown in Figure 3. The mean gestational age at fetal echocardiography was 33 ± 4 weeks. Of the 41 subjects, 8 underwent EAS in the newborn period (6 with aortic/mitral atresia, 1 with aortic atresia/mitral stenosis, and 1 with double-outlet right ventricle with mitral atresia); no subject undergoing EAS, therefore, had anatomy allowing forward flow of blood through the left heart. None of the 10 subjects with aortic and mitral stenosis required EAS. Venous channels decompressing the left atrium were present in 2 of 8 subjects requiring EAS and in 3 of 33 subjects not requiring EAS. Short-term follow-up was available in 8 of 8 subjects requiring EAS and in 30 of 33 subjects not requiring EAS. Survival to hospital discharge after stage 1 Norwood reconstruction was 3/8 (36%) (3 of 8 newborns died before undergoing the Norwood procedure) in EAS subjects, compared with 28 of 38 (74%) in non-EAS subjects.

Pulmonary Venous Doppler Indices

Data comparing PVD indices in subjects requiring EAS with those who did not require EAS are presented in Table 1. Both magnitude and duration of the PVD A wave were increased in the EAS group, reflecting greater pulmonary venous flow reversal during atrial systole. The PVD D-wave velocity was lower in EAS subjects, and the ratio of PVD A wave to D wave increased. The PVD S-wave/D-wave ratio was elevated, and the ratio of forward to reverse pulmonary vein flow was significantly reduced in EAS subjects.

ROC of PVD Indices

Indices with areas under the ROC curve ≥0.90 are presented in Table 2, as well as the “optimal” cutpoints for each PVD index, defined as the positive test value that maximized both sensitivity and specificity in predicting need for EAS. Forward/reverse VTI ratio demonstrated the most favorable ROC curve, with a cutoff value of <5 predicting EAS with a sensitivity and specificity of 88% and 98%, respectively.

Clinical Accuracy and Usefulness of PVD Indices

Sensitivity, specificity, predictive values, and likelihood ratios are presented in Table 3. All PVD indices had high sensitivity (0.88). Specificity was excellent for forward/reverse VTI ratio and A-wave VTI, and the corresponding positive likelihood ratios were also high. The specificity of the S/D ratio, A-wave duration, and A/D ratio was affected by false-positive results and is reflected in lower positive predictive values and positive likelihood ratios. Negative predictive values and negative likelihood ratios for all indices were favorable. The Bayes theorem was applied, and the posttest likelihood of EAS was calculated for both positive and negative tests using the established cutoff values. These results are presented in Table 4. With all PVD indices, a negative test results in a posttest probability (for EAS) of <3%. The value of a positive test, however, was more varied and was substantial only for A-wave VTI >1.4 cm and forward/reverse VTI ratio <5. A positive test using these indices raises the posttest probability of EAS to 60% and 74%, respectively. For the remaining indices, a positive test failed to increase posttest probability above 50%, making these indices substantially less useful.

### Table 1. Median Fetal Pulmonary Venous Doppler Indices for Newborns Who Did or Did Not Require EAS

<table>
<thead>
<tr>
<th>PVD Index</th>
<th>EAS (n=8)</th>
<th>Non-EAS (n=33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-wave velocity, cm/s</td>
<td>45 (21–75)</td>
<td>42 (16–71)</td>
<td>NS</td>
</tr>
<tr>
<td>D-wave velocity, cm/s</td>
<td>14 (4–26)</td>
<td>21 (7–40)</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>S-wave/D-wave ratio</td>
<td>3.2 (2.0–5.0)</td>
<td>1.8 (1.0–5.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A-wave velocity, cm/s</td>
<td>35 (13–54)</td>
<td>17 (7–41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A-wave duration, ms</td>
<td>92 (68–119)</td>
<td>63 (20–88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A-wave VTI, cm</td>
<td>2.5 (0.8–5.3)</td>
<td>0.6 (0.1–2.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Forward flow VTI, cm</td>
<td>5.9 (3.1–10.8)</td>
<td>8.4 (3.1–14.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Forward/reverse VTI ratio</td>
<td>3.4 (0.9–5.8)</td>
<td>13.6 (3.3–48.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>A-wave/D-wave ratio</td>
<td>2.7 (1.3–6.8)</td>
<td>0.7 (0.2–4.3)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

### Table 2. ROC Analysis for PVD Indices With AUC ≥0.90

<table>
<thead>
<tr>
<th>PVD Index</th>
<th>Area Under ROC Curve</th>
<th>95% Confidence Limits</th>
<th>“Optimal” Cutpoint Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S/D-wave velocity ratio</td>
<td>0.90</td>
<td>0.79–1.00</td>
<td>&gt;2.5</td>
</tr>
<tr>
<td>A-wave duration</td>
<td>0.93</td>
<td>0.84–1.00</td>
<td>&gt;77 ms</td>
</tr>
<tr>
<td>A-wave VTI</td>
<td>0.94</td>
<td>0.85–1.00</td>
<td>&gt;1.4 cm</td>
</tr>
<tr>
<td>A/D-wave velocity ratio</td>
<td>0.94</td>
<td>0.87–1.00</td>
<td>&gt;1.35</td>
</tr>
<tr>
<td>Forward/reverse VTI ratio</td>
<td>0.98</td>
<td>0.94–1.00</td>
<td>&lt;5.0</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve.
TABLE 3. Clinical Accuracy of PVD Doppler Indices in Predicting Need for EAS in the Newborn Period

<table>
<thead>
<tr>
<th>PVD Index</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Positive LH Ratio</th>
<th>Negative LH Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-wave duration &gt;77 ms</td>
<td>0.88 (0.47–0.99)</td>
<td>0.82 (0.64–0.92)</td>
<td>0.54 (0.26–0.79)</td>
<td>0.96 (0.80–0.99)</td>
<td>4.8 (2.2–10.4)</td>
<td>0.15 (0.02–0.97)</td>
</tr>
<tr>
<td>S/D ratio &gt;2.5</td>
<td>0.88 (0.47–0.99)</td>
<td>0.85 (0.67–0.94)</td>
<td>0.58 (0.29–0.84)</td>
<td>0.97 (0.80–0.99)</td>
<td>5.8 (2.5–13.5)</td>
<td>0.15 (0.02–0.93)</td>
</tr>
<tr>
<td>A/D ratio &gt;1.35</td>
<td>0.88 (0.47–0.99)</td>
<td>0.91 (0.75–0.98)</td>
<td>0.70 (0.35–0.92)</td>
<td>0.97 (0.81–0.99)</td>
<td>9.6 (3.2–29.2)</td>
<td>0.14 (0.02–0.87)</td>
</tr>
<tr>
<td>A-wave VTI &gt;1.4 cm</td>
<td>0.88 (0.47–0.99)</td>
<td>0.94 (0.78–0.99)</td>
<td>0.78 (0.40–0.96)</td>
<td>0.97 (0.82–0.99)</td>
<td>14.4 (3.7–56.7)</td>
<td>0.13 (0.02–0.84)</td>
</tr>
<tr>
<td>Forward/reverse VTI ratio &lt;5</td>
<td>0.88 (0.47–0.99)</td>
<td>0.97 (0.82–0.99)</td>
<td>0.88 (0.47–0.99)</td>
<td>0.97 (0.82–0.99)</td>
<td>28.9 (4.1–203)</td>
<td>0.13 (0.02–0.80)</td>
</tr>
</tbody>
</table>

LH ratio indicates likelihood ratio; NPV, negative predictive value; PPV, positive predictive value. Values in parentheses are 95% CIs.

Reproducibility and Technical Feasibility of PVD Indices

Both intraobserver and interobserver variability of PVD flow velocities (A-wave velocity, S/D velocity ratio, and A/D velocity ratio) were low, with mean percent errors ranging from 7% to 10%. Mean percent errors for PVD indices using velocity-time integrals (forward/reverse VTI ratio and A-wave VTI) were higher for both intraobserver and interobserver measurements and ranged from 15% to 16%. The forward flow VTI, however, was quite reproducible (intraobserver and interobserver percent errors of 6% and 5%, respectively), suggesting that much of the variability in the forward/reverse VTI ratio most likely arises from the A-wave VTI measurement. Temporal measurement of A-wave duration had intermediate reproducibility with mean percent errors of 10% and 14% intraobserver and interobserver, respectively. We reviewed the most recent consecutive 43 fetal echocardiographic studies performed in fetuses with HLHS; PVD was able to be obtained and analyzed in 41 (95%) of these studies. Technically inadequate PVD did not result in exclusion from study of any fetus requiring EAS.

Discussion

HLHS and its variants are among the most common prenatally diagnosed congenital heart lesions, composing approximately 20% of one large series and 13% of our recent experience (unpublished data). HLHS is complicated by highly restrictive or intact atrial septum (RAS) in approximately 6% to 11% of cases. Although in general, the impact of prenatal diagnosis of HLHS on postoperative outcomes is unproven, prenatal diagnosis of HLHS complicated by RAS currently has the potential to affect both parental counseling and prenatal and postnatal management. HLHS with RAS is associated with significantly increased mortality in infants both undergoing staged surgical palliation and awaiting cardiac transplantation. This is supported by our current experience, in which the mortality among infants requiring EAS was 64%. As such, when HLHS with RAS is diagnosed prenatally, parental counseling should reflect the increased risk to survival of these fetuses and infants.

Postnatal management of the fetus with HLHS and RAS can be extremely challenging. These infants are usually very unstable, with severe hypoxemia and acidosis. Management usually consists of either emergent surgical atrial septectomy or catheter-based atrial septoplasty in the immediate newborn period. Even with expectant management, the presurgical mortality in infants awaiting a first-stage Norwood procedure or a cardiac transplant is high. Moreover, histological changes in the pulmonary arterioles and veins, probably the consequence of chronic in utero left atrial hypertension, are seen in these infants, which may produce further short- to long-term morbidity and mortality. Knowledge of the poor prognosis for the fetus with HLHS and RAS and evolving techniques of percutaneous fetal cardiac intervention has led some centers to propose in utero atrial septoplasty in these fetuses, in an effort to achieve left atrial decompression and modify the poor natural history of this condition.

Given these concerns, it is essential that reliable, clinically accurate means of identifying the fetus with HLHS and RAS are developed. Direct evaluation of the size of the foramen ovale (and the left-to-right shunt) can be performed but is often technically difficult; for these reasons, evaluation of the fossa ovalis was not routinely performed in our study. Pulmonary venous flow alterations in HLHS in association with RAS have been described previously and are technically more easily obtained, and are thought to correlate clinically with the degree of left atrial hypertension produced by the restrictive foramen ovale. Taketazu and colleagues have identified a pattern associated with need for EAS in which a large PVD S-wave velocity and a large A wave are accompanied by a near absence of early diastolic flow (D wave). In our own experience, however, neonates with HLHS requiring EAS often had more variable PVD flow patterns featuring a more prominent D wave (Figure 1). These observations led us to perform the present analysis of the clinical reliability and usefulness of PVD flow analysis in identifying the fetus with HLHS who will ultimately require EAS. This type of analysis becomes particularly important in the current era, in which in utero atrial septoplasty, ex utero intrapartum transfer to extracorporeal membrane oxygenator therapy, or other more aggressive therapies are contemplated for this high-risk population.

TABLE 4. Posttest Probability of EAS for PVD Indices Assuming Pretest Prevalence of 10%

<table>
<thead>
<tr>
<th>PVD Index</th>
<th>Posttest Probability of EAS With Positive Test</th>
<th>Posttest Probability of EAS With Negative Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-wave duration &gt;77 ms</td>
<td>0.32</td>
<td>0.03</td>
</tr>
<tr>
<td>S/D velocity ratio &gt;2.5</td>
<td>0.37</td>
<td>0.03</td>
</tr>
<tr>
<td>A/D velocity ratio &gt;1.35</td>
<td>0.49</td>
<td>0.03</td>
</tr>
<tr>
<td>A-wave VTI &gt;1.4 cm</td>
<td>0.59</td>
<td>0.03</td>
</tr>
<tr>
<td>Forward/reverse VTI ratio &lt;5</td>
<td>0.74</td>
<td>0.03</td>
</tr>
</tbody>
</table>
The present study not only demonstrates that quantitative PVD indices are sensitive and specific indicators of need for EAS in this population but also establishes the most reliable indices, by rigorous analysis, given the relatively low prevalence of RAS in the fetus with HLHS. Modifications of Bayes’ theorem demonstrate that the probability of disease in a patient with a positive diagnostic test is affected by the pretest disease prevalence and will be lower in a disease with low prevalence. Therefore, analyses of diagnostic test accuracy and usefulness using only sensitivity, specificity, and predictive values may be misleading when the prevalence of the disease in question is low. By applying determination of likelihood ratios to a reformulation of Bayes’ theorem, the posttest probability of disease for each PVD index could be evaluated with disease prevalence incorporated into the analysis. The present data suggest that the ratio of forward/reverse pulmonary vein flow has the greatest accuracy, with the highest sensitivity and specificity, and the greatest potential usefulness, with the most favorable positive and negative likelihood ratios, of all PVD indices evaluated. Calculated posttest probability of need for EAS in a fetus with a forward/reverse VTI ratio <5 is 74%; such a result significantly increases clinical suspicion and would be valuable in planning clinical care. Positive tests using other PVD indices increase the posttest probability of EAS from 32% to 59%, where a test increasing posttest probability to 50% is in essence no more useful than a flip of a coin.

This type of analysis is not simply a mathematical exercise in this patient population, because some centers are currently recommending fetal interventional procedures to treat RAS in the fetus with HLHS. Because these interventions do place the fetus and mother at risk, reliable identification of the fetus most likely to require EAS to avoid postnatal hemodynamic instability is, therefore, of significant clinical importance. In fact, our analysis could be adjusted to favor even more certain diagnosis in the setting of a positive test. For our ROC analysis, we arbitrarily chose cutpoints that maximized both sensitivity and specificity in identifying the need for EAS. If one wanted to maximize specificity at the expense of sensitivity, one would simply choose a cutpoint farther to the left on the x axis of the ROC curve. For example, if we chose a cutpoint for forward/reverse VTI <3, the sensitivity in predicting EAS falls to 0.38. The positive likelihood ratio in this case becomes infinite, making a positive test 100% diagnostic; however, a negative test becomes less valuable, because calculated posttest probability remains at approximately 12%, or approximately the same as pretest probability. This may be a preferable approach when one is considering, for example, a high-risk fetal intervention in the event of a positive test, or it could be a means of compensating for the modest measurement variability in PVD indices between observers.

We did not specifically look at longitudinal changes in the PVD indices during gestation but rather chose to evaluate the last PVD assessment before birth. Thus, the mean gestational age at assessment was relatively late (33±4 weeks). These data would therefore be most useful in planning postnatal management with regard to need for EAS and may be less useful in determining candidacy for a fetal atrial septoplasty.

Although in normal fetuses, PVD S- and D-wave velocities increase throughout gestation, and the S/D ratio and A-wave magnitude remain unchanged, further work is needed to confirm the predictive capabilities of second-trimester PVD assessment in this population.

This study has several potential limitations. First, the sample size is relatively small. The present report, however, represents the largest series to date describing PVD in fetal HLHS, as well as the largest number of subjects with clinically restrictive atrial septae, defined as need for emergent septoplasty in the newborn period. Nonetheless, generalization of our findings with regard to performance characteristics of PVD indices (Table 3) should be interpreted in light of the relatively wide confidence limits associated with these estimates.

Another perceived limitation may be that analysis of the relationship between PVD and other factors, such as anatomic subtype, atrial septal morphology, right ventricular function, presence of decompressing veins, or tricuspid regurgitation, was not performed and that these factors may affect PVD findings. We did not attempt to analyze the relationship between these various factors and PVD indices for a number of reasons: (1) because sample size, in our opinion, precludes a valid analysis of the relationship between these factors and PVD findings, and, most importantly, (2) that we were most interested in the “end result” of all factors producing left atrial outflow obstruction and hypertension. In other words, the PVD flow characteristics, regardless of the mechanism of left atrial outflow obstruction, should change, as described in previous reports, as a function of left atrial hypertension and not as a function of specific anatomic or physiological findings. Although elucidation of the anatomic and physiological findings that place the fetus with HLHS at greatest risk for severe left atrial hypertension is an important issue, this study is focused on the ability of PVD to predict severe clinical left atrial hypertension postnatally, defined as need for EAS.

Our data demonstrate that PVD indices are both accurate and reproducible, with mean intraobserver and interobserver differences comparable to previous studies of PVD in both the fetus and the adult. However, there is modest variability in measurement of PVD indices, particularly with regard to the estimate of PVD A-wave magnitude, and therefore, PVD findings should be interpreted in the clinical setting with this foreknowledge.

By applying Bayes’ theorem to our analysis, we have established clinical threshold values for PVD indices that are clinically robust and should provide the clinician with a reliable means of identifying the fetus with HLHS at risk for left atrial hypertension and severe hypoxemia in the newborn period. In the current era, these indices not only will improve counseling and medical care planning but also may provide improved criteria for selecting candidates for evolving fetal therapies aimed at treating the fetus with HLHS and RAS.

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