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DOI:
10.1159/000521694

Neonatology

Clinical Trials

Neonatology
DOI: 10.1159/000521694

Received: August 27, 2021
Accepted: December 23, 2021
Published online: June 17, 2022

Left Ventricular Dysfunction Persists in the First Week after Re-Warming following Therapeutic Hypothermia for Hypoxic-Ischaemic Encephalopathy

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Keywords
Hypoxic-ischaemic encephalopathy · Therapeutic hypothermia · Tissue Doppler imaging

Abstract
Objectives: The aim of this study was to assess serial myocardial function in newborn infants receiving therapeutic hypothermia (TH) as treatment for moderate to severe hypoxic-ischaemic encephalopathy (HIE). ***Methods:*** Serial echocardiography was performed in 20 term infants receiving TH on days 1–3 and again after re-warming. Left ventricular (LV) fractional shortening, LV cardiac output, and tissue Doppler imaging-derived myocardial velocities and myocardial performance index were measured. Similar assessments were obtained from 20 well term infants within 48 h of birth. ***Results:*** LV fractional shortening (LVFS) was similar between cases and controls during all measurements (25.3% vs. 27.4%). The mean LV cardiac output on day 1 was significantly lower in cases (109 mL/kg/min) than in controls (162 mL/kg/min) but increased after re-warming (145 mL/kg/min). All myocardial velocities were significantly lower in cases on day 1, increased during TH, but LV indices remained consistently lower compared to controls even after re-warming. LV myocardial performance index was higher in cases compared to controls on day 1, improved during TH but remained abnormal after re-warming. The right ventricular myocardial performance index was similar between cases and controls. ***Conclusion:*** Among infants affected by moderate to severe HIE, LV function appears to be more affected than right ventricular function with LV dysfunction persisting after completion of TH. LVFS was not useful to determine dysfunction in this cohort.

Introduction

Hypoxic-ischaemic encephalopathy (HIE) following a perinatal asphyxial insult in term babies is a multisystem disorder resulting in death or severe neurological injury.

Dr. Shree Vishna Rasiah has unfortunately died after this study was completed.

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Therapeutic hypothermia (TH) instituted within 6 h of insult reduces the risk of death and adverse neurological outcomes; however, around half of the affected infants still suffer adverse outcomes, and the reasons for such variation remain unknown [1]. HIE affects the cardiovascular system (CVS) in up to 80% of infants [2]. TH may also lead to cardiovascular side effects such as sinus bradycardia, hypotension, and reduced left ventricular (LV) cardiac output (LVCO) [3–5]. It remains unclear whether TH promotes CVS recovery in these infants or contributes to ongoing CVS dysfunction. Optimizing CVS management during TH may improve the long-term outcomes in these infants.

Assessment and management of CVS dysfunction remains challenging due to lack of evidence clarifying the best approach [2, 5]. Various markers of CVS function and myocardial damage have been evaluated in HIE including biomarkers (e.g., troponin-I and B-type natriuretic peptide) [6], heart rate (HR) variability indices [7], specific conventional measures of myocardial function, e.g., LVCO, LV fractional shortening (LVFS), and novel techniques such as myocardial strain, strain rate, and LV rotational mechanics [8–13]. Although cardiac biomarkers and HR variability indices might be useful in predicting the long-term outcome, their use in guiding acute CVS management during the first week of life in HIE is limited.

Pulse-wave-derived tissue Doppler imaging (pwTDI) is a simple technique to assess myocardial function that utilizes established principles of conventional Doppler ultrasound. It has been extensively studied in newborn infants by our group and others. Its relative ease of use, compared to novel techniques such as strain and strain rate that require post-processing away from the cot side, makes it an ideal investigation in HIE [14–18].

The aim of this study was to assess serial myocardial function in infants undergoing TH for HIE using conventional techniques (LVCO, LVFS) and to compare these with pwTDI-derived myocardial velocities (MVs) and myocardial performance index (MPI). pwTDI measures the velocity of myocardial motion in both systole and diastole using Doppler signals obtained from either the mitral or tricuspid valve annuli – the higher the velocity, the better the myocardial function. MPI is a ratio derived by dividing the sum of isovolumetric contraction and relaxation times by the ejection time. It is an assessment of the combined systolic and diastolic function of the heart – the lower the ratio, the better the myocardial function.

Methods

Infants ≥36 weeks gestation diagnosed with HIE and receiving TH on the neonatal intensive care unit at Birmingham Women's Hospital, UK, were eligible for inclusion in to this prospective unblinded observational study. HIE was diagnosed, and severity categorized using established criteria [19]. Infants diagnosed with moderate and severe HIE received 72 h of whole-body TH via Tecotherm® cooling mattress with a target rectal temperature of 33.5°C and were then re-warmed to 37°C at a rate of 0.5°C/h. All infants undergoing TH were monitored using amplitude-integrated electroencephalogram which was categorized as normal, moderately abnormal, and severely abnormal [19]. All infants had invasive blood pressure monitoring, and if the mean BP was lower than gestational age, inotropic support was provided as per local protocol. Routine clinical data including gestational age, birth weight, Apgar scores, and HR were collected in all infants. Mean blood pressure, level of respiratory support, and use of inotropes were noted in cases.

A group of healthy term infants cared for in the postnatal wards was included as controls. These infants were receiving normal newborn care and had no pathological diagnoses. Echocardiograms were performed in the first 24 h of life after obtaining parental consent for the purposes of the research study. Infants with major congenital malformations (including heart defects but excluding patent ductus arteriosus [PDA] and patent foramen ovale) were excluded. Where feasible, daily echocardiographic assessment was performed in cases during TH (days 1–3), and an additional assessment was performed after re-warming (days 4–7). All echocardiograms were performed by the same investigator (P.K.Y.) using a Philips HD11xe ultrasound system with an S12-4-MHz transducer (Philips Healthcare, Best, The Netherlands). Ethical approval, institutional research and development approval, and written informed parental consent were obtained prior to recruitment.

Conventional Echocardiography Assessment

Normal cardiac anatomy was ascertained in all infants, and the presence of PDA was determined using a modified high parasternal long-axis view and colour flow Doppler. LVFS was calculated using M-mode echocardiography in the parasternal long-axis view at the level just distal to the mitral valve leaflets [20]. LVCO was calculated using a previously described technique [21]. The presence of persistent pulmonary hypertension of the newborn (PPHN) was also determined (defined as tricuspid regurgitant velocity ≥2.5 m/s and/or bidirectional PDA).

Tissue Doppler Imaging

MVs were obtained from an apical four-chamber view using a pulse-wave Doppler sample gate of 0.12 cm and an angle of insonation of <20°. Appropriate gain settings were used to clearly define the pwTDI wave forms. MVs were measured from the medial mitral (MMA) and lateral mitral annuli (LMA) representing LV function and from the lateral tricuspid annulus representing right ventricular (RV) function. Peak systolic (S′ – represents systolic function), early diastolic (E′ – ventricular relaxation), and late diastolic (A′ – atrial contraction) MVs were measured. MPI, a sensitive marker of global ventricular function, was calculated using the pwTDI waveforms as previously described [22]. Offline analysis was performed for all measurements on the same ultrasound system averaged over 2–3 cardiac cycles.

Table 1. Baseline characteristics

	Cases (n = 20)	Controls (n = 20)
Gestation, weeks, median (range)	39 (36–41)	40 (37–41)
Birth weight, g, median (range)	3,195 (1,830–4,380)	3,190 (2,620–4,720)
Apgar scores at 1, 5, and 10 min, median	2, 4, 7	9, 9, N/A
Cord pH at birth, median (range)	6.7 (6.6–7.0)	N/A

Statistical Analyses

Data normality was tested using histograms and Shapiro-Wilk tests. Continuous variables are described using median and interquartile range, given they showed skewed distributions. The Mann-Whitney test was used to compare baseline conventional echocardiography and pwTDI measurements between cases (day 1) and control groups. Paired Wilcoxon signed-rank test with last observation carried forward strategy to impute longitudinal missing data was used to evaluate changes in myocardial function during treatment. A mixed-effect model to evaluate the evolution of repeated measures during follow-up was applied. This analysis makes use of all available data and computes the slope of the change of observed parameters. Conventional echocardiography and pwTDI measurements after re-warming were compared with baseline control measures. A Bonferroni correction for multiple comparisons was applied, lowering the significant value to 0.007 to account for the inflation of type I error due to the multiplicity of contrast due to the presence of multiple outcomes (i.e., 7 Doppler parameters). Stata program (StataCorp. 2015; Stata Statistical Software: Release 14; StataCorp LP, College Station, TX, USA) was used for all statistical analyses.

Table 2. Clinical characteristics of cases

Clinical details	Infants, n (%)
Mechanical ventilatory support via ETT	
Day 1	16 (80)
Day 2	10 (50)
Day 3	9 (45)
After attaining normothermia	2 (10)
Requiring inotropic support	
Day 1	10 (50)
Day 2	9 (45)
Day 3	6 (30)
After attaining normothermia	3 (15)
Signs of increased pulmonary pressures (TR jet velocity ≥2.5 m/s and/or bidirectional PDA)	
Day 1	7 (35)
Day 2	2 (10)
Day 3	0

ETT, endotracheal tube; TR, tricuspid regurgitation; PDA, patent ductus arteriosus.

Results

A convenience sample of 20 consecutive infants undergoing TH for HIE (cases) was recruited. This included all infants admitted to the neonatal intensive care unit during a 12-month period between February 2013 and January 2014. All eligible babies were approached, and all were successfully recruited including an infant who sadly died within the first 48 h. For baseline characteristics, see Table 1. Seven out of the 20 cases were classified as severe HIE, and the remaining 13 were classified as moderate HIE. The cardiorespiratory support required by the infants affected by HIE is detailed in Table 2 (two infants died on day 1, and one was transferred out for ECMO to manage PPHN). Twenty well term infants were included as controls.

In cases, 20 day 1 measurements, 16 day 2 measurements, 15 day 3 measurements, and 17 measurements after re-warming were available for analysis. All measurements were available for analysis in control infants (15 scans within 24 h after birth and 5 scans between 24 and 48 h after birth).

Conventional Echocardiography Assessment

No significant structural heart defect was found in any infant. Four infants receiving TH had a PDA >2 mm. One case had PPHN which was managed with mechanical ventilation, inotropic support, and inhaled nitric oxide. This infant was transferred for ECMO support, and TH was discontinued.

The HR was significantly lower in cases on day 1 and increased to normal values after re-warming. LVFS showed no difference between cases and controls on any of the days of assessment. LVCO was significantly lower on day 1 in cases compared to controls but reached similar levels to controls after re-warming. Between days 1 and 3 of TH, LVCO increased, but the difference did not reach statistical significance. See Table 3 for all comparisons.

Tissue Doppler Assessment

MVs at all 3 sites (lateral tricuspid annulus, MMA, and LMA) were significantly lower in cases on day 1. From days 1 to 3 of TH, MVs at all 3 sites increased gradually,

Table 3. Conventional echocardiography assessments

	Baseline comparison†			Slope per day (95% CI)	*p* value**	Cases (LOCF) (*n* = 20), median (P25; P75)	Cases day 1 versus after treatment (LOCF) paired comparison, *p* value#	Comparison between controls and cases (LOCF), *p* value†
	controls (*n* = 20), median (P25; P75)	cases day 1 (*n* = 20), median (P25; P75)	*p* value					
HR, bpm	123.5 (112.5; 131)	94 (85; 110)	<0.001	3.9 (1.8; 6.0)	<0.001	130 (90; 140)	0.004	0.988
LVFS, %	27.3 (23.8; 36.5)	23.4 (21.1; 32.4)	0.655	0.3 (−0.4; 1)	0.434	30.2 (22.7; 37.6)	0.303	0.626
LVCO, mL/kg/min	162 (151; 240)	109 (74; 180)	0.011	14.6 (−9.7; 38.9)	0.238	145 (130; 230)	0.100	0.957

The *Baseline comparison* column shows the difference in measurements between the cases on day 1 and the control infants. The *Slope per day* column shows the change in serial measurements from day 1 to day 3 in cases, with the respective *p* values in the next column. The column *Cases (LOCF)* represents the measurements in cases after re-warming; *Cases day 1 versus after treatment (LOCF) paired comparison* shows the difference in measurements in cases from day 1 to after re-warming. The final column *Comparison between controls and cases (LOCF)* compares the controls to the measurements from cases after re-warming. HR, heart rate; LVFS, left ventricular fractional shortening; LVCO, left ventricular cardiac output; LOCF, last observation carried forward. † Mann-Whitney U test. # Wilcoxon signed-rank test. ** Mixed-effects ML regression; *p* value <0.05 was considered significant.

Table 4. Tissue Doppler assessments

	Baseline comparison			Slope per day (95% IC)	*p* value**	Cases (LOCF) (*n* = 20), median (P25; P75)	Cases day 1 versus after treatment (LOCF) paired comparison, *p* value#	Comparison between controls and cases (LOCF), *p* value†
	controls (*n* = 20), median (P25; P75)	cases day 1 (*n* = 20), median (P25; P75)	*p* value†					
MMA S′	5.1 (4.5; 5.5)	2.7 (2.3; 3.1)	<0.001	0.24 (0.15; 0.33)	<0.001	4.0 (3.3; 4.8)	<0.001	0.002
MMA E′	5.6 (5.0; 6.9)	3.7 (2.4; 4.4)	<0.001	0.22 (0.10; 0.34)	<0.001	4.5 (3.4; 5.0)	0.013	0.007
MMA A′	6.6 (6.2; 7.0)	3.3 (2.6; 5.0)	<0.001	0.53 (0.36; 0.70)	<0.001	6.8 (4.7; 7.3)	0.001	0.910
LMA S′	5.5 (4.8; 6.1)	3.4 (2.6; 4.1)	<0.001	0.27 (0.17; 0.38)	<0.001	5.0 (3.4; 5.8)	0.002	0.033
LMA E′	7.0 (6.7; 8.3)	4.5 (3.1; 5.7)	<0.001	0.30 (0.15; 0.45)	<0.001	5.1 (4.3; 6.7)	0.031	0.004
LMA A′	7.4 (6.1; 8.6)	4.6 (3.5; 6.5)	0.001	0.39 (0.17; 0.61)	0.001	7.2 (4.6; 9.2)	0.007	0.822
LTA S′	6.7 (6.4; 8.6)	4.1 (3.2; 5.2)	<0.001	0.44 (0.30; 0.58)	<0.001	6.1 (5.8; 6.6)	0.001	0.054
LTA E′	8.1 (7.0; 9.6)	5.0 (3.1; 6.7)	<0.001	0.37 (0.22; 0.52)	<0.001	7.0 (6.3; 7.6)	0.001	0.016
LTA A′	11.4 (10.5; 12.3)	4.9 (3.2; 7.7)	<0.001	0.54 (0.25; 0.82)	<0.001	8.5 (7.9; 10.1)	0.001	0.024
MMA MPI	0.56 (0.48; 0.59)	0.78 (0.66; 0.91)	<0.001	0.003 (−0.02; 0.03)	0.828	0.68 (0.61; 0.99)	0.155	<0.001
LMAMPI	0.57 (0.48; 0.63)	0.74 (0.56; 0.96)	<0.001	−0.012 (−0.04; 0.01)	0.322	0.71 (0.57; 0.97)	0.793	0.002
LTA MPI	0.52 (0.45; 0.6)	0.65 (0.49; 0.86)	0.018	−0.03 (−0.05; −0.01)	0.014	0.55 (0.45; 0.62)	0.013	0.386

MMA, medial mitral annulus; LMA, lateral mitral annulus; LTA, lateral tricuspid annulus; S′, peak systolic velocity; E′, early diastolic velocity; A′, late diastolic velocity; MPI, myocardial performance index; LOCF, last observation carried forward. † Mann-Whitney U test; # Wilcoxon signed-rank test; ** Mixed-effects ML regression; *p* value ≤0.007 was considered significant.

indicating improving myocardial function. After completion of re-warming, all MVs, except LV-E′, were significantly higher in cases compared to day 1. After completion of re-warming, compared to controls, only LV S′ and E′ at MMA and LV E′ at LMA remained significantly lower in cases. All RV MVs were similar in cases and controls after completion of re-warming.

LV MPI at MMA and LMA was significantly higher in cases on day 1 compared to controls indicating worse LV myocardial function. RV MPI was higher in cases compared to controls on day 1 but did not reach pre-determined statistical significance for this study ($p \leq 0.007$). From days 1 to 3, LV MPIs did not show significant improvement. After completion of re-warming, LV MPIs remained significantly higher in cases compared to controls, whereas RV MPI reached values similar to controls. See Table 4 for results of all pwTDI assessments.

Discussion

We have demonstrated using pwTDI that biventricular systolic and diastolic function is abnormal in infants after the initial insult, and the LV may be more severely affected than the RV. We have previously shown that MPI derived from TDI is a sensitive marker for detecting subclinical myocardial dysfunction in newborn babies [17, 18].

Other groups have demonstrated myocardial dysfunction using TDI in infants affected by HIE [11, 23, 24]. Cetin et al. [11] reported TDI measures of myocardial dysfunction that correlated with the degree of myocardial damage measured using cardiac troponin-T. They also demonstrated that the dysfunction persisted at 1 month of age. Wei et al. [23] also demonstrated that the LV peak systolic velocity measured by TDI was a more sensitive indicator than LVFS in infants affected by HIE. However, infants did not receive TH in any of these studies.

The current study utilizes pwTDI-derived MVs and MPIs to serially assess myocardial function in infants undergoing TH and compare with LVFS and LVCO. On day 1, all MVs in cases were significantly lower, which may indicate biventricular myocardial dysfunction or a physiological response to commencing TH following perinatal hypoxic insult. From days 1 to 3, biventricular MVs improved; however, LV MPIs did not show significant improvement by day 3 (compared to day 1) which suggests that LV function might remain impaired for longer compared to RV function. After completion of re-warming, LV systolic and diastolic function measured at MMA and LMA remained abnormal in cases compared to controls. RV MPI was higher in cases on day 1 but showed gradual improvement reaching similar values to controls after completion of rewarming. This suggests that in HIE, the LV might be more affected than the RV. It is difficult to speculate if this is due to LV having a higher metabolic need after birth or due to its structure, and further large studies are required to confirm this finding.

The effect of TH on myocardial function remains inconclusive. Nestaas et al. [10] utilized strain and strain rate measurements to measure myocardial function in infants affected by HIE. They demonstrated that myocardial function in infants treated with TH was comparable to healthy controls after re-warming, whereas in HIE infants not treated with TH, myocardial dysfunction persisted into the first week of life. In the current study, LV function as assessed by pwTDI remained abnormal even after re-warming. The severity of the hypoxic insult in our cohort was greater (mean initial pH 6.7 in our study vs. 7.07 in Nestaas et al. [10]), and it is plausible that the LV function of HIE cases in the current study might have been more compromised at birth, and hence, the pwTDI values remained relatively abnormal even after completion of re-warming. Recent studies in infants affected by varying severity of HIE also found similar results to the current study where biventricular function was significantly affected in the first 24 h, and compared to infants with mild HIE, those with moderate-severe HIE had worse myocardial function [25]. It is also worth noting that the changes in myocardial function seen in infants with HIE might be a result of the original hypoxic insult, but it is likely that the standard treatments provided to such infants, i.e., TH, mechanical ventilation, and cardiovascular support, will have some effect on myocardial function, and it is difficult to determine the effect of each of these factors.

In the current study, LVFS showed no difference between cases and controls, which has been demonstrated previously [8, 10]. It is well established that M-mode-derived LVFS is unreliable for assessment of LV systolic function in newborns due to the differences in neonatal ventricular geometry (compared to adults), which is partly due to the high pulmonary pressures in the immediate postnatal period leading to a flat inter-ventricular septum and non-homogeneity of LV wall motion [26]. These findings suggest that in infants undergoing TH, LVFS is not useful to detect myocardial dysfunction. Comparatively, day 1 LVCO was significantly lower in cases and showed improvement from days 1 to day 3 of TH. After completion of re-warming, LVCO reached similar levels to controls. These changes are similar to previously documented findings [8, 9]. Mild hypothermia (33–35°C) can lead to increased peripheral vascular resistance (cardiac afterload) and relative depletion of intravascular volume by suppression of antidiuretic hormone secretion (cardiac preload) [27]. Both these effects can influence LVCO, making it unreliable as an accurate marker of myocardial function in infants undergoing TH.

TDI is a well-validated technique in both term and preterm infants and can serve as a very useful modality for assessing cardiac dysfunction at the cot side. Our study has the following limitations. The sample size is small, and hence, care must be taken when applying these results in a clinical context. Although TDI has been shown to be better at assessing myocardial function, it is still affected by loading conditions and measures myocardial function only in the longitudinal plane, thus underestimating myocardial motion in other planes. For RV systolic function, pwTDI can be considered as reliable as tri-

cuspid annular plane systolic excursion as both these techniques measure RV systolic motion in the longitudinal plane. Around 50% of the HIE infants were receiving inotropes on day 1, and this reduced to 30% by day 3 of life. Inotropes can potentially affect myocardial function, and in the current study, we did not measure the effect of different inotropes and different doses of inotropes on myocardial function. In the current study, the measurements from control infants were acquired only once in the first 48 h of life, and ideally, the measurements from cases after re-warming to normal temperature (acquired between days 4 and 7 of life) should be compared with measurements from well infants at similar age. It is known that pwTDI values evolve with age in the first week of life [16], but to keep the collection of data pragmatic, control infants were scanned only once in the first 48 h of life.

Conclusions

Infants receiving TH for moderate to severe HIE demonstrate significant myocardial dysfunction during the first 3 days of life when compared to well-term infants at birth. LV function seems to be more affected than RV function in these infants. pwTDI is feasible in infants receiving TH for HIE and may be a more sensitive indicator of myocardial dysfunction than LVFS and LVCO. Being able to assess and monitor myocardial function with pwTDI, alongside conventional assessments, could help optimize cardiovascular management in this group of infants.

Statement of Ethics

The authors assert that all procedures contributing to this work comply with the ethical standards of the National Research Ethics Service Committee (West Midlands – The Black Country), England and Wales, and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Research and Development department at Birmingham Women's Hospital (REC reference 06/Q2702/86), West Midlands, United Kingdom. Written informed consent was obtained from all parents/carers for performing the echocardiograms, collecting anonymized clinical data and the data from the scans, and using the results of the study for teaching, presentation, and publication.

Conflict of Interest Statement

All the authors declare no conflict of interest.

Funding Sources

This research received no specific grant from any funding agency, commercial or not-for-profit sectors. Open Access funding was provided by the Qatar National Library.

Author Contributions

P.K.Y., R.J.S.N., S.V.R., and A.K.E. were involved in the design of the study. P.K.Y. performed the study investigations, collected and analysed the results, drafted the initial manuscript, and was involved in revising and finalizing the manuscript. R.J.S.N. provided supervision during the collection and analysis of data. J.Z. and N.P. performed the statistical analysis. J.Z., N.P., R.J.S.N., S.V.R., and A.K.E. were involved in interpreting the results. P.K.Y., J.Z., N.P., R.J.S.N., and A.K.E. revised and finalized the manuscript. All the co-authors agree with this authorship statement. The authorship, conflict of interest statement, and author contribution statement have been shared with, and no objections were raised by the institution responsible for the research of Dr. Rasiah.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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