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Biventricular function on Early Echocardiograms in Neonatal Hypoxic-ischemic Encephalopathy

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Abbreviations:

ECHO: Echocardiogram

ECMO: extracorporeal membrane oxygenator

EIs: eccentricity index in systole

EId: eccentricity index in diastole

LVO: left ventricular output

MPI: myocardial performance index

PPHN: Persistent pulmonary hypertension of the newborn

RVO: right ventricular output

S/D: Ratio of systolic to diastolic durations

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ABSTRACT:

Aim: To compare early (<24 hours) echocardiograms (ECHOs) in infants with perinatal hypoxic-ischemic encephalopathy (HIE) undergoing a)therapeutic hypothermia (TH) b) normothermia and c) normal controls.

Methods: This was a single center retrospective review of clinical early ECHOs of term infants with moderate or severe HIE and controls (with a normal ECHO <72 hours of age).

Right (RVO) and left ventricular output (LVO), RV and LV myocardial performance index (MPI), systolic to diastolic duration ratio (S/D) and eccentricity indices (EI) in systole and diastole were compared using ANOVA.

Results: Among infants with HIE (n=56, 38 in the TH and 18 in normothermia groups), 14 (25%) infants died and 42 survived. Significantly elevated biventricular MPI, lower RVO and LVO and pulmonary hypertension (abnormal EI, higher RV S/D and bidirectional or right-to-left ductal shunt) were found in groups with HIE, compared to controls (n=35). LV MPI was lower in HIE-TH, compared to the HIE-normothermia group. Infants with HIE who died (n=14) had a significantly lower EId [0.77 (0.09) vs. 0.83 (0.08), p=0.021] compared to survivors (n=42).

Conclusion: Infants with perinatal HIE have ventricular dysfunction; those who died had significantly lower EId than survivors; this association needs to be further validated.

Key Notes:

- Limited data suggest decreased cardiac output in infants with perinatal hypoxic-ischemic encephalopathy during therapeutic hypothermia.
- We compared early (<24 hours) echocardiogram measures in groups of infants with hypoxic-ischemic encephalopathy undergoing a)therapeutic hypothermia (TH) b) normothermia and c) normal controls and evaluated their association with death.
- Infants with perinatal HIE have profound cardiac dysfunction, compared to controls. Those who died had significantly lower eccentricity index in diastole.

The incidence of neonatal hypoxic-ischemic encephalopathy (HIE) due to asphyxia is 1-4/1,000 live births in the developed world (1). HIE is the fifth commonest cause of death in children below 5 years and accounts for 23% of all neonatal deaths worldwide each year (2). The Cochrane meta-analysis of randomized controlled trials on therapeutic hypothermia (TH) in HIE demonstrates a beneficial effect, with a reduction in mortality or major neurodevelopmental disability at 18 months of age (RR 0.76; 95% C.I. 0.65-0.89) (3). Despite this, mortality remains significant at 26% (4). Cardiac dysfunction may be a primary cause of death in this population.

The major randomized controlled trials of TH in HIE have reported that the majority of infants have hypotension during TH (5-7). In the National Institute of Child Health and Human Development Neonatal Research Network TH trial, 59% of infants required pressor support at any of 4 time points until 72 hours and 19% were on pressor support throughout the 72 hours of TH (5). The reported rates of hypotension and severe hypotension were 55% and 3% in cooled infants in the CoolCap study (6). In the Total Body Hypothermia for Neonatal Encephalopathy Trial, persistent hypotension, defined as mean BP < 40 mm Hg was noted in 77% of cooled infants (7). In the Infant Cooling Evaluation trial of 221 infants, hypotension requiring inotropes was noted in 46% of infants (8). In small studies, up to 60-80% of neonates with HIE have cardiac dysfunction on echocardiograms (ECHOs), compared to controls (9-13). The few studies which have evaluated ECHOs of infants with HIE undergoing TH have demonstrated a decrease in cardiac output (CO), heart rate (HR) and stroke volume during TH with recovery following rewarming (14-17). In the current study, we sought to compare multiple early (within 24 hours of age) ECHO measures of biventricular function in groups of infants with HIE undergoing a) TH or b) normothermia and c) normal controls and to evaluate their association, if any, with death.

PATIENTS AND METHODS:

This was a retrospective review of ECHOs performed for clinical indications at < 24 hours of age in term or late preterm (≥ 36 weeks gestational age) infants with moderate or severe HIE and admitted to the Neonatal Intensive Care Units (NICUs) at Children's Hospital of Michigan or Hutzel Women's Hospital between July 2002 and December 2012. Study infants were identified from the NICU database using "HIE (diagnosis) and ECHO (Procedure)" as search words. The study was approved by the Institutional Review Board of Wayne State University as was waiver of parental consent. Moderate or severe HIE was defined using NICHD screening criteria along with moderate or severe encephalopathy on neurologic examination (modified Sarnat staging) or seizures (5). At our center, infants with moderate or severe HIE have received whole body TH to 33.5^0C for 72 hours with the Cincinnati Subzero Hypothermia system initiated within 6 hours of age since 2006. Rewarming is done at 0.5^0 C per hour until the esophageal temperature is ≥ 36.5^0 C for 4 hours. Healthy controls were identified from the ECHO database as having normal ECHOs within 72 hours of age for evaluation of a murmur. Infants with major congenital or chromosomal abnormalities, severe growth restriction (≤ 1800gm birth weight), moribund infants in whom further aggressive treatment was limited and congenital heart disease other than a ventricular septal defect, patent foramen ovale or patent ductus arteriosus (PDA) were excluded.

ECHOs were performed using neonatal transducers on the Philips machine and reviewed by a single pediatric cardiologist (SA), who was blinded to clinical details. Each ECHO included M-Mode, 2 dimensional (subcostal, apical, left parasternal and suprasternal notch views), Doppler and Tissue Doppler imaging. The following ECHO functional measurements were performed offline:

A) Systolic function:

1. ***LV and RV output (LVO and RVO):*** Aortic and pulmonary valve annulus diameters and velocity time integral (VTI) were measured from parasternal long-axis and apical 5-chamber views respectively on Doppler ultrasound (18). LVO and RVO were calculated using standard formulae. HR was taken as the average of 3 readings during the ECHO.
2. ***Fractional Shortening (FS)*** was obtained on M-mode imaging as the ratio of the difference between the LV end-diastolic and end-systolic diameters to the LV end-diastolic diameter (18). FS has limitations in neonates because of high right sided pressures and reduced septal motion (19,20).

B) RV and LV Global myocardial function:

1. ***LV and RV MPI:*** were assessed by dividing the sum of isovolumic contraction and relaxation times by the ejection time and standard formula (21). MPI is inversely related to myocardial function and an increase in MPI indicates impaired global myocardial function. It is independent of HR and blood pressure, relatively load-independent and is unaffected by angle insonation or PDA.
2. ***RV S/D*** ratio was measured offline in triplicate from the best Doppler signal of tricuspid regurgitation (TR) on either apical 4-chamber view or parasternal long axis view. The systolic duration was calculated from the onset to the termination of TR and diastolic duration as the time between two jets of TR (22, 23).

***D)* PDA:** A high parasternal ductal view was utilized to assess presence, size and direction of ductal shunt.

E) LV mass: LV internal dimension, posterior wall thickness, interventricular septum thickness and LV mass were measured in systole and end-diastole from M-mode ECHOs according to American Society of Echocardiography recommendations (24). Left ventricular mass index (LVMI) was indexed to height in $cms^{2.7}$

F) Eccentricity index (EI): The EI in diastole (EId) and systole (EIs) were calculated as the ratio of perpendicular diameters in parasternal short axis at the level of papillary muscle, using the method of Ryan et al (25).

Data Collection: Demographic data (gestational age, gender) and clinical characteristics (birth weight, severity of HIE, cord pH, mode of delivery, Apgar scores at 5 minutes, perinatal events), need for inotropes, high frequency ventilation, nitric oxide and length of stay were collected.

Data analyses: Calculated means of 3 cardiac cycles were used for ECHO parameters. ECHO data were described as mean (SD), median (IQR) or 95% CI as appropriate. Comparisons of ECHO measures between groups was done using t-tests and Analysis-Of-Variance (ANOVA) with Bonferroni correction for posthoc comparisons for continuous variables. Chi square test was used for comparisons of categorical data. Statistical analysis was performed using SPSS Version 19 (SPSS, Chicago, IL, USA) and a p value<0.05 taken as significant.

RESULTS:

Our study cohort included 56 infants with moderate or severe HIE with a mean (SD) GA of 38.7 (1.6) weeks and birth weight of 3.385 (0.719) kg. Males comprised 50% of the cohort; 38 infants underwent TH and 18 did not, either because they (n=12) were born before the TH era or admitted after 6 hours of age (n=6). ECHO was done at a mean (SD) age of 10.4 (4.8) hours of age. C-section was the mode of delivery in the majority [38 (67.9%)] of cases. The documented perinatal events included uterine rupture [5 (8.9%)], fetal decelerations [21 (37.5%)], placental abruption [3 (5.4%)] and meconium stained amniotic fluid [2 (3.6%)] among others. The median (IQR) cord pH was 6.93 (6.82-7.06) and 5-minute Apgar score was 4 (1-6). Pressors were required in 48 (85.7%) infants with 34 (60.7%) infants requiring 2 or more pressors. High frequency ventilation was administered in 25 (44.6%) infants and inhaled nitric oxide in 30 (53.6%) infants. Fourteen (25%) infants died, 7 of whom had severe HIE, 3 moderate HIE and 4 had missing information. Among the 42 infants who survived, the mean (SD) length of hospital stay was 24.0 (16.2) days and the length of ventilation was 15.1 (11.7) days.

There were no significant differences in clinical characteristics between infants with HIE who underwent TH or normothermia except for a higher requirement of inhaled nitric oxide in the normothermia group (Table 1). The normal control infants (n=35), 17 (48.6%) of whom were males, had a mean (SD) birth weight of 3.103 (0.638) kg. A comparison of ECHO measures in the two groups of infants with HIE who underwent TH and normothermia and normal controls is shown (Table 2). There was no significant difference in mean (SD) birth weight or GA between the three groups. Significantly elevated biventricular MPI, lower biventricular VO and EI in infants with HIE, compared to normal controls, confirmed cardiac dysfunction in this population. The mean HR among infants with HIE who underwent normothermia was significantly higher than in those who underwent TH. The only ECHO measure that was significantly different in the two groups of infants with HIE was LV MPI. Among the controls, 3 (8.6%) infants had mild tricuspid regurgitation (TR); in infants with HIE who underwent TH and were normothermic, 11 (29.0%) and 4 (22.2%) had mild and 8 (21.1%) and 4 (22.2%) had moderate TR (combined p =0.002). One infant with HIE in the normothermia had severe TR. LVO below 150 ml/kg/min and RV S/D ratio above 1.3 were also analyzed in view of previous data establishing these cut-offs (18, 23). In infants with HIE, none of the ECHO parameters were associated with clinical severity measures such as need for high frequency ventilation, nitric oxide, pressors or severity of HIE. Table 3 shows a comparison of ECHO measures between the groups of infants with HIE who died (n=14) and survived (n=42). The only significant difference was in the EId.

DISCUSSION

This was a retrospective analysis of ECHOs performed within 24 hours of age for clinical indications in a cohort of infants with moderate or severe HIE. The majority (54%) of our study cohort received inhaled nitric oxide therapy for pulmonary hypertension and 86% of infants were on pressor therapy. About half the infants in whom data were available had severe HIE and 25% died.

On a detailed early ECHO, infants with HIE had evidence of decreased biventricular outputs, global systolic and diastolic dysfunction reflected by elevated biventricular MPI and pulmonary hypertension (abnormal EI, higher RV S/D and bidirectional or right-to-left shunt across the PDA), compared to normal controls. The FS values were comparable to those of control infants. Previous studies in small numbers of asphyxiated infants have reported ventricular dysfunction as reflected in a reduced FS, tricuspid insufficiency or elevated LV and RV MPI, compared to controls, although results of specific measures have varied (9, 11, 12). Other ECHO measures such as longitudinal peak systolic strain and peak systolic strain rate by tissue Doppler in 18 segments of the heart on day 1 of life in 20 asphyxiated neonates were significantly lower than in the 48 healthy term controls. FS was similar in the two groups [29.2% (26.8, 31.5) vs. 29.0% (27.9, 30.1); p = 0.874] (10).

A few previous studies have evaluated ECHO measures of ventricular function, coronary and superior venacaval flow in infants with HIE who underwent TH (14-17). Since the most notable changes in hemodynamics following perinatal asphyxia occur in the first days of life (26), we limited our study to ECHOs within the initial 24 hours of life and for those who underwent TH, within a few hours of induction of TH. We found that infants who underwent TH had decreased biventricular outputs, elevated MPIs and abnormal EIs, compared to controls. The only significant differences between infants who underwent TH and normothermia were the significantly lower HRs and LV MPI in the TH group. Whether the improvement in LV MPI, a sensitive marker of function, represents some degree of cardioprotection remains to be determined. Consistent with our data, the few previous studies done during the TH era have shown lower CO, HR, superior venacaval and coronary flows and Doppler deformation indices of myocardial function and impaired peak systolic strain rate and LV MPI, compared to controls (14-17, 26). Other studies have also shown that the decrease in ventricular function in infants with HIE is transient during TH, with subsequent recovery (14, 16).

We also evaluated measures of pulmonary hypertension in infants with HIE receiving TH in the current study. We found the EIs and RV S/D ratio to be significantly deranged, compared to controls. The directionality of the shunt across PDA confirmed the pulmonary hypertension in infants with HIE. The association between persistent pulmonary hypertension of the newborn and perinatal asphyxia, either because of direct effects of hypoxia and acidosis on pulmonary vascular resistance or due to indirect effects of coexisting morbidities such as meconium aspiration syndrome and sepsis/pneumonia has been previously recognized (27). Pulmonary hypertension, in turn, is associated with ventricular dysfunction. In one previous study, measures of pulmonary hypertension such as pulmonary arterial diastolic pressure, pulmonary arterial resistance, and pulmonary arterial resistance/ systemic resistance ratio were all significantly elevated in 40 term infants with HIE, compared to 40 healthy controls on day 1 of life (28).

When we compared infants with HIE who died and survivors, the mean EId was significantly different between groups. A few previous studies have examined ECHO measures as biomarkers of mortality with largely negative results. In one study of 34 term newborns with mild to severe HIE, only 1 of 9 infants who died had mild decrease in ejection fraction in the initial 24-48 hours of life (29). In another study of 25 asphyxiated and 20 non-asphyxiated term infants, FS and Doppler tissue imaging measures done during the initial 72 hours of age did not show any significant predictive value for mortality (9). We have previously shown RV S/D ratio, an index of RV function, was significantly higher in infants with persistent pulmonary hypertension or congenital diaphragmatic hernia who died or required ECMO, compared to survivors without ECMO (30, 22). RV S/D ratio >1.3 had a sensitivity of 93% for prediction of death (22). In the current data set, while the proportion of infants with RV S/D > 1.3 was greater in those who died, the association did not reach statistical significance. The correlation of EId with mortality may be a reflection of pulmonary hypertension in infants with severe, rather than moderate HIE.

We acknowledge the limitations of our study. Since we evaluated ECHOs done for clinical indications, our cohort included a group of "sick" infants. While such children have not been previously studied in any detail, this was a selection bias. Since the numbers of infants who underwent normothermia was relatively small, the comparative effects of TH on ventricular function and hemodynamics could be studied in a limited way. Whether the cardiac dysfunction was related to intrapartum birth events resulting in HIE, effects of HIE itself or TH could not be ascertained. The difference in ages between the groups with HIE and normal controls (< 72 hours of age) was a source of potential bias. Nonetheless, the current observational study adds to our understanding of the cardiac function in infants with HIE undergoing TH through a comprehensive ECHO within the initial day of life. Specifically, novel ECHO measures of pulmonary hypertension such as EId appear to correlate with survival outcomes in this population. Further studies are needed to validate this association in larger numbers of infants.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Table 1: A comparison of clinical characteristics between infants with HIE who underwent TH or normothermia

Mean (SD) or n (%)	HIE-TH (n=38)	HIE-Normothermia (n=18)	P value
Birth weight (grams)	3365 (689)	3429 (803)	0.766
GA (weeks)	38.7 (1.5)	38.7 (2.0)	0.949
Male gender	18 (47.4%)	10 (58.8%)	0.562
C-section	29 (76.3%)	9 (50%)	0.116
Perinatal event:			0.733
Uterine rupture	3 (7.9%)	2 (11.2%)	
Fetal decelerations	14 (36.8%)	7 (38.9%)	
Placental abruption	2 (5.2%)	1 (5.6%)	
Cord pH	6.89 (0.18)	6.94 (0.18)	0.432
5-min Apgar<5	27 (71.1%)	9 (50%)	0.229
Severe HIE	12/24 (50%)	3/7 (42.8%)	0.693
Pressors in initial 72 hrs:			0.087
None	6 (15.8%)	0 (0%)	
1 pressor	11 (29%)	3 (16.7%)	
2 or more pressors	21 (55.3%)	15 (83.3%)	
Age at ECHO (hours)	10.4 (5.1)	12.5 (1.4)	0.579
Nitric oxide	17 (44.7%)	13 (72.2%)	0.041
High frequency oscillation	15 (39.5%)	10 (55.6%)	0.245
Days of ventilation	13.0 (12.7)	12.4 (8.6)	0.868
Days of hospital stay	19.6 (17.2)	19.7 (13.9)	0.988
Death	8 (21.1%)	6 (33.3%)	0.322

Table 2: A comparison of ECHO measures in the two groups of infants with HIE who underwent TH and normothermia and normal controls (n=35)

Mean (SD)	Normal controls (n=35)	HIE-TH (n=38)	HIE-Normothermia (n=18)	Combined P value
HR (bpm)	137 (17)	124 (32)*	161 (23)**	0.0001
RVO (ml/kg)	343 (123)***	195 (73)	216 (83)**	0.0001
RVO<150 ml/kg	0	11 (29.0%)	4 (11.1%)	0.012
LVO (ml/kg)	393 (107)***	269 (87)	292 (101)**	0.0001
LVO <150 ml/kg	0	3 (7.9%)	2 (11.1%)	0.169
FS (%)	0.38 (0.07)	0.35 (0.07)	0.34 (0.09)	0.074
RV MPI	0.25 (0.08)***	0.58 (0.21)	0.66 (0.23)**	0.0001
LV MPI	0.29 (0.06)***	0.47 (0.16)*	0.60 (0.13)**	0.0001
RV S/D	1.10 (0.14)***	1.58 (0.44)	1.73 (0.26)**	0.0001
RV S/D > 1.3	2 (5.7%)	24 (63.2%)	15 (83.3%)	0.0001
LV mass	7.25 (2.14)	8.05 (2.12)	7.41 (2.89)	0.304
LVMI (g/m 2.7)	46.65 (12.40)	51.49 (12.72)	46.45 (16.93)	0.322
EIs	0.87 (0.16)***	0.75 (0.11)	0.76 (0.13)#	0.001
EId	0.90 (0.09)***	0.81 (0.09)	0.81 (0.07)**	0.0001
PDA	12 (34.3%)	33 (86.8%)	13 (72.2%)	0.0001
PDA shunt:				0.0001

Right-left	0	0	2 (11.1%)	
Bidirectional	0	21 (55.3%)	5 (27.8%)	
PDA size (cm)	0.19 (0.06)***	0.33 (0.15)	0.35 (0.13)**	0.002

*Posthoc analyses P< 0.01 HIE-TH compared to HIE-normothermia, **P<0.01 HIE-normothermia compared to controls ***P< 0.01 HIE-TH compared to controls **# P=0.021 HIE-normothermia compared to controls

Table 3: A comparison of ECHO measures in the two groups of infants with HIE who survived (n=42) and died (n=14)

Mean (SD) or n (%)	Survivors (n=42)	Infants who died (n=14)
HR (bpm)	133 (34)	139 (32)
RVO (ml/kg)	200.4 (73.5)	198.9 (87.0)
LVO (ml/kg)	273.1 (93.1)	279.2 (87.0)
FS (%)	0.35 (0.07)	0.34 (0.09)
RV MPI	0.59 (0.20)	0.63 (0.26)
LV MPI	0.49 (0.15)	0.56 (0.18)
RV S/D	1.59 (0.40)	1.72 (0.42)
RV S/D > 1.3	25 (59.5%)	13 (92.9%)
LV mass	7.92 (2.16)	7.45 (3.02)
LVMI (g/m2.7)	50.66 (11.67)	47.78 (20.26)
EIs	0.77 (0.11)	0.72 (0.11)
EId	0.83 (0.08)	0.77 (0.09)*

- *P=0.021