Right Ventricular Systolic-to-Diastolic Time Index: Hypoplastic Left Heart Fetuses Differ Significantly from Normal Fetuses

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Right Ventricular Systolic-to-Diastolic Time Index: Hypoplastic Left Heart Fetuses Differ Significantly from Normal Fetuses

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Background: A growing body of evidence indicates that right ventricular dysfunction in patients with palliated hypoplastic left heart syndrome (HLHS) originates in fetal life. In this study, the systolic-to-diastolic time index (SDI) was used to study the presence of ventricular dysfunction in single right ventricles in fetuses with HLHS or evolving HLHS and to assess whether this dysfunction is related to increase preload, myocardial performance, or interventricular interaction.

Methods: Echocardiograms from 78 fetuses with HLHS and 10 with evolving HLHS were retrospectively compared with those of 78 normal control fetuses. Fetuses with HLHS were further grouped according to morphology of the left ventricle (LV): not visible \( (n = 35) \) or visible \( (n = 43) \). Spectral Doppler signals obtained from right ventricular inflow (blood pool) and tissue Doppler from the tricuspid lateral annulus were analyzed. The SDI was calculated as the ratio of the ejection time plus isovolumic contraction and relaxation times to the diastolic filling time. E/A and E/e\(^0\) ratios, cardiac output, preload index, and Tei index were also calculated.

Results: Fetuses with HLHS demonstrated significantly elevated right ventricular SDI values by both blood pool Doppler and Doppler tissue imaging compared with control subjects (1.89 ± 0.33 vs 1.58 ± 0.29 \( [P < .001] \) and 2.1 ± 0.57 vs 1.66 ± 0.31 \( [P < .001] \), respectively). Changes in filling time rather than ejection time predominated. Fetuses with HLHS with visible LVs and those with evolving HLHS had significantly higher SDI values than fetuses with HLHS without visible LVs (no visible LV, 1.75 ± 0.22; visible LV, 2 ± 0.36; \( P = .001 \); evolving HLHS, 2.19 ± 0.68; \( P < .001 \)). SDI was correlated with the Tei index \( (R = 0.58) \) and was more sensitive than the Tei index in identifying differences between the HLHS subgroups.

Conclusions: Fetuses with evolving and overt HLHS exhibit abnormally increased SDI values in utero. This difference is likely related to inherently pathologic interventricular interactions and/or diastolic dysfunction of the right ventricle in fetuses with HLHS. (J Am Soc Echocardiogr 2015;::

Keywords: HLHS, Fetal echocardiography, Systolic-to-diastolic time interval

Patients with hypoplastic left heart syndrome (HLHS) undergoing single-ventricle palliation can develop right ventricular dysfunction and heart failure.\(^1\)\(^-\)\(^3\) This dysfunction is progressive in nature, but the timing of onset is unclear. Recently, evidence has accumulated suggesting that right ventricular dysfunction can start in utero.\(^4\)\(^-\)\(^7\) In particular, a small series has demonstrated evidence of diastolic dysfunction with preserved systolic function in fetuses with HLHS.\(^7\) However, in practice, the assessment of ventricular function in fetuses is challenging and is currently based largely on qualitative assessment.

A quantitative echocardiographic index, the systolic-to-diastolic time index (SDI), has shown validity in detecting ventricular dysfunction in dilated\(^8\) and restrictive cardiomyopathy.\(^9\) Normal values have been established postnatally.\(^10\) The index consists of the sum of the ejection time (ET), the isovolumic contraction time (ICT) and the isovolumic relaxation time (IRT) divided by the filling time (FT) (Figure 1). This index differs from the Tei index in that it incorporates the FT in its calculation. This may allow higher sensitivity in the detection of pathologies affecting ventricular filling. The index has shown good intraobserver and interobserver variability in previous studies.\(^8\)\(^-\)\(^11\)

Our aims were to (1) compare FT and SDI in fetuses with HLHS with those in normal fetuses and among different morphologic subtypes of HLHS and (2) compare the SDI with the Tei index in fetuses with HLHS.

METHODS

We performed a retrospective case-control study reviewing fetal echocardiograms at the University of California, San Francisco, fetal cardiovascular program from 1999 to 2013 with fetal diagnoses of HLHS. This study was approved by the local institutional review board. All pregnant mothers underwent standard two-dimensional,
Spectral Doppler, and color Doppler examinations using a Siemens Sequoia or S2000 ultrasound system (Siemens Medical Solutions USA, Mountain View, CA) equipped with 8.0- or 6.0-MHz curved linear transducers. Images were acquired and stored in standard Digital Imaging and Communications in Medicine format. We analyzed the first fetal echocardiogram performed at our institution for all fetuses with HLHS presenting during the study period. HLHS was defined as mitral stenosis or atresia, a small left ventricle (LV), aortic valve hypoplasia or atresia, left-to-right flow across the foramen ovale, and retrograde flow in the aortic arch. We included fetuses with evolving HLHS (defined as aortic stenosis with a dilated LV, retrograde transverse aortic arch Doppler color flow, and left-to-right atrial shunt) as a separate group. Patients with unbalanced atrioventricular canals and double-outlet right ventricles were excluded. Studies missing tricuspid valve inflow blood pool Doppler or with poor-quality Doppler imaging rendering measurement of the time intervals impossible or questionable were also excluded.

The included subjects with HLHS were divided into groups: LV not visible and LV visible. We further categorized the fetuses with LV visible on the basis of a subjective assessment of the left ventricular morphology: slitlike LV with no endocardial fibroelastosis or small, round LV with endocardial fibroelastosis (Table 1). The additional group with evolving HLHS (with dilated LVs) was included to further delineate the effect of the presence of a large dysfunctional LV on the SDI of the right ventricle.

A convenience sample control group of fetuses presenting to our program during the same time period was included in the analysis. This group included singleton fetuses with no structural cardiac disease. The indications for fetal echocardiography in the controls were family history of congenital heart disease, referral for inability to accurately assess the cardiac anatomy or for suspected heart defect on obstetric scan, and volunteers without risk factors or abnormalities.

Abbreviations

- **ET** = Ejection time
- **FT** = Filling time
- **HLHS** = Hypoplastic left heart syndrome
- **ICC** = Intraclass correlation coefficient
- **ICT** = Isovolumic contraction time
- **IRT** = Isovolumic relaxation time
- **LV** = Left ventricle
- **SDI** = Systolic-to-diastolic time index

We excluded fetal echocardiograms obtained for maternal diabetes, maternal teratogen intake, family history of cardiomyopathy or maternal autoantibody disease, increased nuchal translucency (>95th percentile) on the 11- to 13-week scan, and presence of known or suspected congenital anomalies or genetic defects.

Our initial database query for the period from 1999 to October 2013 yielded 111 fetal diagnoses of HLHS. Eight patients were missing fetal echocardiograms in the digital database, and their studies from the videotape archives could not be obtained. Five patients had associated atrioventricular canals or double-outlet right ventricles, and 20 patients had either absent (14 fetuses) or poor-quality tricuspid valve inflow Doppler (six patients). We thus had available for analysis fetal echocardiograms from 78 patients with HLHS. Seventy-eight normal fetal control subjects of similar mean gestational age meeting the criteria described above and with echocardiograms obtained during the same time period were selected.

The measurement of SDI was performed using previously archived images in all patients as follows: FT and cycle length were measured from right ventricular inflow spectral-pulse-wave blood pool Doppler. If available, measurement was also performed from the tissue Doppler velocity at the lateral tricuspid valve annulus and analyzed separately. We did not interchange the blood pool Doppler-derived and the tissue Doppler-derived measurements. ET plus ICT and IRT was calculated by subtracting FT from total cycle length:

\[
(\text{ICT} + \text{ET} + \text{IRT}) = \text{Total cycle length} - \text{FT}.
\]

The SDI was then calculated as

\[
\text{SDI} = \frac{(\text{ICT} + \text{ET} + \text{IRT})}{\text{FT}}.
\]

Individual components of the ratio were also recorded, and ET, total isovolumic time (ICT + IRT), and FT were indexed individually to total cycle length (to correct for heart rate). All measurements were performed on three consecutive heartbeats during fetal apnea, and the average was used in the statistical analysis (Figure 1).

To assess the factors that may influence FT, we calculated the preload index from the Doppler sample obtained in the inferior vena cava,

\[
\text{Preload index} = \frac{\text{Peak "S" wave velocity}}{\text{Peak "a" wave velocity}}
\]

as previously described. To assess for diastolic dysfunction, peak tricuspid inflow velocities (peak E and peak A) and peak lateral tricuspid annular early diastolic tissue velocity (e’5) were measured on three consecutive beats during fetal apnea and averaged, and the E/A and E/e’ ratios were calculated for each fetus. Right ventricular output was estimated as

\[
\text{Estimated fetal weight (kg)} = \frac{\pi \times [\text{Pulmonary valve diameter (cm)/2}]^2 \times \text{RVOT VTI (cm/sec)} \times \text{HR (beats/min)}}{\text{Output}}.
\]

The Tei index, defined as the sum of ICT and IRT divided by ET,\(^{14}\) was also calculated. For blood pool Doppler Tei index, we measured ET and heart rate (cycle length) from the pulmonary outflow Doppler images and FT from tricuspid inflow, allowing calculation of Tei as follows:

\[
\text{Tei index} = \frac{(\text{Total cycle length} - \text{FT} - \text{ET})}{\text{ET}}.
\]

For tissue Doppler Tei index, the lateral tricuspid annular Doppler trace was used and calculation made in a similar manner. Tricuspid
inflow and pulmonary outflow Doppler measurements were obtained from tracings with similar heart rates. Significant heart rate differences (>10%) in the right ventricular inflow and outflow tracing resulted in rejection of the patient for Tei index calculation.

To assess intraobserver variability, the right ventricular inflow blood pool Doppler measurements for 10% of the fetuses with HLHS and 10% of the control fetuses were repeated 1 month after the same observer completed the initial measurements. Additionally, the same subset of patients in each group had all measurements independently performed by a second observer. Each observer was blinded to the original measurements.

### Statistical Analysis

Data are expressed as mean ± SD and range. We used one-way analysis of variance with post hoc Tukey tests to compare the different variables across groups. Unpaired Student’s t-tests were used to compare the means between the groups.

### Table 1 Demographic data and results of sample population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal control subjects</th>
<th>Fetuses with HLHS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (wk)</td>
<td>21.6 ± 4.1 (13–39) (n = 78)</td>
<td>25.7 ± 6.2 (15–39) (n = 78)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>145.3 ± 7.7 (121–163) (n = 78)</td>
<td>139.5 ± 9.6 (118–162) (n = 78)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>LV morphology</td>
<td>NA</td>
<td>No visible LV: 36 Small LV without EFE: 15 Small LV with EFE: 27</td>
<td>NA</td>
</tr>
<tr>
<td>SDI</td>
<td>1.58 ± 0.29 (1.09–2.6) (n = 78)</td>
<td>1.89 ± 0.33 (1.19–2.76) (n = 78)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Indexed FT</td>
<td>0.39 ± 0.04 (0.28–0.48) (n = 78)</td>
<td>0.35 ± 0.04 (0.26–0.46) (n = 78)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Indexed ET</td>
<td>0.41 ± 0.03 (0.29–0.49) (n = 66)</td>
<td>0.4 ± 0.03 (0.32–0.47) (n = 55)</td>
<td>.30</td>
</tr>
<tr>
<td>Indexed ICT + IRT</td>
<td>0.21 ± 0.05 (0.12–0.35) (n = 66)</td>
<td>0.25 ± 0.05 (0.13–0.32) (n = 55)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Tissue Doppler SDI</td>
<td>1.66 ± 0.31 (0.92–2.37) (n = 66)</td>
<td>2.1 ± 0.57 (1.39–3.4) (n = 15)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.65 ± 0.09 (0.46–0.99) (n = 72)</td>
<td>0.66 ± 0.09 (0.45–0.87) (n = 55)</td>
<td>.95</td>
</tr>
<tr>
<td>E/e ratio</td>
<td>6.5 ± 1.5 (3.9–11.1) (n = 61)</td>
<td>8.15 ± 3.12 (3.5–11.5) (n = 6)</td>
<td>.26</td>
</tr>
<tr>
<td>Preload index</td>
<td>Not collected</td>
<td>0.5 ± 0.18 (0.09–0.93) (n = 47)</td>
<td>NA</td>
</tr>
<tr>
<td>Tei index</td>
<td>0.52 ± 0.16 (0.27–0.94) (n = 66)</td>
<td>0.62 ± 0.14 (0.31–0.9) (n = 55)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Indexed RV output (mL/kg/min)</td>
<td>Not collected</td>
<td>136.1 ± 44.5 (47.6–214.6) (n = 23)</td>
<td>NA</td>
</tr>
</tbody>
</table>

EFE, Endocardial fibroelastosis; NA, not applicable; RV, right ventricular.

Data are expressed as mean ± SD (range). SDI, indexed FT, indexed ET, indexed ICT + IRT, tissue Doppler SDI, E/A ratio, E/e ratio, preload index, and Tei index are ratios and thus are reported without units. Indexed ET and indexed ICT + IRT are reported for the fetuses in whom calculation of the Tei index was feasible. Comparison between the means was performed using unpaired Student’s t-tests.
subgroups of HLHS. We used multivariate regression to assess the contributions of different factors to the differences in SDI. Differences in preload index, E/A ratio, and E/e0 ratio between groups were assessed using unpaired Student’s t tests. We performed Pearson correlation tests to examine the relations between fetal SDI and preload index, Tei index, and E/A ratio to try to detect associations with these physiologic surrogates. For all significance testing, a difference was considered significant at \( P < .05 \).

For assessment of reproducibility, the intraobserver and interobserver variability for the blood pool–derived SDI was assessed using intra-class correlation coefficients (ICCs) and mean percentage differences. The mean percentage difference was calculated as the absolute value of the difference between the two repeated measurements, divided by the average of the two observations and expressed as a percentage.

Statistical analysis was performed using SPSS version 22 (IBM, Armonk, NY) and Stata version 13 (StataCorp LP, College Station, TX).

**RESULTS**

**Study Population and Effect of Heart Rate and Gestational Age**

The demographic properties of the patients and the control subjects are shown in Table 1. Although the gestational age was significantly different between the patients and the control subjects (25.7 ± 6.2 vs 21.6 ± 4.1 weeks, respectively, \( P < .001 \)), there was no correlation between gestational age and FT, ET, or SDI (Figure 2). The mean heart rate of the control group was significantly higher than that of the HLHS group (145.3 ± 7.7 vs 139.5 ± 9.6 beats/min, respectively, \( P < .001 \)), and there was a weak correlation between heart rate and SDI in both the control group (\( R = 0.25, P = .029 \)) and the HLHS group (\( R = 0.21, P = .06 \)) (Figure 3). We assessed the contribution of differences in gestational age and heart rate to the differences in SDI in a multivariate regression analysis model. The variables included in the model were heart rate and gestational age. The differences in SDI were not attributable to differences in gestational age (\( R^2 \) 95% CI, 0.002–0.03; \( P = .02 \)) and only slightly to differences in heart rate (\( R^2 \) 95% CI, 0.004 to 0.016 (\( P = .001 \)) for heart rate, and the \( R^2 \) 95% CI was 0.23 to 0.44 (\( P < .001 \)) for the variable HLHS versus controls. Thus, HLHS was the main contributor to the differences in SDI, with minimal contribution from heart rate and no contribution of gestational age.

Abnormal SDI in Fetuses with HLHS and Evolving HLHS Compared with Normal Control Fetuses

Fetuses with HLHS had statistically significantly higher SDI values than control fetuses (1.89 ± 0.33 vs 1.58 ± 0.29, respectively, \( P < .05 \)) (Table 1). Moreover, the post hoc Tukey test (Tables 2 and 3, Figure 4) showed that fetuses with HLHS with visible LVs had significantly higher SDI values than control subjects (\( P < .001 \)), while fetuses with HLHS without visible LVs demonstrated a trend toward higher SDI values that did not reach statistical significance (\( P = .08 \)).
Fetuses with HLHS with visible LVs, both without endocardial fibroelastosis and with endocardial fibroelastosis, had higher SDI values than control fetuses, but SDI was elevated to a lesser degree in fetuses with HLHS without visible LVs than control fetuses. The additional analysis of 10 patients with evolving HLHS demonstrated that SDI values were higher in this group than control subjects, similar to the findings in fetuses with HLHS with visible LVs. The model included FT and ICT + IRT. Only FT independently contributed to differences in SDI (R² = 0.97, P < .001). There was a positive correlation between the SDI and the Tei index (r = 0.58, P < .001). There was no correlation between FT indexed to heart rate or SDI and preload index (P = 0.65 and P = 0.59, respectively), right ventricular output (P = .66 and P = .67, respectively), or E/A ratio (P = .19 and P = .16, respectively).

Superiority of SDI to Tei Index in Detecting Abnormality

The SDI was more sensitive than the Tei index in detecting differences between different HLHS groups. Although the Tei index showed a difference between control subjects and all patients with HLHS (0.52 ± 0.16 vs 0.62 ± 0.14, respectively, P < .05), it was (unlike the SDI) unable to differentiate between the subtypes of HLHS with visible LV, HLHS without visible LV, and evolving HLHS (Table 3).

Other/Individual Time Intervals and Measures of Preload, Diastolic, and Global Function

Individual components of the SDI (FT, ET, and ICT + IRT), the Tei index, and surrogates of preload (preload index) and diastolic function (E/A ratio and E/e' ratio) in the HLHS and control groups are presented in Table 1. There was a significant difference in FT and EFE between different HLHS groups. Although the Tei index showed a difference between control subjects and all patients with HLHS (0.52 ± 0.16 vs 0.62 ± 0.14, respectively, P < .05), it was (unlike the SDI) unable to differentiate between the subtypes of HLHS with visible LV, HLHS without visible LV, and evolving HLHS (Table 3).

Measurement Variability

The intraobserver and interobserver variability for the blood pool–derived SDI was assessed by ICC and the mean percentage difference. The intraobserver ICCs were 0.96 and 0.9 for control subjects and fetuses with HLHS, respectively. The interobserver ICCs were 0.8 and
0.79 for control subjects and fetuses with HLHS, respectively. The intraobserver and interobserver variability using the mean percentage difference was 10.1% and 18.6%, respectively. The intraobserver and inter-observer variability for indexed FT using the mean percentage difference was acceptable at 6.1% and 10.8%, respectively.

**DISCUSSION**

Our results from measurement of SDI in fetuses with various morphologic subtypes of HLHS support the presence of abnormal right ventricular function in fetal life. As a group, the fetuses with HLHS in our study had shorter right ventricular FTs and higher SDI values than normal fetuses. Furthermore, we demonstrate that fetuses with HLHS with visible LVs had even shorter right ventricular FTs and higher SDI values compared with fetuses with HLHS without visible LVs. In summary, taken together, the SDI results were abnormal in all fetuses with HLHS and with evolving HLHS, with measurements modestly elevated if no LV was visible, moderately to severely elevated if the LV was visible, and worst if there was evidence of LV ischemia (endocardial fibroelastosis or severe aortic stenosis with LV dilation and dysfunction).

Friedberg and Silverman11 showed that diastolic time intervals are shorter in children with palliated HLHS and that systolic time intervals are longer. This pattern was further accentuated in the presence of right ventricular dysfunction and changed with different stages of palliation. This suggests that time intervals are dependent on the loading conditions as well and are likely not purely a measure of myocardial function. Because of these prior reports in postnatal patients, we attempted to further investigate the individual physiological causes that may have brought about our findings in our prenatal patients. As in prior studies, we found signs of elevated right atrial pressure in the form of elevated preload index in some patients.11 However, we found no consistent correlation between the preload index and the SDI. In fact, 23 of the fetuses with HLHS had fused E and A waves, which may be indicative of diastolic dysfunction, rather than increased preload in the face of slightly lower heart rate than normal (which should increase FT and accentuate the difference between the E and A peaks, rather than causing them to fuse). We also found significantly elevated Tei indices in the HLHS group with normal ETs. This is a further indicator of the presence of diastolic dysfunction. The Tei index in our cohort was not different between the HLHS subgroups with and without visible LVs. This is in concordance with previous studies that showed no difference in the Tei index between the different HLHS subtypes.15,16 Additionally, the E/A and E/e' ratios were not as discriminating in our cohort as the SDI. Thus, the SDI may be more sensitive than the E/A ratio, E/e' ratio, and Tei index in detecting subtle abnormalities of cardiac function.

Our work contributes to that of multiple investigators who have shown the presence of abnormal cardiac mechanics and time intervals in fetuses with HLHS.4,5,7 Natarajan et al.5 found that fetuses with morphologic LVs and endocardial fibroelastosis had lower E/A ratios, higher E/e' ratios, and higher Tei indices measured by tissue Doppler than controls. Similarly, Szawast et al.13 showed that fetuses with HLHS had preserved systolic performance and mainly diastolic dysfunction. Their cohort did not show differences between the presence and absence of a morphologic LV. This may be attributed to the use of the Tei index as the marker of diastolic dysfunction in the presence of normal systolic performance. The SDI incorporates more of diastole and thus may be a more powerful tool in detecting diastolic dysfunction. Conversely, our data do not agree with those of Brooks et al.,4 who showed no difference in the SDI between fetuses with HLHS and control subjects. The difference in results is likely attributable to the difference in populations: only 27% of the fetuses in Brooks et al.'s study had mitral stenosis, while in our cohort, 62% had mitral stenosis and morphologic LVs.

**Clinical Implications**

Some investigators have reported worse outcomes in patients with HLHS with morphologic LVs,17,18 whereas other investigators could not replicate this finding.19,20 The impact of a morphologic LV on right ventricular function in HLHS has been the topic of much research. Although systolic function does not appear to be affected,13,15,21 there is evidence that diastolic function is affected in older postnatal patients. Schlangen et al.21 demonstrated increased right ventricular myocardial stiffness in patients with HLHS with larger left ventricular area using conductance catheters. Furthermore, the presence of an LV clearly affects myocardial mechanics when evaluated by two-dimensional speckle-tracking.22,23 There is decreased strain and strain rate in the region of the interventricular septum and more dyssynchrony between the single right ventricular segments.22 Histologic myocardial necrosis, calcification, and interstitial fibrosis are more commonly seen in patients with HLHS in the presence of an LV.23 Our work suggests that these changes begin in fetal life in some patients.

**Limitations**

Our study was limited in that it was a retrospective study. The absence of an invasive gold standard for the measurement of diastolic function, preload, and afterload in fetuses makes it difficult to draw conclusions on the separate effect of each factor on the SDI. Additionally, our sample size did not allow us to correlate between the SDI and the long-term outcome of ventricular function or to detect the specific effects of endocardial fibroelastosis on diastolic time. In calculation of the Tei index, the individual isovolumic times were not measured in this cohort but were calculated using the equation isovolumic time = cycle length – FT – ET. The Tei index and the SDI thus share two measured parameters: FT and cycle length. This may confound the results of the correlation that we detected between the two indices.

There was acceptable but not negligible interobserver variability using the SDI. We attribute this to the mathematical nature of the equation used. Any variability detected in the measure is doubled, as shortening of FT will lead to prolongation of cycle length – FT by the same magnitude.

**CONCLUSION**

Fetuses with HLHS have abnormally high SDI values due primarily to shorter FTs. Patients with HLHS with morphologically visible LVs have even higher SDI values and shorter FTs than those with no discernible LVs. The systolic-to-diastolic time ratio is currently a research tool for the assessment of ventricular dysfunction in fetuses but awaits validation to be incorporated into clinical use.

**REFERENCES**


