Research paper

Cite as: Brunets N, Brunets V, Wójcik-Sęp A, Bokiniec R: Evaluation of left ventricular function using various echocardiographic techniques in hypoxic neonates during therapeutic hypothermia and after rewarming. J Ultrason 2025; 25: 33. doi: 10.15557/JoU.2025.0033.

**Submitted:** 13.09.2025
**Accepted:** 23.12.2025
**Published:** 30.12.2025

# Evaluation of left ventricular function using various echocardiographic techniques in hypoxic neonates during therapeutic hypothermia and after rewarming

Natalia Brunets[1], Veronika Brunets[2], Agata Wójcik-Sęp[3], Renata Bokiniec[4]

[1] *Department of Prematurity and Neonatal Pathology, Żelazna Medical Center Ltd St. Sophia's Specialist Hospital Medical Center, Poland*
[2] *Medical Faculty of Medicine, Uczelnia Łazarskiego: Warsaw, Poland*
[3] *Neonatal and Intensive Care Department, Medical University of Warsaw, Poland*
[4] *Head of Neonatal and Intensive Care Department, Medical University of Warsaw, Poland*

*Corresponding author: Natalia Brunets; e-mail: brunat1108@gmail.com*

DOI: 10.15557/JoU.2025.0033

**Keywords**

hypoxic-ischemic encephalopathy; therapeutic hypothermia; left ventricular diastolic and systolic function

**Abstract**

**Aim:** The aim of this study was to evaluate left ventricular function in hypoxic neonates undergoing therapeutic hypothermia using echocardiography. **Materials and methods:** This multicenter, prospective, case-control, observational study involved 113 neonates, including 55 in the hypothermic group and 58 non-hypothermic controls. Echocardiographic measurements were taken by two neonatologist (NB and RB) during therapeutic hypothermia and after rewarming using various techniques. **Results:** There was a significant difference between the study group and controls in mean blood pressure ($p$ <0.001) and heart rate ($p$ = 0.004) during therapeutic hypothermia. Significantly higher post-rewarming heart rate was observed in the study group compared to controls ($p$ <0.001). Significantly lower mean A-wave (A mv) ($p$ = 0.04) and E-wave (E mv) ($p$ = 0.003) mitral valve velocities, as well as reduced mitral annular plane systolic excursion ($p$ <0.001), cardiac output ($p$ <0.001), and left ventricular internal diameter in diastole ($p$ <0.001) were observed in the study group compared to controls during therapeutic hypothermia. The mean left ventricular myocardial performance index was significantly higher in the study group ($p$ = 0.006). Tissue Doppler imaging showed significantly lower left ventricular E' velocity ($p$ <0.001) and E'/A' ratio during therapeutic hypothermia in the study group compared to controls. Left ventricular A' ($p$ = 0.006), E' ($p$ <0.001), and S' ($p$ = 0.003) velocities were significantly lower, while myocardial performance index ($p$ <0.001) was significantly higher in the study group during therapeutic hypothermia than after rewarming. **Conclusions:** Hypothermic neonates exhibit more severe global impairment compared to healthy controls. This is reflected in higher myocardial performance index values and lower E'/A' ratio, which indicates diastolic dysfunction.

## Introduction

Newborns with perinatal asphyxia (PA) experience an acute reduction in oxygen delivery to all organs, leading to multi-organ dysfunction during the first days of life (DOL), with acute heart failure (HF) being a common complication. Therapeutic hypothermia (TH) for 72 h is now considered the standard of care.

The initial injury and ongoing hypoxia disrupt the physiological adaptation of fetal circulation, leading to persistently elevated pulmonary vascular resistance and pulmonary hypertension (HT) in the newborn[1]. Right and left heart functions are closely linked, with severe left ventricular (LV) dysfunction causing pulmonary venous stasis, resulting in secondary increases in pulmonary artery pressure, and subsequently impairing right ventricular function[2,3].

Bradycardia is the most common and apparent cardiovascular response following the initiation of TH. The reduced heart rate (HR) is likely due to slowed sinus node repolarization caused by decreased intracellular calcium release during TH[2]. Both LV systolic and diastolic function are impaired.

During TH, LV cardiac output (CO) decreases to approximately 67% of the post-rewarming level, mainly due to reduced HR, but also as a result of decreased stroke volume (SV)[4,5]. Myocardial relaxation and ventricular filling are critical for normal systolic performance.

An increase in the LV myocardial performance index (LVMPI) indicates impaired global systolic and diastolic function[6]. Diastolic dysfunction, often resulting from myocardial ischemia, is associated with increased mortality.

The impact of rewarming (RW) on the cardiovascular system and LV function is not well understood, with only limited data available[5,7]. Physiologically, RW increases HR, improves CO, and increases systemic pressure. After normothermia is restored, HR normalizes rapidly; however, hypoxia and myocardial ischemia may persist, resulting in persistently reduced LVSV and LVCO.

Cardiovascular support in the acute phase of cardiac dysfunction is a key component of modern treatment and is considered crucial for reducing neurodevelopmental damage[8,9].

This study presents an assessment of LV function during TH and RW using various echocardiographic (ECHO) modalities, including pulsed wave (PW) Doppler, tissue Doppler imaging (TDI), and M-mode ECHO.

## Patients and methods

### Study population

This multicenter, prospective, case-control, observational study was conducted between December 2021 and February 2024. Neonates were enrolled from the Neonatal Department and Intensive Care Medical University of Warsaw and the Department of Prematurity and Neonatal Pathology at the ŻELAZNA Medical Center Ltd St. Sophia's Specialist Hospital Medical Centre.

Written informed consent was obtained from parents, and the study was approved by the Ethical Committee of the Medical University of Warsaw, Poland (KB 55/2021). ClinicalTrials.gov ID: NCT05574855

A total of 113 neonates were included in the study: 55 in the hypothermic study group (SG) and 58 in the healthy control group (CG).

Neonates with a gestational age ≥35 weeks who experienced perinatal ischemia and were qualified for TH based on the Standards of Medical Care of Neonates in Poland were enrolled in SG ($n$ = 55) [10]. Healthy term neonates who underwent ECHO due to difficult adaptation or maternal gestational diabetes were enrolled in CG1 ($n$ = 14), and those who underwent ECHO after ductus arteriosus closure or with only a trace, hemodynamically insignificant ductus, were enrolled in CG2 ($n$ = 44). Lack of parental or guardian consent for participation in the study, congenital cardiac or genetic abnormalities, and small for gestational age below the 10th percentile were exclusion criteria. The characteristics of the neonates are shown in Tab. 1.

### ECHO measurements

Echo measurements were performed at two key time points in SG: No echo was performed on passive TH.

1. Since qualification for TH takes place up to 6 hours of life (HOL), the first examination in SG was performed between 6 and 54 HOL, after reaching a body temperature of 33.5°C (SG1).
2. The second examination (SG2) was performed after TH was completed and after RW, when the body temperature reached 36.6°C, i.e., after 90 HOL, but no later than 7 DOL.

Similar at the healthy term neonates, echo measurement was performed at two key time points:
1. Healthy term neonates (CG1) underwent ECHO at 1/2 DOL;
2. Those enrolled in CG2 underwent ECHO between 3 and 7 DOL.

All cardiac scans were performed using standard ECHO projections with a high-frequency (8–12 MHz) sector probe on a Philips Epiq ultrasound system (Philips N.V., Amsterdam, The Netherlands) by two neonatologist NB and RB with appropriate PTU certification. ECHO was performed with continuous ECG recording integrated into the ultrasound machine. To minimize the examination time to 10–15 min, ECHO measurements were performed using recorded film clips or analyzed using the Image Arena echocardiographic program. LV systolic and diastolic functions were assessed using PW Doppler, M-mode, and TDI. The assessed parameters were also determined using the MPI, a measure of global tissue efficiency.

*Evaluation of LV systolic and diastolic functions using PW Doppler and M-mode ECHO*

Left ventricular systolic function was evaluated by calculating CO in the apical five-chamber view using the following formula: CO (mL/min) = velocity time integral (VTI) × aortic area × HR. VTI was defined as the aortic stroke distance, and the aortic area was derived from the aortic diameter measured in the parasternal long-axis view. LV systolic function was also assessed using M-mode ECHO by calculating fractional shortening (FS%) in the parasternal long-axis view, using the following formula: FS% = [LV internal diameter at end diastole (LVIDd) – LVID at end systole (LVIDs)]/LVIDd × 100%.

Diastolic function was evaluated using Doppler, based on two diastolic filling waves recorded during the mitral valve (MV) opening phase in the apical four-chamber view: the early diastolic (E) wave and the late atrial (A) wave, with calculation of the E/A ratio.

*Evaluation of LV ECHO parameters using TDI*

Myocardial velocity was measured in the apical four-chamber view using color-coded TDI. Spectral Doppler gate was placed exactly in the central region of the lateral LV wall, below the mitral annulus, ensuring the ultrasound beam angle does not exceed 30°. The recorded cardiac cycle was viewed on the ultrasound system screen as three waves: systolic velocity (S'), early diastolic myocardial velocity (E'), and late diastolic myocardial velocity (A'), corresponding to atrial contraction. The E'/A' ratio was calculated. Subsequently, the LV MPI was calculated using TDI as (a – b)/b, where interval (a) was defined as the time between the end of A' and the onset of E', corresponding to the sum of the isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT), and ejection time (ET). Interval (b) (ET) was measured as the duration of S'. The sum of ICT and IRT was obtained by subtracting b from a.

**Tab. 1.** Clinical characteristics of neonates

| | SG (n = 55) | CG (*n* = 58) | | *P* value | |
|---|---|---|---|---|---|
| | | CG1 (*n* = 14) | CG2 (*n* = 44) | SG/CG1 | SG/CG2 |
| **Gestational age (weeks) ± SD** | 38.7 ± 1.7 (range: 35.1–41.1) | 39 ± 0.9 (range: 37–41) | 39.1 ± 1.0 (range: 37–41.6) | 0.69 | 0.25 |
| **Male sex (*n*; %)** | 30 (54%) | 7 (50%) | 27 (61%) | 0.76 | 0.54 |
| **Birth weight (g) (mean ± SD)** | 3255.5 ± 455.1 (range: 2300–4150) | 3788.6 ± 417.5 (range: 3200–4400) | 3714.3 ± 409 (range: 2980–4680) | <0.001 | <0.001 |
| **Cesarean delivery (*n*; %)** | 20 (36%) | 10 (71%) | 19 (44%) | 0.07 | 0.24 |
| **Vacuum (*n*; %)** | 6 (11%) | N/A | 1 (2%) | 0.07 | 0.24 |
| **1-min Apgar score (median)** | 3 (range: 0–10) | 10 (range: 8–10) | 10 (range: 10) | <0.001 | <0.001 |
| **5-min Apgar score (median)** | 6 (range: 3–10) | 10 (range: 10) | 10 (range: 10) | <0.001 | <0.001 |
| **10-min Apgar score (median)** | 7 (range: 3–10) | 10 (range: 10) | 10 (range: 10) | <0.001 | <0.001 |
| **pH (umbilical cord), median** | 6.9 (range: 6.6–7.5) | 7.3 (range: 7.3–7.4) | 7.3 (range: 7.3–7.4) | <0.001 | <0.001 |
| **$pCO_2$ (umbilical cord), median** | 73.4 (range: 23.6–153) | 43 (range: 34–66) | 40.7 (range: 31–69) | <0.001 | <0.001 |
| **BE (umbilical cord), median** | −15 (range: −29 –(+0.3)) | −0.8 (range: 2.4–(2.0)) | −2.3 (range: −5.8–(3.5)) | <0.001 | <0.001 |
| **pH (1 h), median** | 7.1 (range: 6.7–7.4) | N/A | N/A | N/A | N/A |
| **Intubation 1 DOL (*n*; %)** | 36 (65%) | N/A | N/A | N/A | N/A |
| **Non-intubation** | 19 (35%) | N/A | N/A | N/A | N/A |
| **CPAP 1 DOL (*n*; %)** | 27 (49%) | 1 (7%) | N/A | N/A | N/A |
| **Mechanical ventilation (days) (median)** | 4 (range: 1–8) | N/A | N/A | N/A | N/A |
| **NCPAP (days) (median)** | 2 (range: 1–9) | 1 (range:1) | N/A | N/A | N/A |
| **Seizure (*n*; %)** | 14 (25%) | 0 | 0 | N/A | N/A |
| **iNO (*n*; %)** | 3 (5%) | 0 | 0 | N/A | N/A |
| **MAS (*n*; %)** | 3 (5%) | 0 | 0 | N/A | N/A |
| **Surfactant (*n*; %)** | 9 (16%) | 0 | 0 | N/A | N/A |
| **Meningitis (*n*; %)** | 2 (4%) | 0 | 0 | N/A | N/A |
| **INF (*n*; %)** | 0 | 0 | 0 | N/A | N/A |
| **Pneumonia (*n*; %)** | 8 (14%) | 0 | 0 | N/A | N/A |
| **Hemorrhagic infarction (*n*; %)** | 1 (2%) | 0 | 0 | N/A | N/A |
| **Metabolic disease (*n*; %)** | 0 | 0 | 0 | N/A | N/A |
| **Abnormal MRI head** | 11 (20%) | 0 | 0 | N/A | N/A |
| **Death (*n*; %)** | 0 | 0 | 0 | N/A | N/A |

Data are presented as mean ± SD; P values indicate comparisons between individual groups.
BE – base excess; CG – control group; CPAP – continuous positive airway pressure; INF – infection; iNO – inhaled nitric oxide; MAS – meconium aspiration syndrome; MRI – magnetic resonance imaging; N/A – not applicable; NCPAP – nasal continuous positive airway pressure; SG – study group

*Evaluation of LV MPI calculated using PW Doppler versus TDI*

For LV MPI measurement using PW Doppler, the sample volume was placed below MV, directed toward the ventricular septum. The PW Doppler tracing captured both E/A (positive) and the aortic (negative) blood flow waveforms. ICT, IRT, and ET were measured, and MPI was calculated using the following formula: (ICT+IRT)/ET, which can also be expressed as (a–b)/b.

### Statistical analysis

In the initial stage of analysis, simple descriptive statistics were calculated for each variable. Differences between levels of qualitative variables were tested using the $\chi 2$ test or Fisher's exact test, depending on sample size, with a cut-off of $n = 5$. For quantitative variables, nonparametric tests were applied due to deviations from the normal distribution, as assessed using Q-Q plots. For independent samples with two levels of the variable, the Wilcoxon rank-sum test was used, whereas for samples with more than two levels, the Kruskal–Wallis test was applied. To analyze changes in variables during the treatment, the Wilcoxon signed-rang test was applied. Spearman correlation coefficients were used to analyze relationships between quantitative variables. A $p$-value <0.05 was considered statistically significant. All statistical analyses were performed using SAS/STAT software, version 15.2 (SAS Institute Inc., Cary, NC, USA).

## Results

### Baseline parameters

No statistically significant differences were observed between SG and CG regarding gestational age ($p = 0.69$ for SG/ CG1; $p = 0.25$ for SG/ CG2), gender ($p = 0.76$ for SG/CG1; $p = 0.54$ for SG/CG2), or route of delivery ($p = 0.07$ for SG/CG1; $p = 0.24$ for SG/CG2). However, significant differences were observed in body weight ($p$ <0.001); umbilical cord blood gas parameters: pH ($p$ <0.001), BE ($p$ <0.001), and median Apgar score (AS) at 1 min ($p$ <0.001) and 5 min ($p$ <0.001). Patient characteristics for each group are detailed in Tab. 1.

### ECHO parameters

Adequate ECG tracing was obtained in all newborns during the ECHO examination. The results of the ECHO assessments are presented in Tab. 2 and Tab. 3.

A significant difference was found between SG1 and CG1 in mean blood pressure (MBP), which was lower in SG ($p$ <0.001), and HR, which was also lower in SG ($p = 0.007$/ $p = 0.04$). After RW, HR increased significantly from SG1 to SG2 ($p$ <0.001), as did MBP ($p$ <0.001).

There was no significant difference in HR and MBP between CG 1 vs CG2. HR was significantly higher in SG2 than in CG2 ($p$ <0.001), as opposed to MBP.

*Assessment of LV diastolic function*

Among PW-Doppler parameters, SG1 showed significantly lower values for MV E velocity than CG1 and SG2 ($p = 0.003$ and $p$ <0.001), respectively; similarly, MV A velocity was $p = 0.04$ and $p$ <0.001, respectively. PW-Doppler revealed no statistically significant difference in the E/A ratio between SG and CG.

Tissue Doppler parameters showed SG1 with significantly lower E' velocities than in CG1 and SG2 ($p$ <0.001 and $p$ <0.001). The A' velocity was significantly lower in SG1 than SG2 $p = 0.006$, but with no significant difference vs CG1. However, the E'/A' ratio was significantly lower in SG1 than in CG1 ($p = 0.01$), with no significant difference between SG1 and SG2 (Tab. 2, Tab. 3).

We observed significantly lower mitral annular plane systolic excursion (MAPSE) values in SG1 compared with SG2 ($p$ <0.001) and between SG1 and CG1 ($p$ <0.001). No difference was found between SG2 and CG2 (Tab. 2).

*LV systolic function*

Significant differences were found in LV systolic function parameters, specifically CO and LV S' wave, with no significant differences in FS%.

Cardiac output values were significantly lower in SG1 vs CG1 ($p$ <0.001) and SG2 ($p$ <0.001), and were significantly higher in SG2 vs CG2 ($p = 0.02$). This finding aligns with tissue Doppler results: S' velocity was significantly lower in SG1 than in SG2 (after RW) ($p = 0.003$). Furthermore, S' velocity was significantly higher in SG2 than in CG2 ($p = 0.003$) (Tab. 2, Tab. 3).

*M-mode ECHO parameters*

No significant differences were found among groups regarding M-mode parameters, including LV posterior wall diameter at end-diastole (LVPWd) and interventricular septum diameter at end-diastole (IVSd). However, LVIDd values were significantly lower in SG1 vs SG2 ($p$ <0.001) and CG1 ($p$ <0.001). There was no difference between CG1and CG2 (Tab. 2).

*MPI*

PW-Doppler-based MPI showed significantly higher values in SG1 vs CG1 ($p = 0.006$) and SG2 ($p = 0.002$). Additionally, the value was significantly higher in SG2 than in CG2 ($p = 0.04$). MPI was higher in CG1 vs CG2; however, the difference was not significant.

Tissue Doppler-based MPI was significantly higher in SG1 than in SG2 ($p$ <0.001). MPI was also higher in CG1 vs CG2, although no significant difference was found between SG1 ($p = 0.08$) and CG1 ($p = 0.3$) (Tab. 2, Tab. 3).

## Discussion

Perinatal asphyxia and the changes in blood redistribution can lead to reduced myocardial perfusion and ischemia. Additionally, cardiac contractility may be negatively impacted due to acidosis and hypoxia. Therapeutic hypothermia improves the late effects in moderate and severe cases of HIE. Bradycardia is the major physiological response to TH[11]. Studies have shown that higher HR before, during, and after TH are associated with adverse outcomes[12,13]. In our study, HR and MBP were significantly lower during TH and increased after RW; however, only HR was significantly higher compared to CG. Although this publication did not detail the use of inotropic and sedative drugs, these therapeutic interventions could have contributed to the observed correlation between tachycardia and adverse outcomes.

Among PW Doppler parameters, significantly lower MV A and E velocities, as well as MAPSE were observed during TH in SG vs CG.

**Tab. 2.** Left ventricular echocardiographic measurements using pulsed wave Doppler

| Variable | Time point | SG | | CG | | *P* value* |
|---|---|---|---|---|---|---|
| **Mean blood pressure (mmHg)** | 1 | 47 range (34–64) | *P* value** | 60 range (45–74) | *P* value** | <0.001 |
| | 2 | 52 range (39–92) | <0.001 | 57 range (37–88) | 0.87 | 0.13 |
| **Heart rate (beats/min)** | 1 | 100 range (76–160) | *P* value** | 122 range (97–149) | *P* value** | 0.007 |
| | 2 | 139 range (96–179) | <0.001 | 121 range (98–163) | 0.85 | <0.001 |
| **E mv (cm/s)** | 1 | 37.5 range (19.4–59.6) | *P* value** | 45 range (34.9–60.4) | *P* value** | 0.003 |
| | 2 | 49.4 range (13.5–67.5) | <0.001 | 45.4 range (32.2–66.2) | 0.70 | 0.09 |
| **A mv (cm/s)** | 1 | 41.9 range (18.1–78.1) | *P* value** | 48.5 range (33.1–82.5) | *P* value** | 0.04 |
| | 2 | 58.7 range (33.5–92) | <0.001 | 52.5 range (38.8–85.6) | 0.08 | 0.15 |
| **E/A ratio** | 1 | 0.91 range (0.54–1.7) | *P* value** | 0.95 range (0.73–1.11) | *P* value** | 0.40 |
| | 2 | 0.88 range (0.24–1.3) | 0.25 | 0.91 range (0.46–1.03) | 0.09 | 0.97 |
| **MPI** | 1 | 0.42 range (0.25–0.88) | *P* value** | 0.35 range (0.23–0.47) | *P* value** | 0.006 |
| | 3 | 0.36 range (0.24–0.60) | 0.002 | 0.34 range (0.17–0.44) | 0.62 | 0.04 |
| **MAPSE** | 1 | 0.71 range (0.5–1.1) | *P* value** | 0.89 range (0.75–1.1) | *P* value** | <0.001 |
| | 2 | 0.83 range (0.58–1.1) | <0.001 | 0.83 range (0.67–1.1) | 0.06 | 0.69 |
| **IVSd (mm)** | 1 | 0.34 range (0.27–0.47) | *P* value** | 0.34 range (0.3–0.44) | *P* value** | 0.93 |
| | 2 | 0.35 range (0.28–0.59) | 0.81 | 0.36 range (0.28–0.50) | 0.02 | 0.03 |
| **LVPWd (mm)** | 1 | 0.33 range (0.25–0.48) | *P* value** | 0.31 range (0.27–0.38) | *P* value** | 0.23 |
| | 2 | 0.32 range (0.21–0.57) | 0.27 | 0.32 range (0.24–0.46) | 0.37 | 0.89 |
| **LVIDd (mm)** | 1 | 1.73 range (1.37–2.1) | *P* value** | 1.9 range (1.8–2.1) | *P* value** | <0.001 |
| | 2 | 1.89 range (1.6–2.2) | <0.001 | 1.9 range (1.7–2.28) | 0.63 | 0.18 |
| **CO LVOT (L/min/kg)** | 1 | 0.4 range (0.2–0.9) | *P* value** | 0.6 range (0.5–0.8) | *P* value** | <0.001 |
| | 2 | 0.7 range (0.3–1.56) | <0.001 | 0.6 range (0.3–1.5) | 0.61 | 0.02 |
| **FS%** | 1 | 34.6 range (28.6–47) | *P* value** | 32.85 range (30–38.9) | *P* value** | 0.19 |
| | 2 | 34 range (27–54) | 0.28 | 33.5 range (29–44) | 0.81 | 0.52 |

Data are presented as medians. *P values indicate significant differences among the groups; **P values indicate comparisons between subgroups.
A mv – peak late diastolic (atrial) mitral wave velocity; CG – control group; CO – cardiac output; E mv – peak early diastolic mitral wave velocity; FS% – fractional shortening; IVSd – interventricular septal diameter in diastole; LV – left ventricle; LVIDd – left ventricular internal diameter at end diastole; LVOT – left ventricular output; LVPWd – left ventricular posterior wall diameter; MAPSE – mitral annular plane systolic excursion; MPI – myocardial performance index; SG – study group

These parameters normalized after RW. A similar change in E' velocity was observed using TDI. These findings are consistent with those reported by Sobeih *et al.*[14]. In contrast, Matter *et al.* found no significant difference between newborns with asphyxia and controls using PW Doppler[15]. TDI showed a statistically significantly lower E'/A' ratio in SG1 vs CG1, which may be in partial agreement with the findings presented by Matter *et al.*[15].

In our study, significant differences in diastolic function between the SG and CG were found using both conventional PW Doppler and TDI, with TDI providing more precise measurements.

Diastolic dysfunction often results from myocardial ischemia and is a significant cause of increased mortality. Myocardial relaxation and ventricular filling are essential for normal systolic performance.

**Tab. 3.** Left ventricular measurements using tissue Doppler imaging

| Variable | Time point | SG | | CG | | *P* value* |
|---|---|---|---|---|---|---|
| **Mean blood pressure (mmHg)** | 1 | 47 range (34–64) | *P*** value | 60.5 range (45–74) | *P*** value | <0.001 |
| | 2 | 52 range (39–92) | <0.001 | 57 range (37–88) | 0.88 | 0.14 |
| **Heart rate (beats/min)** | 1 | 100 range (74–160) | *P*** value | 125 range (96–156) | *P*** value | 0.004 |
| | 2 | 144 range (106–187) | <0.001 | 121.5 range (90–159) | 0.81 | <0.001 |
| **E' LV (cm/s)** | 1 | 4.9 range (2.4–8.8) | *P*** value | 6.3 range (4.7–8.4) | *P*** value | <0.001 |
| | 2 | 6.1 range (3.11–10.3) | <0.001 | 5.9 range (3.18–8.04) | 0.19 | 0.24 |
| **A' LV (cm/s)** | 1 | 7.4 range (3.4–11.6) | *P*** value | 7.52 range (5–10) | *P*** value | 0.64 |
| | 2 | 7.98 range (4.6–15.9) | 0.006 | 7.71 range (4.93–13.8) | 0.87 | 0.20 |
| **E'/A' LV ratio** | 1 | 0.71 range (0.31–1.38) | *P* value** | 0.85 range (0.62–1.40) | *P* value** | 0.01 |
| | 2 | 0.75 range (0.42–1.13) | 0.14 | 0.76 range (0.42–1.02) | 0.10 | 0.76 |
| **S'LV(cm/s)** | 1 | 4.97 range (2.94–11.9) | *P*** value | 5.11 range (3.3–11.6) | *P*** value | 0.69 |
| | 2 | 5.79 range (3.77–8.74) | 0.003 | 5.04 range (3.36–8.36) | 0.60 | 0.003 |
| **MPI** | 1 | 0.41 range (0.14–0.9) | *P*** value | 0.37 range (0.23–0.58) | *P*** value | 0.30 |
| | 2 | 0.31 range (0.18–0.6) | <0.001 | 0.31 range (0.15–0.51) | 0.08 | 0.30 |

Data are presented as medians. * *P* values indicate significant differences among the groups; ** *P* values indicate comparisons between subgroups.
A'LV – atrial contraction left ventricular; CG – control group; E'LV – early diastolic myocardial velocity left ventricular (when the valve annulus moves away from the apex); MPI (Tei index) – myocardial performance index; SG – study group; S LV' – systolic left ventricular (when the valve cusps migrate towards the apex)

Delayed relaxation can contribute to heart failure with preserved ejection fraction, as 50–60% of diastole occurs during IRT, and intact myocardium is essential for normal early diastolic function.

Among TDI measurements, significantly lower S' velocity was observed during TH vs RW, correlating with significantly reduced CO during TH relative to CG and post-RW measurements. All parameters normalized post-RW. No significant difference was found in FS. The observed increase in CO was due to an increase in HR. This finding is consistent with another study, where post-RW increases in FS and SV did not reach statistical significance[7,16].

In our study, both PW Doppler- and TDI-based MPI values were significantly higher during TH than post-RW in both the SG and CG. Additionally, PW Doppler-based MPI values were significantly higher in SG vs CG. Although TDI-based MPI values were higher in SG than in CG, the difference was not statistically significant. A similar trend was observed in CG, with higher TDI-based MPI values at 1/2DOL vs 3/7 DOL.

This is consistent with Matter *et al.*, Jiang *et al.*, and Sobeih *et al.*, who reported higher left and right ventricular MPI values in asphyxiated newborns[14,15,17]. In contrast, Karpuz *et al.* found higher MPI values measured by PW Doppler for both ventricles in the HIE group, but the differences were not statistically significant[18].

Kanik suggests that compensatory mechanisms after birth might obscure ECHO findings, such as LV dysfunction[19], which could explain the higher MPI values at 1 DOL[6].

It is important to assess global myocardial systolic and diastolic function using both PW Doppler and TDI, including MPI.

When comparing systolic function between SG and CG, significant differences were found only in conventional PW Doppler measurements.

Cardiac output does not appear to have prognostic significance, as similar values have been reported in neonates with normal development, as well as those with short-term and long-term complications[16,20].

These changes are generally well tolerated, and although CO is reduced, it likely remains sufficient to meet the metabolic demands of the neonate, particularly during TH, when metabolic activity is further decreased. Eriksen *et al.* identified reduced metabolism, rather than myocardial dysfunction, as the primary cause of decreased CO during hypothermia[21].

## Conclusion

Hypothermic neonates exhibit more severe global impairment compared to healthy controls. This is reflected in higher MPI values and lower E'/A' ratio, which indicates diastolic dysfunction.

**Acknowledgments**

The authors would like to thank Editage for the language and technical editing of this manuscript.

**Conflict of interest**

*The authors do not report any financial or personal connections with other persons or organizations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.*

**Funding**

None.

**Author contributions**

NB initiated and designed the study, performed and assessed Doppler examinations, wrote the first draft of the paper, and incorporated co-authors' comments after each revision. VB and AWS actively participated in preparing the results. RB performed and assessed Doppler examinations, contributed to the study design and critically revised the manuscript for important intellectual content. Each author listed on the manuscript has reviewed and approved the submission of this version and takes full responsibility for its content.

## References

1. Lapointe A, Barrington KJ: Pulmonary hypertension and the asphyxiated newborn. J Pediatr 2011; 158(2 Suppl): e19–24. doi: 10.1016/j.jpeds.2010.11.008.
2. Nestaas E, Walsh BH: Hypothermia and cardiovascular instability. Clin Perinatol 2020; 47: 575–592. doi: 10.1016/j.clp.2020.05.012.
3. Pang R, Mintoft A, Crowley R, Sellwood M, Mitra S, Robertson NJ: Optimizing hemodynamic care in neonatal encephalopathy. Semin Fetal Neonatal Med 2020; 25: 101139. doi: 10.1016/j.siny.2020.101139.
4. Breatnach CR, Forman E, Foran A, Monteith C, McSweeney L, Malone F *et al.*: Left ventricular rotational mechanics in infants with hypoxic ischemic encephalopathy and preterm infants at 36 weeks postmenstrual age: a comparison with healthy term controls. Echocardiography 2017; 34: 232–239. doi: 10.1111/echo.13421.
5. Gebauer CM, Knuepfer M, Robel-Tillig E, Pulzer F, Vogtmann C: Hemodynamics among neonates with hypoxic-ischemic encephalopathy during whole-body hypothermia and passive rewarming. Pediatrics 2006; 117: 843–850. doi: 10.1542/peds.2004-1587.
6. Bokiniec R, Własienko P, Borszewska-Kornacka MK, Madajczak D, Szymkiewicz-Dangel J: Myocardial performance index (Tei index) in term and preterm neonates during the neonatal period. Kardiol Pol 2016; 74: 1002–1009. doi: 10.5603/KP.a2016.0056.
7. Wu TW, Tamrazi B, Soleymani S, Seri I, Noori S: Hemodynamic changes during rewarming phase of whole-body hypothermia therapy in neonates with hypoxic-ischemic encephalopathy. J Pediatr 2018; 197: 68–74.e2. doi: 10.1016/j.jpeds.2018.01.067.
8. Kluckow M: Functional echocardiography in assessment of the cardiovascular system in asphyxiated neonates. J Pediatr 2011; 158 (2 Suppl): e13–8. doi: 10.1016/j.jpeds.2010.11.007.
9. Giesinger RE, Bailey LJ, Deshpande P, McNamara PJ: Hypoxic-ischemic encephalopathy and therapeutic hypothermia: the hemodynamic perspective. J Pediatr 2017; 180: 22–30.e2. doi: 10.1016/j.jpeds.2016.09.009.
10. Standardy opieki medycznej nad noworodkiem w Polsce 2021. Zalecenia Polskiego Towarzystwa Neonatologicznego. Media-Press 2021.
11. Thoresen M, Whitelaw A: Cardiovascular changes during mild therapeutic hypothermia and rewarming in infants with hypoxic-ischemic encephalopathy. Pediatrics 2000; 106: 92–99. doi: 10.1542/peds.106.1.92.
12. Thomsen JH, Hassager C, Bro-Jeppesen J, Søholm H, Nielsen N, Wanscher M *et al.*: Sinus bradycardia during hypothermia in comatose survivors of out- of-hospital cardiac arrest – a new early marker of favorable outcome? Resuscitation 2015; 89: 36–42. doi: 10.1016/j.resuscitation.2014.12.031.
13. Drury PP, Gunn ER, Bennet L, Gunn AJ: Mechanisms of hypothermic neuroprotection. Clin Perinatol 2014; 41: 161–175. doi: 10.1016/j.clp.2013.10.005.
14. Sobeih AA, El-Baz MS, El-Shemy DM, Abu El-Hamed WA: Tissue Doppler imaging versus conventional echocardiography in assessment of cardiac diastolic function in full term neonates with 566 perinatal asphyxia. J Matern Fetal Neonatal Med 2021; 34: 3896–3901. doi: 10.1080/14767058.2019.1702640.
15. Matter M, Abdel-Hady H, Attia G, Hafez M, Seliem W, Al-Arman M: Myocardial performance in asphyxiated full-term infants assessed by Doppler tissue imaging. Pediatr Cardiol 2010; 31: 634–642. doi: 10.1007/s00246-010-9661-5.
16. Hochwald O, Jabr M, Osiovich H, Miller SP, McNamara PJ, Lavoie PM: Preferential cephalic redistribution of left ventricular cardiac output during therapeutic hypothermia for perinatal hypoxic-ischemic encephalopathy. J Pediatr 2014; 164: 999–1004.e1. doi: 10.1016/j.jpeds.2014.01.028.
17. Jiang K, Li Y, Xu X, Sun C: Application of the Tei index in neonates with perinatal asphyxia. Int J Clin Exp Med 2016; 9: 13111–13116.
18. Karpuz D, Celik Y, Giray D, Tasdelen B, Hallioglu O: Therapeutic hypothermia and myocardium in perinatal asphyxia: a microvolt T-wave alternans and Doppler echocardiography study. Bratisl Lek Listy 2017; 118: 765–771. doi: 10.4149/BLL_2017_144.
19. Kanik E, Ozer EA, Bakiler AR, Aydinlioglu H, Dorak C, Dogrusoz B *et al.*: Assessment of myocardial dysfunction in neonates with hypoxic-ischemic encephalopathy: is it a significant predictor of mortality? J Matern Fetal Neonatal Med 2009; 22: 239–242. doi: 10.1080/14767050802430834.
20. Montaldo P, Cuccaro P, Caredda E, Pugliese U, De Vivo M, Orbinato F *et al.*: Electrocardiographic and echocardiographic changes during therapeutic hypothermia in encephalopathic infants with long-term adverse outcome. Resuscitation 2018; 130: 99–104. doi: 10.1016/j.resuscitation.2018.07.014.
21. Eriksen VR, Trautner S, Hahn GH, Greisen G: Lactate acidosis and cardiac output during initial therapeutic cooling in asphyxiated newborn infants. PLoS One 2019; 14: e0213537. doi: 10.1371/journal.pone.0213537.