Prenatal Diagnosis Improves the Postnatal Cardiac Function in a Population-Based Cohort of Infants with Hypoplastic Left Heart Syndrome

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Background: Prenatal diagnosis of hypoplastic left heart syndrome (HLHS) enables planning of perinatal care and is known to be associated with more stable preoperative hemodynamics. The impact on postnatal myocardial function is poorly known. The aim of this study was to determine the impact of prenatal diagnosis of HLHS on postnatal myocardial function.

Methods: A consecutively encountered cohort of 66 infants with HLHS born between 2003 and 2010 in Finland was retrospectively reviewed. Twenty-five infants had prenatal diagnoses. Postnatal global and segmental right ventricular fractional area change, strain rate, and myocardial velocity were analyzed from the apical four-chamber view using Velocity Vector Imaging. Preoperative hemodynamic status and end-organ damage measurements were the lowest arterial pH, highest lactate, alanine aminotransferase, and creatinine. Early mortality was studied until 30 days after Norwood procedure.

Results: Prenatally diagnosed infants had better cardiac function (fractional area change, 27.9 ± 7.4% vs 21.1 ± 6.3%, $P = .0004$; strain rate, 1.1 ± 0.6/1.3 ± 1.0 vs 0.7 ± 0.2/0.7 ± 0.3 1/sec, $P = .004/.003$; myocardial velocity, 1.6 ± 0.6/2.0 ± 1.1 vs 1.3 ± 0.4/1.4 ± 0.4 cm/sec, $P = .0035/.0009$). Mechanical dyssynchrony was similar in both groups ($P > .30$). Infants diagnosed prenatally had less acidosis (pH = 7.30 vs 7.25, $P = .005$) and end-organ dysfunction (alanine aminotransferase, 33 ± 38 vs 139 ± 174 U/L, $P = .0001$; creatinine, 78 ± 18 vs 81 ± 44 mmol/L, $P = .05$). No deaths occurred among the prenatally diagnosed infants, but four deaths were recorded among postnatally diagnosed infants ($P = .15$).

Conclusions: A prenatal diagnosis of HLHS is associated with improved postnatal right ventricular function, reduced metabolic acidosis, and end-organ dysfunction. (J Am Soc Echocardiogr 2013;26:1073-9.)

Keywords: Hypoplastic left heart syndrome, Prenatal diagnosis, Cardiac function, Velocity Vector Imaging

Hypoplastic left heart syndrome (HLHS) is characterized by a small left ventricle incapable of maintaining systemic cardiac output. HLHS can be identified using four-chamber screening and is one of the most common severe congenital cardiac defects diagnosed prenatally.[1-3] Prenatal diagnosis of this disorder enables planning for birth with optimized postnatal stabilization of these affected infants. Prenatally diagnosed infants have been shown to have superior postnatal hemodynamics and less severe acidosis and organ failure compared with postnatally diagnosed infants.[4-8] Subjective observations have also suggested that a prenatal diagnosis might improve myocardial function in the neonatal period, but no quantitative evaluation of right ventricular (RV) function in this patient population has been reported thus far.

Vector Velocity Imaging (VVI; Siemens Healthcare, Erlangen, Germany) measures myocardial velocities, myocardial deformation, and mechanical synchrony. VVI is independent of the angle of insonation and the geometry of the ventricle[9,10] and is an important tool for measuring both myocardial function and mechanical synchrony in patients with HLHS.[11-17] The accuracy of subjective evaluation of myocardial function in comparison with magnetic resonance imaging has been poor in patients with HLHS.[18]

The aim of the present study was to determine whether prenatal diagnosis of HLHS improves postnatal quantitative global or

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Abbreviations

FAC = Fractional area change

HLHS = Hypoplastic left heart syndrome

MA/AA = Mitral and aortic atresia

MS/AA = Mitral stenosis and aortic atresia

MS/AS = Mitral and aortic stenosis

RV = Right ventricular

VVI = Vector Velocity Imaging

segmental RV myocardial function of affected infants and whether prenatal diagnosis has any impact on early (<30-day) mortality outcomes after a Norwood operation in a country (Finland) where all cardiac surgeries have been centralized.

METHODS

This retrospective, population-based study involved a cohort of 66 consecutive infants with HLHS born in Finland between January 2003 and December 2010. These patients were divided into two groups on the basis of whether they had prenatal or postnatal diagnoses of HLHS. All the infants in our study cohort who had prenatal diagnosis were delivered at the University Hospital of Helsinki. Prostaglandin infusion was started immediately after birth before admission to the intensive care unit. Respiratory support and inotropes were not routinely started. Infants who had not received intrauterine diagnoses were born in delivery hospitals around Finland and were transported to Helsinki University Hospital after diagnosis and stabilization. The mean transportation distance from delivery hospital to operative center was 225 ± 202 km.

Patients with major extracardiac defects or chromosomal abnormalities were excluded from our study cohort. None of the infants had significant atrial septal restriction needing postnatal septostomy. Assessment of restrictive atrial septum was based on pulmonary venous Doppler prenatally and anatomy of the atrial septum and clinical picture postnatally. Clinical data were collected from medical records. Preoperative hemodynamic status was assessed by measurement of the lowest arterial pH and highest lactate level. Kidney function was assessed by assessing the highest preoperative creatinine and liver function through the maximum alanine aminotransferase concentrations. The study was approved by the hospital research committee.

Cardiac Evaluations

Cardiac function was retrospectively evaluated in 59 infants using an Xcelera (Philips Medical Systems, Andover, MA) database of ultrasound images. The first detailed diagnostic echocardiography was performed immediately after the infant was admitted to our unit. The images analyzed in this study were obtained later at the time of preoperative functional assessment, performed at a median age of 1 day (range, 0–12 days) for prenatally diagnosed infants and 2 days (range, 0–8 days) for postnatally diagnosed infants ($P = .30$). These images were recorded in accordance with a standardized ultrasound protocol at the time of the preoperative evaluation after stabilization at our institution. Seven infants were excluded from the VVI analysis because their postnatal cardiac ultrasound was missing or of insufficient quality for VVI analysis: one from the prenatal and six from the postnatal diagnosis group ($P = .24$). Aortic, pulmonary, mitral, and tricuspid valve dimensions were measured by one of the authors (H.K.M.) according to published recommendations.[19] The severity of tricuspid and pulmonary valve insufficiency was classified as hemodynamically significant (moderate or severe) or insignificant (none, trivial, or mild), taking into account the vena contracta width and the area of color Doppler flow. All infants were divided into three categories according to the morphology of the mitral and aortic valves: mitral and aortic stenosis (MS/AS), mitral stenosis and aortic atresia (MS/AA), and mitral and aortic atresia (MA/AA). For functional analysis, cardiac ultrasound data were transferred in a standard Digital Imaging and Communications in Medicine format to the VVI analysis program (syngo USWP 3.0; Siemens Healthcare). Originally, the images were acquired at a frame rate of 30 to 95 Hz, although digital storage reduces the effective frame rate to 30 Hz. The data were then stored in a research archive with code numbers. All cardiac functional analyses were performed by one of the authors (H.K.M.), who was blinded to the clinical presentation and outcomes of the patients with HLHS.

RV fractional area change (FAC) values, global and segmental myocardial velocities and strain rates, and mechanical synchrony were analyzed from the apical four-chamber view using the VVI technique. Manual tracing of the RV subendocardial surface was performed in a single still frame in midsystole. Tracing began at the edge of the tricuspid valve annulus, extended to the apex of the ventricle without incorporation of the papillary muscle complex, and returned basally to the other edge of the tricuspid valve annulus. Velocity vectors were then automatically calculated for each frame of the cardiac cycle by the VVI algorithm and displayed for the complete loop (Figure 1). The software divided the right ventricle automatically into six segments for regional and synchrony analysis. Tracings were accepted only if the subendocardial border was correctly followed throughout the whole cardiac cycle. If necessary, individual regions of the border were adjusted until the border was correctly tracked for each frame. Left ventricular end-diastolic volume was estimated from the apical four-chamber view using the Auto Left Heart program (syngo USWP 3.0). To minimize intraobserver variability, all measurements were repeated three times, and the mean value was used in the analyses. Mechanical synchrony was measured as the time to peak strain rate and velocity values from the beginning of the QRS complex in all six segments. The degree of mechanical dyssynchrony was quantified as the standard deviation of these values among six different cardiac segments. For intraobserver and interobserver variability, 10 randomly selected studies were analyzed twice by the same investigator (H.K.M.) 4 weeks later and once by another investigator (T.H.O.).

Statistical Analysis

Clinical demographics and global cardiac functional data for the study groups were compared using *t* tests or Mann-Whitney *U* test for continuous parameters, Cochran-Mantel-Haenszel tests for noncontinuous parameters, and Fisher's exact tests or Pearson's χ^2 tests for frequencies. Segmental cardiac analyses were evaluated statistically by repeated-measures analysis of variance using the segment as the repeating factor. In case of a significant segment–to–study group interaction, post hoc analyses were performed within segments using Bonferroni-corrected *t* tests between study groups. Logarithmic transformation was used to normalize skewed distributions for the *t* tests and repeated-measures analysis of variance models. Correlations (*R* values) were calculated using Pearson's correlation coefficient for normally distributed data and Spearman's rank correlation coefficient for abnormally distributed data. Intraobserver and interobserver reproducibility was assessed for 10 randomly selected patients for FAC, velocities, and strain rate. Reproducibility was assessed from the corresponding repeated measures using intraclass correlation coefficients with 95% confidence intervals. For global variables, reproducibility was good (intraclass correlation coefficient > 0.83)

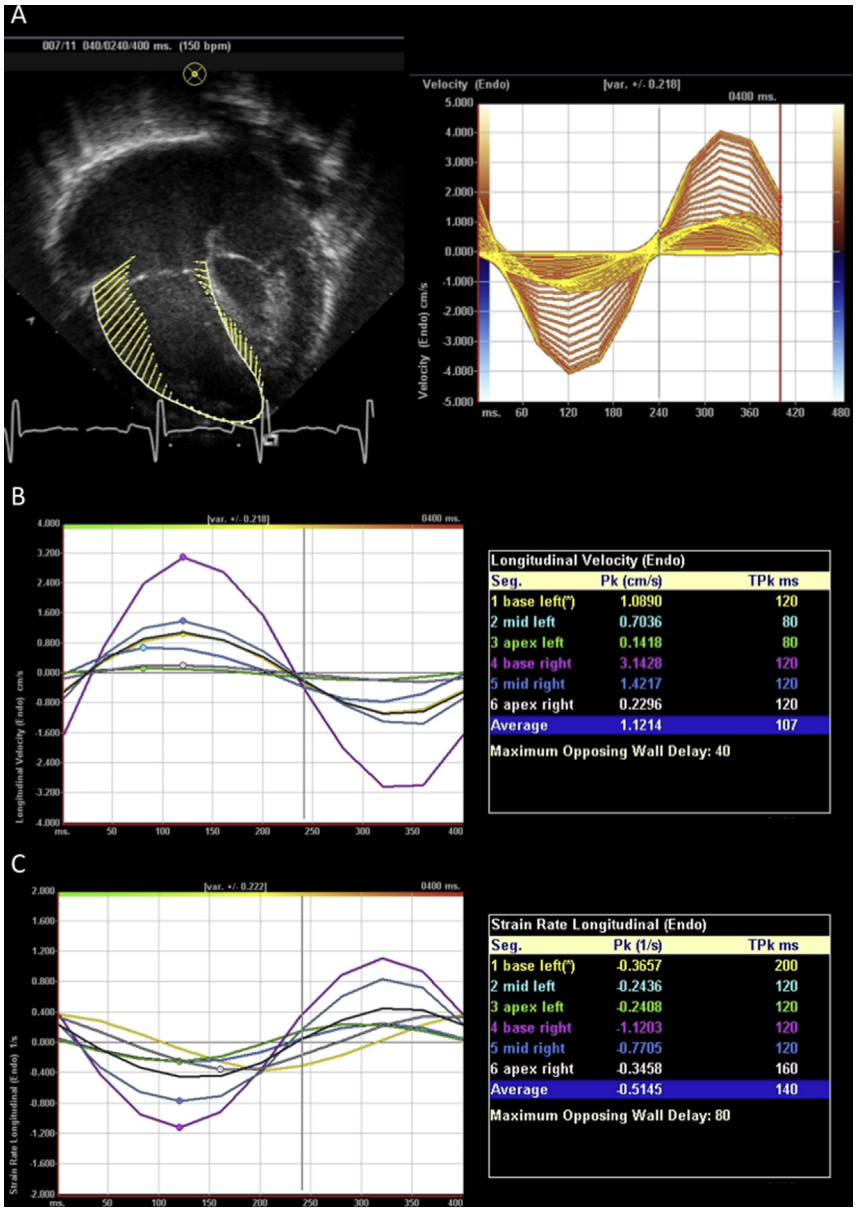

Figure 1 **(A)** Tracing of velocity vectors during systole. Segmental myocardial velocities **(B)** and strain rate **(C)** among the six segments of the right ventricle analyzed (*color coded*) are displayed as a function of time. In the tables, peak longitudinal velocity and strain rate are given for six segments of the right ventricle and the total average value.

(Figure 2). A P value $< .05$ was used to define significance. SPSS for Windows version 19.0 (SPSS, Inc./IBM Corporation, Somers, NY) and SAS version 9.2 (SAS Institute Inc., Cary, NC) were used to perform statistical analyses.

RESULTS

Of the 66 infants with HLHS, 25 (38%) had received prenatal diagnoses, and 41 (62%) were postnatally diagnosed. The prevalence of a prenatal diagnosis of HLHS increased during the study era (from 22% to 75%). There were no significant differences between the clinical demographics of the study groups and the morphology of HLHS (Table 1). For the postnatally diagnosed infants, the median time lag from delivery to diagnosis was 1 day (range, 0–7 days). Oxygen saturation screening for the detection of cardiac defects was started after 2008 at most delivery hospitals in Finland. Early oxygen saturation screening was performed for eight postnatally diagnosed infants. Postductal saturation in oxygen saturation screening was initially normal (>95%) for two infants (25%) with postnatal diagnoses of HLHS, and in both of these neonates, saturation became abnormal (<95%) before discharge. The majority, 33 of 41 (80%), of postnatally diagnosed infants did not undergo oxygen saturation screening. Five had delayed diagnoses >72 hours after birth. There was no delayed diagnosis among infants with oxygen saturation screening.

Laboratory Values

Less preoperative acidosis and lower peak concentrations of creatinine and alanine aminotransferase suggesting less end-organ dysfunction were observed in the prenatally diagnosed compared with the

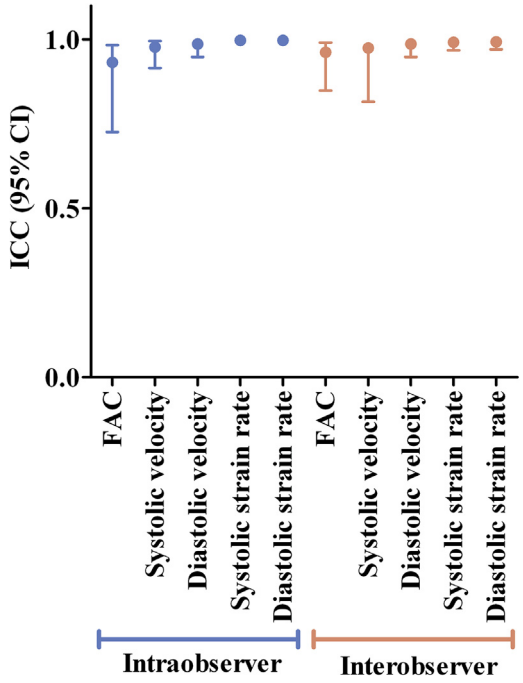

Figure 2 Intraobserver and interobserver reproducibility of FAC, velocities, and strain rate represented as intraclass correlation coefficients (ICCs) and 95% confidence intervals (CIs).

postnatally diagnosed infants with HLHS (Table 1). No differences in the highest recorded lactate concentrations were detected between the study groups, although lactate values were above the normal range in both groups.

Impact of Intrauterine Diagnosis on Ventricular Function

Global RV function, measured using FAC, was higher in the prenatally compared with the postnatally diagnosed patients with HLHS (27.9 ± 7.4% vs 21.1 ± 6.3%, respectively, $P = .0004$). The global strain rate, in both systole and diastole, was also higher in the prenatally diagnosed group (1.1 ± 0.6/1.3 ± 1.0 vs 0.7 ± 0.2/0.7 ± 0.3 1/sec, $P = .004/.003$, respectively), as was global myocardial velocity (1.6 ± 0.6/2.0 ± 1.1 vs 1.3 ± 0.4/1.4 ± 0.4 cm/sec, $P = .0035/.0009$, respectively). By segmental analysis, patients with prenatal diagnoses had better myocardial function in all six segments, as measured by strain rate and velocity in both systole and diastole (Figure 3). Mechanical synchrony measurements via the mean standard deviation of the time to peak strain rate (27.4 ± 15.3 vs 32.5 ± 17.3 ms, $P = .30$) or to peak myocardial velocity (28.6 ± 24.4 vs 31.1 ± 23.2 ms, $P = .70$) were found not to differ between the study groups. No correlation was found between mechanical synchrony and myocardial function. Infants with early postnatal diagnosis (<3 days) tended to have better myocardial function than those with delayed postnatal diagnosis (>3 days) (Figure 4).

The incidence of significant tricuspid valve insufficiency was similar in both study groups (12.0% vs 27.5%, $P = .20$), and its severity was not related to myocardial function or mechanical synchrony. There was a weak correlation between left ventricular size and FAC ($R = -0.30$, $P = .014$). The size of the left ventricle and the diameter of the ascending aorta were not correlated with global or segmental myocardial strain rate or velocity measurements ($R < 0.20$, $P > .50$). HLHS morphology category MS/AS had lower FAC compared with categories MS/AA and MA/AA (20.8 ± 6.5% vs 27.1 ± 6.8% vs 25.4 ± 8.1%, $P = .013$, respectively). Morphology category had no impact on myocardial strain rate or velocity ($P > .40$).

Early (<30-Day) Postoperative Mortality

Compassionate care was chosen by the parents for one postnatally diagnosed infant, who died at 7 days. This infant was excluded from the early mortality analysis. There were no early deaths among the prenatally diagnosed infants. Early deaths, however, occurred in four infants diagnosed postnatally (10%; $P = .15$). Deaths occurred in 2003, 2005, 2008, and 2009. There was no significant difference in preoperative FAC between the infants who died ($n = 3$; FAC, 18.0%) and survivors ($n = 53$; FAC, 24%) ($P = .10$). One postnatally diagnosed infant died preoperatively because of severe myocardial dysfunction and hemodynamic compromise (morphology category MA/AA; FAC, 10.3%). All other infants ($n = 64$) underwent Norwood procedures at a median age of 7.0 days (range, 3–17 days). Infants with prenatal diagnosis were operated earlier than infants with postnatal diagnosis (Table 1). The only operative factor variable was the type of shunt operation, with no difference between the study groups (Table 1). One infant died during surgery (morphology category MA/AA; preoperative FAC, 25%). Two infants died postoperatively suddenly, with no obvious explanation at autopsy (both in morphology category MA/AS; preoperative FAC, 12.5% and 24%). None of the early (<30-day) deaths were related to shunt occlusion in postmortem examinations. There was no difference in the size of the aorta between deceased infants and survivors (3.7 ± 1.4 vs 3.8 ± 2.2 mm, $P = .90$).

In the Norwood operation, the mean perfusion time was shorter in infants who died postoperatively ($n = 3$; 70.0 ± 48.8 min) compared with survivors ($n = 55$; 170.3 ± 38.7 min) ($P < .001$). This may have been related to the more frequent use of Blalock-Taussig shunts, associated with shorter operative times, at our institution, which was more common in infants who died than in survivors (66.7% vs 35%, $P = .30$).

DISCUSSION

This is the first study to quantitatively demonstrate the benefits of a prenatal diagnosis of HLHS on the postnatal RV myocardial function of affected infants. Global RV systolic function, measured by FAC, was significantly better in infants with prenatal diagnoses of HLHS than in those with postnatal diagnoses. Systolic and diastolic global strain rate and myocardial velocity values were also higher in prenatally diagnosed infants. On segmental analysis, differences between the prenatal and postnatal diagnosis study groups were evident in all cardiac segments. These results are consistent with previous subjective observations suggesting that prenatal diagnosis of HLHS leads to improved ventricular function outcomes.[4] Infants diagnosed after 3 days of age had a tendency toward myocardial dysfunction compared with those with early postnatal diagnosis. Oxygen saturation screening did not have an impact on myocardial function, but there was no delayed diagnosis in infants with oxygen saturation screening.

Because the prenatal diagnosis of HLHS enables careful planning of delivery, with optimized early postnatal stabilization and treatment, the improvements in global myocardial function are most likely due to more stable postnatal hemodynamics.[4-8] The infants with prenatal diagnoses of HLHS were delivered at the operative

Table 1 Clinical characteristics of the 66 patients with HLHS divided into two study groups on the basis of whether a prenatal diagnosis had occurred

Variable	Prenatal diagnosis (n = 25)	Postnatal diagnosis (n = 41)	P
Birth data			
Maternal age (y)	29 (22–36)	27 (20–40)	.70
Gestational weeks at birth (wk)	39 (37–41)	40 (36–42)	.80
Male (%)	13 (52%)	25 (61%)	.50*
Birth weight (g)	3,440 (2,690–4,300)	3,520 (2,220–4,572)	.70
Apgar score (points)	9 (7–9)	9 (6–10)	.70†
Morphology group			.20‡
MS/AS	8 (32%)	19 (48%)	
MS/AA	5 (20%)	10 (25%)	
MA/AA	12 (48%)	11 (28%)	
Laboratory values			
Lowest arterial pH	7.30 ± 0.04	7.25 ± 0.09	.005
Highest lactate (mmol/L)	3.5 ± 1.9	3.8 ± 3.9	.10
Highest creatinine (μmol/L)	78 ± 18	81 ± 44	.05
Highest alanine aminotransferase (U/L)	33 ± 38	139 ± 174	.0001
Operative management			
Blalock-Taussig shunt (%)	7 (28%)	16 (49%)	.40*
Sano shunt (%)	18 (72%)	34 (51%)	.40*
Operative age (d)	6 (3–9)	7 (3–17)	.008
Early (<30-d) postoperative mortality	0 (0%)	4 (10%)	.15*

Data are expressed as median (range), number (percentage), or mean ± SD. P values are from t tests except as indicated.
*Fisher's exact test.
†Cochran-Mantel-Haenszel test.
‡Pearson's χ^2 test.

center, thus avoiding the need for transportation. In these infants, prostaglandin infusion for maintaining ductal patency was started immediately after birth to avoid ductal constriction. This may be one of the reasons for the benefits of prenatal diagnosis. In postnatally diagnosed infants, ductal constriction may have taken place, leading to hemodynamic compromise. Postnatally diagnosed infants were also routinely intubated for transportation because of the risk for apnea caused by prostaglandin therapy. Thus, additional problems during transportation such as hyperventilation or hypoventilation may have also affected the hemodynamic stability of postnatally diagnosed infants. In our present study cohort, all of the infants with HLHS had lactate concentrations above the normal range.[20] This probably reflected the hemodynamic vulnerability of these infants during the transition period rather than birth distress, because the Apgar scores were normal in both groups. Our observations of higher creatinine and alanine aminotransferase concentrations are in keeping with potential end-organ damage related to poor systemic perfusion among the neonates who were diagnosed only postnatally and are consistent with earlier reports.[4-8] It is of note that in the present study, myocardial function analysis was performed after early stabilization at the average age of 2 days. If VVI measurements had been performed immediately after admission, the differences between prenatally and postnatally diagnosed infants could very well have been more pronounced.

In healthy infants with no congenital heart defects, birth asphyxia leads to impaired global left ventricular function[21,22] when evaluated using strain and strain rate analysis. The impact of compromised circulatory and possible coronary perfusion in infants with HLHS with a single systemic right ventricle is poorly understood during the early transitional period. In the present study, the hemodynamic benefits of prenatal diagnosis on RV function were global (i.e., there was no one area that was more sensitive than any other). Infants with HLHS have been shown to have mechanical dyssynchrony unrelated to myocardial function.[15,16] Similarly, in the present study, myocardial dysfunction was not associated with mechanical dyssynchrony. The impact of preoperative RV dysfunction on long-term myocardial function after staged single-ventricle palliation requires further exploration.

Impaired myocardial function is a risk factor for poor survival after a Norwood procedure and during the interstage period in HLHS infants.[1,4,23-28] In agreement, we found no early deaths in our present cohort of prenatally diagnosed HLHS infants but a 10% mortality rate in their postnatally diagnosed counterparts. Our inability to show a statistical difference in early mortality was likely due to small numbers of affected patients in the two groups as well as to low overall mortality. Although there was no statistical difference in myocardial function between survivors and infants who died, two of the four infants who died had poor myocardial function preoperatively in the present study. Therefore, poor myocardial function before the Norwood operation can be a risk factor for perioperative mortality.[29] The prenatal diagnosis of HLHS is likely to have a strong impact on the preoperative state and early postoperative outcomes of these infants after a Norwood operation, particularly in a country such as Finland, where cardiac operations have been centralized. Prenatal diagnosis enables optimal stabilization and early treatment after delivery and preventing stress of transportation in this hemodynamically vulnerable patient population.

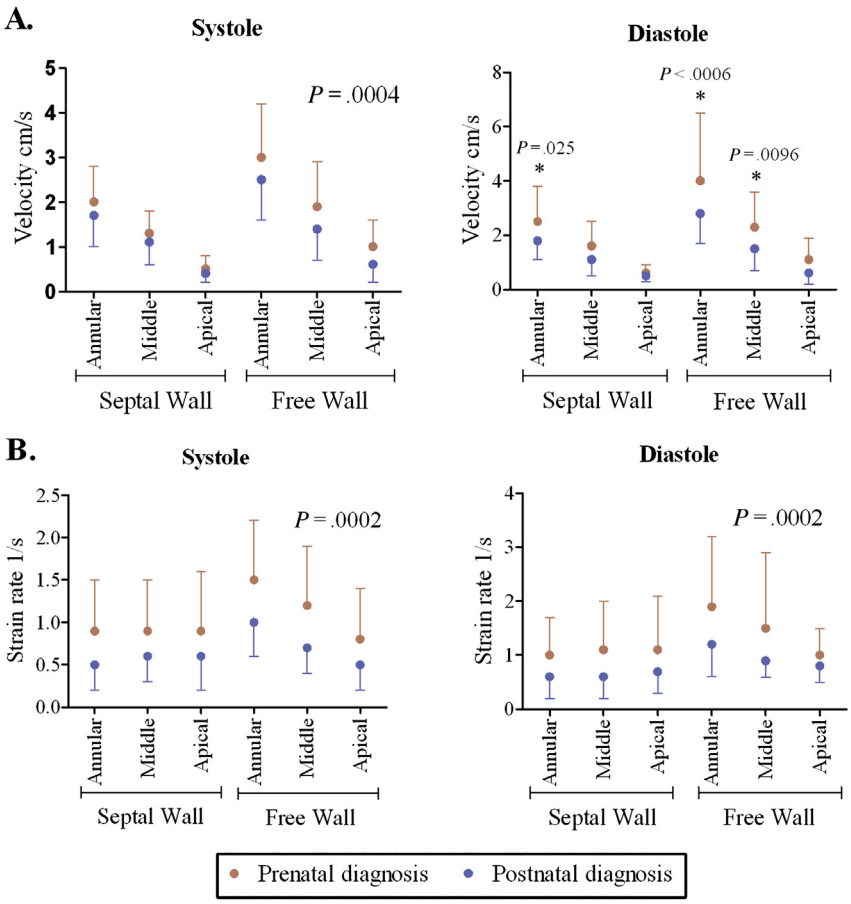

Figure 3 Segmental myocardial function measurements presented as mean ± SD of **(A)** myocardial velocities and **(B)** strain rates in prenatally and postnatally diagnosed infants. Systolic velocity and systolic and diastolic strain rates were significantly higher in all cardiac segments in infants prenatally diagnosed with HLHS (*P* values from repeated-measures analysis of variance). For diastolic velocities, differences were significant in areas marked by asterisks (segment–to–study group interaction, $P < .0001$; pairwise *P* values from Bonferroni-corrected *t* tests).

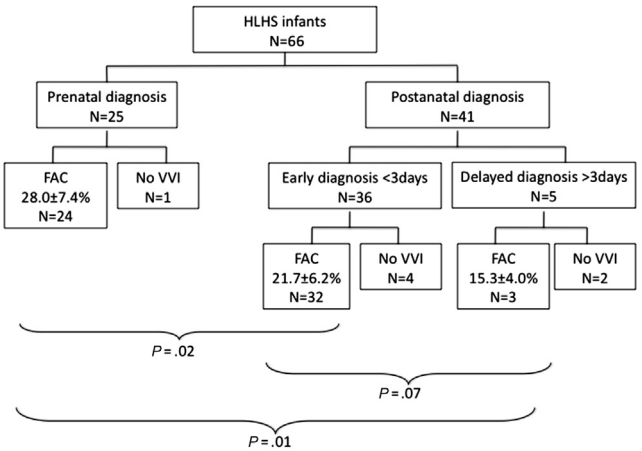

Figure 4 Impact of timing of diagnosis of HLHS on infants' myocardial function.

Study Limitations

This study was limited by its retrospective design. Additionally, the small size of the study cohort may have limited our ability to detect certain differences between the study groups.

CONCLUSIONS

A prenatal diagnosis of HLHS improves postnatal RV function and is associated with less metabolic acidosis and less end-organ dysfunction. Because the prenatal diagnosis of HLHS enables preplanning for delivery, it provides an opportunity to avoid early hemodynamic issues during the fragile transitional period, especially in countries where the distances to operative centers may be a factor. However, the long-term benefits of a prenatal diagnosis of HLHS on myocardial function or survival remain unknown.

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