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′ 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 2016;29:143-9.)

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,

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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

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 curvilinear 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.[12] 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.

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

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 pulsed-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.[13] To assess for diastolic dysfunction, peak tricuspid inflow velocities (peak E and peak A) and peak lateral tricuspid annular early diastolic tissue velocity (e′) 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

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