Annals of Neonatology

OPEN ACCESS
ISSN: 2636-3596

Original Article

The Immediate Impact of Therapeutic Hypothermia on Cardiac Function of Neonates with Hypoxic Ischemic Encephalopathy

Reham Wagdy[1]*, Rasha Nassra[2] , Hossam El-Morsy[3] , Marwa Farag[4]
DOI: 10.21608/anj.2023.232256.1073
***Correspondence:** Department of Pediatrics, cardiology unit, faculty of Medicine, Alexandria university, Egypt
Email: rehamwagdy@gmail.com

Abstract

Background: It is still debatable whether therapeutic hypothermia (TH) protects the myocardium of neonate with hypoxic-ischemic encephalopathy (HIE). **Aim:** The study aimed to evaluate the effect of TH on the cardiac function of neonates with HIE by echocardiography. **Subjects &Methods:** A prospective study was conducted on one hundred neonates with HIE, admitted to our institute Neonatology Unit from April 2022 till April 2023 and were eligible for TH through using Blanketrol-III device or Ice/pack jell method. Clinical profile, laboratory markers of hypoxia and troponin I level were collected. All patients had subjected to three echocardiographic scans along the three clinical phases of TH, before cooling, after 48 hours of active cooling and after rewarming in which data were analyzed and compared. **Results:** The study population gestational age was; 38±1weeks, birth weight was 3.2 ± 0.4 Kg included: 43% mild, 51% moderate and 6% severe HIE cases. High initial troponin level was found in 54% of cases. The mean of left ventricle ejection fraction (EF), fraction shortening and indices of right ventricle function increased significantly along the clinical phases of TH, P value< 0.001. After cooling, insignificant difference was found between echocardiographic indices in Blanketrol-III subgroup when compared to ICE jell /pack subgroup except in EF and Tei index being improved in Blanketrol-III subgroup, P<0.001 but not normalized. **Conclusion:** Therapeutic hypothermia (TH) could be cardioprotective in neonates with HIE even with mild encephalopathy. In absence of Blanketrol III device, ICE/Pack method for cooling might be accepted alternative.

Key words: Myocardial performance index,; reversible neonatal cardiomyopathy; Blanketrol III device; Cardiac troponin; Whole body cooling

Introduction

Perinatal hypoxia in the form of hypoxic-ischemic encephalopathy (HIE) occurs in 3–5 of 1,000 neonates in developed countries and is significantly higher in developing countries up to 25 of 1,000 neonates [1] . Cardiovascular impairment which may, be present sub clinically is a frequent complication among neonates with HIE up to 80% of infants [2, 3]. Hypoxia adversely affects the myocardium either in the primary insult and or during the reperfusion phases of injury. There is no doubt that, sick myocardium result in circulatory insufficiency which delays the brain reoxygenation and might aggravate multi-organ damage [4, 5].

Although therapeutic hypothermia (TH) had been established as the standard of care treatment for neonatal HIE as neuroprotective, the effect of whole-body cooling on myocardial function is still challenging [6, 7].

Whole body cooling could be achieved by many means, and Blanketrol-III hyper-hypothermia system offers simple programmable body temperature with minimal fluctuations in water temperature [8, 9]. However, it is still expensive and not available for all asphyxiated neonates especially in low- and middle-income countries. A reduced fractional shortening after perinatal asphyxia has been found in some studies [10] but not in others [11]. Tissue Doppler derived indices as myocardial performance index (MPI) could be more sensitive and reliable tools for assessment of cardiac function in newborn [11].

Aim of the study

The current study aimed to compare the myocardial function before and immediately after therapeutic hypothermia for neonates with HIE using echocardiography and TDI derived MPI.

Patients and Methods

Study design and setting

The current study is a prospective study, approved by ethical committee of our institute according to Declaration of Helsinki with IBR number; 0107176. All

cooled neonates with HIE, born at Alexandria Main Maternity Hospital (AMMH), admitted to the neonatal intensive care unit (NICU) of Alexandria main university hospital (AUH) over one year period; from April 2022 to April 2023 were enrolled in the present study after informed parental consent.

Patients: All the enrolled neonates with HIE between gestational age 35– 42 weeks, were selected consecutively and planned for therapeutic hypothermia with respect to the criteria of The American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) of birth asphyxia [12].

According to NICU protocol in our institute, neonates with mild HIE and low Apgar score (< 6) and or poor arterial blood gases were also eligible for the present study [13]. Neonates with congenital cyanotic heart disease, multiple congenital anomalies, GA ≤ 34 weeks or birth weight <1800 gram were excluded.

Methods: Neonates with HIE received whole-body cooling within the first 6 hours after birth, with a target rectal temperature between 33.5 °C and 34.5 °C for 72 h under close monitoring with a probe and were then rewarmed to 37 °C at a rate of 0.5 °C/h.

Active cooling is done either through Blanketrol-III device or through passive cooling combined with hot and cold jell packs. The choice between the two methods is related to the availability of the device. If the Blanketrol III is already was occupied by a patient, we made for use passive cooling combined with cold jell packs. The Blanketrol III hyper-hypothermia system is a product of GENTHERM Company (serial No: 106130311862072(21)202311419) with minimal fluctuations in water temperature. While, effective passive cooling method was done according to Queensland guidelines through turning off the warmer or incubator, removing clothes, and not covering the baby with a

blanket and adding cool packs over his body [14].

Patients' data: In the current work, one hundred and eleven neonates with HIE were eligible. However, only one hundred patients completed the study till the third scan echocardiography as illustrated in figure (1). Patient data were obtained prospectively from medical records, including gestational age, Apgar score at 1, 5 and 10 minutes, complete blood count (CBC), initially measured cardiac Troponin I (cTnI) (Roche Diagnostics, GmbH, Mannheim, Germany; cTnI levels were determined with a one- step enzyme-linked immunosorbent assay (ELISA) applied to the RxL Dimension analyser. The lower limit of detection was 0.01 ng/ml as declared by the manufacturers.), arterial blood gas values, and history of the inotropic medication. For each participant, three echocardiography scans were done for assessment of myocardial function. The first was on day 1, in the first 6 hours of life and before cooling (intervention), the second scan was at 48 hours, during cooling, and the third scan was on day 4, after rewarming and all these data were compared.

Echocardiography: Echocardiography was performed using GE Vivid IQ premium machine (serial No: 5720863 S1727016 Rev6), through 5–11 MHz GE, 12 S-RS probes, with M mode, 2D-dimentional, Pulsed wave Doppler (PW) and Pulsed Wave Tissue Doppler (TDI) modalities by single operator. Biventricular systolic and diastolic function were evaluated through measuring the following parameters; Ejection fraction (EF: Normal >55%), Fractional shortening (FS: Normal >28%), Tricuspid annular plane systolic excursion (TAPSE: >8mm), E/A ratio (normal>0.8) and MPI by TDI for left and right ventricles (RV-MPI $<0.42 \pm 0.14$) (LV-MPI $<0.37 \pm 0.10$) in first days of life [15-18]. In addition to, measurement of parameters of pulmonary hypertension defined as tricuspid regurgitant velocity ≥2.5 m/s and/or bidirectional PDA with

assessment of pulmonary acceleration time (PAAT) [19]

The patients were further subdivided into two subgroups according to the modality of TH: subgroup I (Ice/Pack) and subgroup II (Blanketrol-III). The clinical profile, laboratory data and the cardiac function of both subgroups were compared.

Ethics Approval

The study was approved by the Faculty of Medicine, Alexandria University Research Ethics Committee, and the confidentiality of patients' data was respected. The ethical approval number is 0107176 on 21-4 -2022.

Informed parental consents were obtained from caregivers of all enrolled newborns.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 26.0. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to verify the normality of distribution. Qualitative data and quantitative data were described. Significance of the obtained results was judged at the 5% level. Chi-square test, Fisher's Exact or Monte Carlo correction, Student t-test, Mann Whitney test, Repeated measures ANOVA Friedman's, ANOVA test, Cochran's Q, Pearson coefficient and Spearman coefficient.

Results

In total, one hundred cooled neonates with HIE during the study period were eligible and included in the data analysis. The mean gestational age of cases was 38±1 week, birth weight 3.2 ± 0.4 Kg, mean of 12.5 % for BMI with low mean of APGAR score at 5 minutes of 6±1 as shown table (1). Fifty one cases out of the 100 cases were classified as moderate HIE, and 43 were classified as mild HIE and only 6 cases were severe based on Sarnat staging system. Nineteen neonates had PPHN and were mechanically ventilated, while 23% of cases received inotropes. The initial vital sign, laboratory markers of hypoxia and cardiac enzymes were summarized in table (2). High troponin level was found among 54% of

study population (> 0.030 ng/ml). During cooling period there were no reported cases of significant bradycardia. However, the heart rate was significantly lower in cases on day 1 and increased to normal values after re-warming as shown in table (3).

Echocardiography: The RV systolic and diastolic performance, including (TAPSE, E/A) ratio as well as RV-MPI increased significantly along the clinical phases of TH (before cooling, after 48 hours of cooling and after rewarming), P value< 0.001 as shown in table 3. Also, LV-EF and LVFS were significantly improved after rewarming when compared to corresponding values before TH, P value< 0.001 as shown in table (3). While, the mean of LV E/A and LV-MPI showed no statistical difference before cooling and after rewarming as shown in table (3).

A negative correlation between core body temperature and LV-EF (r = -0.204, P= 0.041) and positive correlation between core body temperature and LV-MPI (rho = 0.408, P= <0.001*)

No other correlations were found between echo variables and core body temperature during cooling or with oxygen saturation before cooling.

Of noted, in the current study, forty-seven cases had TH by Blanketrol III device (sub-group II) and another fifty three cases had TH by passive cooling/ Ice Jell packs (sub-group I). No significant difference was found in the clinical or laboratory profile of both subgroups I & II except in LDH, CRP, platelet count and AST.

Figure (2) showed the pattern of heart rate variability in both subgroups along phases of TH and it was almost similar with no significant difference. Comparing echocardiographic variables of subgroups, I & II revealed no significant difference in echo variables of RV function during cooling or after rewarming as shown in tables (4 & 5). While, for LV, the EF and LV-MPI were significantly changed, respectively in subgroup II compared to subgroup I

during TH and after rewarming as shown in tables (4 & 5).

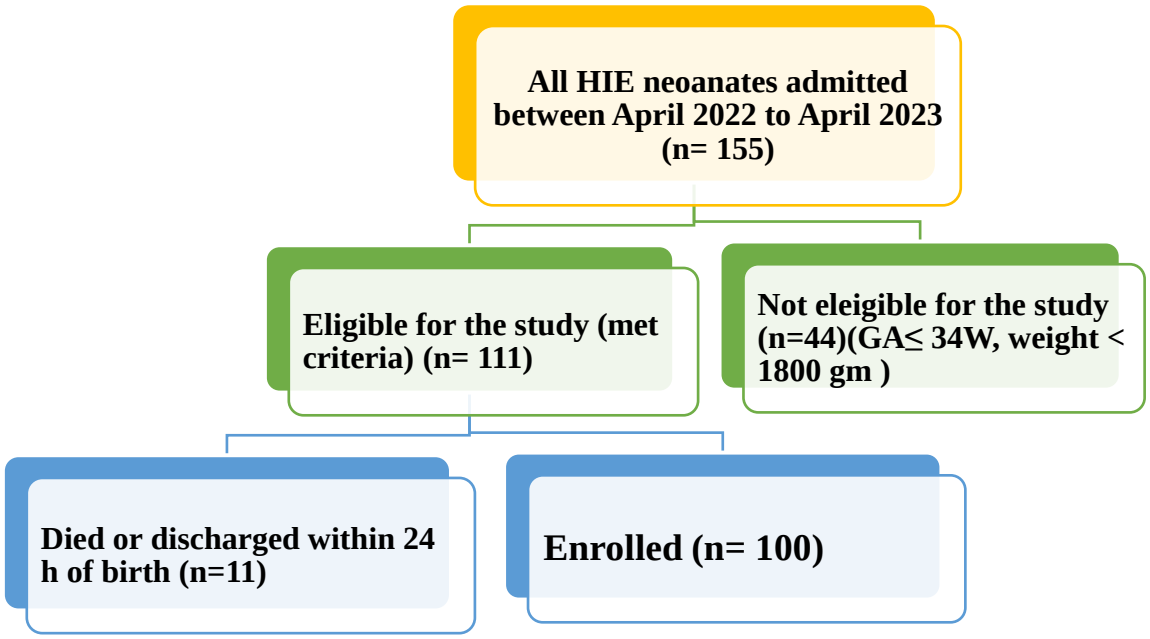

Figure 1. Flowchart describing the recruitment of eligible patients.
HIE = hypoxic ischemic encephalopathy.

Table (1): Distribution of demographic data, resuscitation data and perinatal risk factors

Type of data		No.	%
Gender	Male	49	49.0%
	Female	51	51.0%
Consanguinity	Positive	45	45.0%
	Negative	55	55.0%
MOD	NVD	46	46.0%
	CS	54	54.0%
Resuscitation	Initial steps	37	37.0%
	PPV	57	57.0%
	ETT + Ambu	5	5.0%
	ETT + CPR	1	1.0%
GA (weeks)			
Min. – Max.		35 – 42	
Mean ± SD.		38 ± 1	
Weight (Kg)			
Min. – Max.		2100 – 4400	
Mean ± SD.		3217 ± 456	
APGAR at 1 min			
Min. – Max.		2 – 6	
Mean ± SD.		4 ± 1	
APGAR at 5 min			
Min. – Max.		4 – 9	
Mean ± SD.		6 ± 1	
Sarnat classification: Mild Moderate Severe		43 (43%) 51 (51%) 6 (6%)	
ASS morbidities			
RD		1 (1%)	
IDM		3 (3%)	
Sepsis		13 (13%)	
PPHN		19 (19%)	
None		64 (64%)	

MOD: Mode of delivery; NVD: Normal vaginal delivery; CS: Cesarean section PPV: Positive pressure ventilation; ETT: Endotracheal tube CPR: Cardiopulmonary resuscitation; PROM: Prolonged rupture of membrane IQR: Inter quartile range; SD: Standard deviation; DM: Diabetes mellitus; PET: Preeclampsia

Table (2): The initial vital signs and laboratory profile of the studied cases before TH

Item	Min. – Max.	Mean ± SD.	Median (IQR)
Vital signs			
HR beat/M	58 –112	93 ± 9.56	95
Systolic BP (mmHg)	34-87	57.1± 2.3	55.5
Diastolic BP(mmHg)	15-44	30.4± 3.4	30.5
Temperature C	35.0 – 37.2	36.4 ± 0.6	36.5 (35.9 – 36.9)
CBC			
HB (gr/dL)	11.1 – 21.1	16.0 ± 2.2	16.1 (14.6 – 17.5)
HCT %	32.0 – 61.0	46.0 ± 6.6	45.1 (42.1 – 50.3)
WBC (x1000/µL)	5.5 – 43.0	16.1 ± 7.5	14.3 (11.0 – 19.5)
PLT (x1000/µL)	103 – 756	312 ± 134	298 (211 – 383)
CRP (mg/dL)	0.0 – 50.0	4.6 ± 6.4	2.5 (1.2 – 5.4)
Troponin I (ng/mL)	0.0 – 0.70	0.10 ± 0.13	0.07 (0.03 – 0.10)
CKMB (ng/mL)	3.9 – 163.0	27.5 ± 24.65	18.45 (13.0 – 34.0)
LDH (U/L)	90 – 989	467 ± 302	385 (172 – 765)
ALT (U/L)	11 – 44	21 ± 6	19 (17 – 25)
AST (U/L)	33 – 128	80 ± 18	79 (66 – 93)
BUN (mg/dl)	12 – 66	37 ± 11	38 (30 – 44)
Creatinine (mg/dl)	0.2 – 2.1	1.05 ± 0.42	1.1 (0.7 – 1.4)
ABG			
PH	6.90 – 7.27	7.09 ± 0.13	7.10 (7.10 – 7.26)
PCO2(mmHg)	13 – 100	49 ± 16	49 (36 – 60)
HCO3(mEq/L)	5.0 – 28.0	17.7 ± 3.9	18.0 (15.1 – 19.8)
BE(mmol/L)	-24.5 – 12	-16.8 ± 5.3	-14.1 (-12.9 – -6.1)

CBC: complete blood count. CRP-Cero active protein; IQR: Inter quartile range; SD: Standard deviation

Table (3): Comparison between echocardiographic parameters of biventricular function before cooling to after 48 hours to after off cooling of the studied cases (n=100).

Item		Before TH	After 48 hrs	After off cooling	Test of sig.	P
HR (beat/M)	(Min. – Max.)	58 – 112	80 – 114	134 – 172	F=1422.63*	<0.001*
	Mean ± SD.	93 ± 9.56	94.6 ± 7.98	155.2 ± 9.03		
Sig. bet. grps.		p1=0.686,p2<0.001*,p3<0.001*				
EF (%)	Min. – Max.	23 – 72	22 – 72	23 – 77		
	Mean ± SD.	45.9 ± 10.4	43.7 ± 10.4	52.6 – 11.1	Fr = 36.373	<0.001*
Sig. bet. grps.		p1 (0.359), p2 (<0.001*), p3 (<0.001*)				
FS (%)	Min. – Max.	11 – 37	10 – 39	9 – 40		
.	Mean ± SD	21 ± 5	20 ± 6	24 ± 7	Fr = 19.882	<0.001*
Sig. bet. grps.		p1 (0.648), p2 (<0.001*), p3 (0.007*)				
RV E/A ratio	Min. – Max.	0.33 – 1.40	0.30 – 1.40	0.30 – 1.60		
	Mean ± SD.	0.79 ± 0.26	0.71 ± 0.23	0.85 ± 0.24	Fr = 49.887	<0.001*
Sig. bet. grps.		p1 (0.002*), p2 (<0.001*), p3 (0.001*)				
LV E/A ratio	Min. – Max.	0.49 – 1.33	0.54 – 1.57	0.10 – 1.23		
	Mean ± SD.	0.84 ± 0.19	0.98 ± 0.19	0.85 ± 0.13	Fr = 30.122	<0.001*
Sig. bet. grps.		p1 (<0.001*), p2 (<0.001*), p3 (0.730)				
TAPSE (Cm)	Min. – Max.	0.30 – 1.90	0.40 – 2.00	0.30 – 2.10		
	Mean ± SD.	0.85 ± 0.35	0.88 ± 0.37	1.03 ± 0.36	Fr = 33.356	<0.001*
Sig. bet. grps.		p1 (1.000), p2 (<0.001*), p3 (<0.001*)				
PAAT (msec)	Min. – Max.	21 – 114	28 – 135	8 – 114		
	Mean ± SD.	56 ± 14	65 ± 21	59 ± 18	Fr = 2.437	0.296
TR (M/sec))	Min. – Max.	10 – 66	9 – 56	8 – 55		
	Mean ± SD.	27 ± 12	29 ± 13	22 ± 11	Fr = 34.478	<0.001*
Sig. bet. grps.		p1 (0.688), p2 (<0.001*), p3 (<0.001*)				
IVC	>50 %	70 (70%)	77 (77.0%)	86 (86.0%)	Cochran's Q	0.028*
	<50 %	30 (30.0%)	23 (23.0%)	14 (14.0%)	7.148	
Sig. bet. grps.		p1 (0.730), p2 (0.401), p3 (0.023*)				
DA	Open	76 (76.0%)	26 (26.0%)	26 (26.0%)	Cochran's Q	<0.001*
	Closed	24 (24.0%)	74 (74.0%)	74 (74.0%)	64.935	
Sig. bet. grps.		p1 (<0.001*), p2 (1.000), p3 (<0.001*)				
RV MPI	Min. – Max.	0.04 – 0.48	0.20 – 0.45	0.20 – 0.49		
	Mean ± SD.	0.33 ± 0.07	0.34 ± 0.06	0.36 ± 0.06	Fr = 26.950	<0.001*
Sig. bet. grps.		p1 (0.537), p2 (<0.001*), p3 (0.001*)				
LV MPI	Min. – Max.	0.45 – 0.89	0.38 – 1.00	0.45 – 0.94		
	Mean ± SD.	0.65 ± 0.10	0.65 ± 0.14	0.64 ± 0.12	Fr = 1.828	0.401

Ejection fraction (EF:) Fractional shortening (FS: Tricuspid annular plane systolic excursion (TAPSE), myocardial performance index (MPI), Tricuspid resurge (TR) & pulmonary artery acceleration time (PAAT).DA:ductus arteriosus. χ^2: Chi-square test

Fr: for Friedman's ANOVA test, pairwise comparison between every 2 groups were done using Dunn- Bonferroni Post Hoc method,

p1: p-value for comparing between before TH and after 48 hrs

p2: p-value for comparing between after 48 hrs and after off cooling

p3: p-value for comparing between before TH and after off cooling *: Statistically significant at $p \leq 0.05$

Table (4): Comparison of the indices of myocardial function at 48 hours after therapeutic hypothermia of the studied subgroups

		Cooling		Test of sig.	P
		ICE Pack n= 53	Blanketrol-III n= 47		
EF (%)	Min. – Max.	18 – 72	15 – 63	U= 892.5	0.014*
	Mean ± SD.	35 ± 12	39 ± 9		
	Median (IQR)	32 (26 – 43)	39 (33 – 44)		
	Low	45 (90.0%)	48 (96.0%)		FEp= 0.436
	Normal	5 (10.0%)	2 (4.0%)		
FS (%)	Min. – Max.	7 – 36	8 – 32		
	Mean ± SD.	16 ± 7	17 ± 4	U= 980	0.062
	Median (IQR)	16 (11 – 19)	17 (14 – 19)		
	Low	43 (86.0%)	47 (94.0%)		0.182
	Normal	7 (14.0%)	3 (6.0%)		
RV E/A ratio	Min. – Max.	0.32 – 1.40	0.30 – 1.40		
	Mean ± SD.	0.72 ± 0.24	0.69 ± 0.23		
	Median (IQR)	0.65 (0.52 – 0.90)	0.67 (0.56 – 0.76)	U= 1214	0.804
	Low	32 (64.0%)	38 (76.0%)		
	Normal	18 (36.0%)	12 (24.0%)		0.190
LV E/A ratio	Min. – Max.	0.79 – 1.23	0.54 – 1.57		
	Mean ± SD.	0.95 ± 0.10	1.00 ± 0.25	U= 1080	0.241
	Median (IQR)	0.94 (0.88 – 0.99)	0.97 (0.88 – 1.10)		
TAPSE (cm)	Min. – Max.	0.40 – 2.00	0.40 – 1.80		
	Mean ± SD.	0.87 ± 0.39	0.89 ± 0.35	U= 1167	0.565
	Median (IQR)	0.75 (0.60 – 1.20)	0.80 (0.60 – 1.00)		
	Low	10 (20.0%)	6 (12.0%)		0.275
	Normal	40 (80.0%)	44 (88.0%)		
PAAT (msec)	Min. – Max.	33 – 135	28 – 135		
	Mean ± SD.	66 ± 20	64 ± 23	U= 1140.5	0.450
	Median (IQR)	62 (55 – 73)	59 (48 – 78)		
TR (M/sec)	Min. – Max.	10 – 56	9 – 50		
	Mean ± SD.	33 ± 13	26 ± 11	U= 813	0.003*
	Median (IQR)	35 (21 – 43)	23 (18 – 32)		
IVC >50 %		38 (76.0%)	39 (78.0%)		0.812
<50 %		12 (24.0%)	11 (22.0%)		
DA open		13 (26.0%)	13 (26.0%)		1.000
Closed		37 (74.0%)	37 (74.0%)		
RV MPI	Min. – Max.	0.21 – 0.45	0.20 – 0.44		
	Mean ± SD.	0.33 ± 0.06	0.35 ± 0.05	U= 1020	0.111
	Median (IQR)	0.34 (0.31 – 0.37)	0.36 (0.33 – 0.38)		
LV MPI	Min. – Max.	0.38 – 1.00	0.48 – 0.81		
	Mean ± SD.	0.71 ± 0.16	0.60 ± 0.07	t= 4.670	<0.001*
	Median (IQR)	0.71 (0.57 – 0.84)	0.59 (0.54 – 0.66)		

Ejection fraction (EF:) Fractional shortening (FS: Tricuspid annular plane systolic excursion (TAPSE), myocardial performance index (MPI) Tricuspid resurge (TR) & pulmonary artery acceleration time (PAAT).DA: ductus arteriosus. χ^2: Chi-square test

Table (5): Comparison the indices of myocardial function after rewarming of the studied subgroups

Item		Cooling		Test of sig.	P
		ICE Pack n= 53	**Blanketrol-III n= 47**		
EF (%)	Min. – Max.	15 – 70	24 – 68		
	Mean ± SD.	43 ± 12	49 ± 10	t= -2.842	0.005*
	Median (IQR)	43 (35 – 50)	49 (44 – 56)		
Low		41 (82.0%)	32 (64.0%)		0.043*
Normal		9 (18.0%)	18 (36.0%)		
FS (%)	Min. – Max.	6 – 37	10 – 32		
	Mean ± SD.	20 ± 7	21 ± 5	t= -0.788	0.432
	Median (IQR)	20 (15 – 26)	21 (17 – 24)		
Low		36 (72.0%)	39 (78.0%)		0.488
Normal		14 (28.0%)	11 (22.0%)		
RV E/A ratio	Min. – Max.	0.30 – 1.60	0.36 – 1.32		
	Mean ± SD.	0.90 ± 0.28	0.81 ± 0.19	U= 1024	0.118
	Median (IQR)	0.90 (0.70 – 1.10)	0.80 (0.73 – 0.90)		
Low		16 (32.0%)	22 (44.0%)		0.216
Normal		34 (68.0%)	28 (56.0%)		
LV E/A ratio	Min. – Max.	0.10 – 1.00	0.69 – 1.23		
	Mean ± SD.	0.83 ± 0.14	0.87 ± 0.11	U= 1103.5	0.312
	Median (IQR)	0.84 (0.77 – 0.93)	0.87 (0.79 – 0.95)		
TAPSE (cm)	Min. – Max.	0.30 – 2.10	0.40 – 1.50		
	Mean ± SD.	1.02 ± 0.44	1.05 ± 0.26	U= 1117	0.357
	Median (IQR)	1.00 (0.70 – 1.20)	1.10 (0.90 – 1.20)		
Low		8 (16.0%)	3 (6.0%)		0.110
Normal		42 (84.0%)	47 (94.0%)		
PAAT (msec)	Min. – Max.	8 – 114	23 – 87		
	Mean ± SD.	63 ± 20	55 ± 15	U= 937	0.031*
	Median (IQR)	61 (51 – 73)	50 (45 – 66)		
TR (M/sec)	Min. – Max.	10 – 55	8 – 40		
	Mean ± SD.	26 ± 12	19 ± 9	U= 773.5	0.001*
	Median (IQR)	23 (17 – 34)	18 (10 – 25)		
IVC >50 %		45 (90.0%)	41 (82.0%)		0.249
<50 %		5 (10.0%)	9 (18.0%)		
DA Open		16 (32.0%)	10 (20.0%)		0.171
Closed		34 (68.0%)	40 (80.0%)		
RV MPI	Min. – Max.	0.20 – 0.49	0.21 – 0.45		
	Mean ± SD.	0.35 ± 0.06	0.37 ± 0.06	U= 1066.5	0.204
	Median (IQR)	0.37 (0.31 – 0.39)	0.38 (0.35 – 0.40)		
LV MPI	Min. – Max.	0.48 – 0.94	0.45 – 0.81		
	Mean ± SD.	0.70 ± 0.13	0.62 ± 0.09	t= 3.653	<0.001*
	Median (IQR)	0.69 (0.59 – 0.83)	0.61 (0.55 – 0.68)		

Ejection fraction (EF:) Fractional shortening (FS: Tricuspid annular plane systolic excursion (TAPSE), myocardial performance index (MPI) Tricuspid resurge (TR) & pulmonary artery acceleration time (PAAT).DA: ductus arteriosus. χ^2: Chi-square test FE: Fisher Exact t: student t test U: Mann Whitney test. p: p-value for comparing between the two studied groups

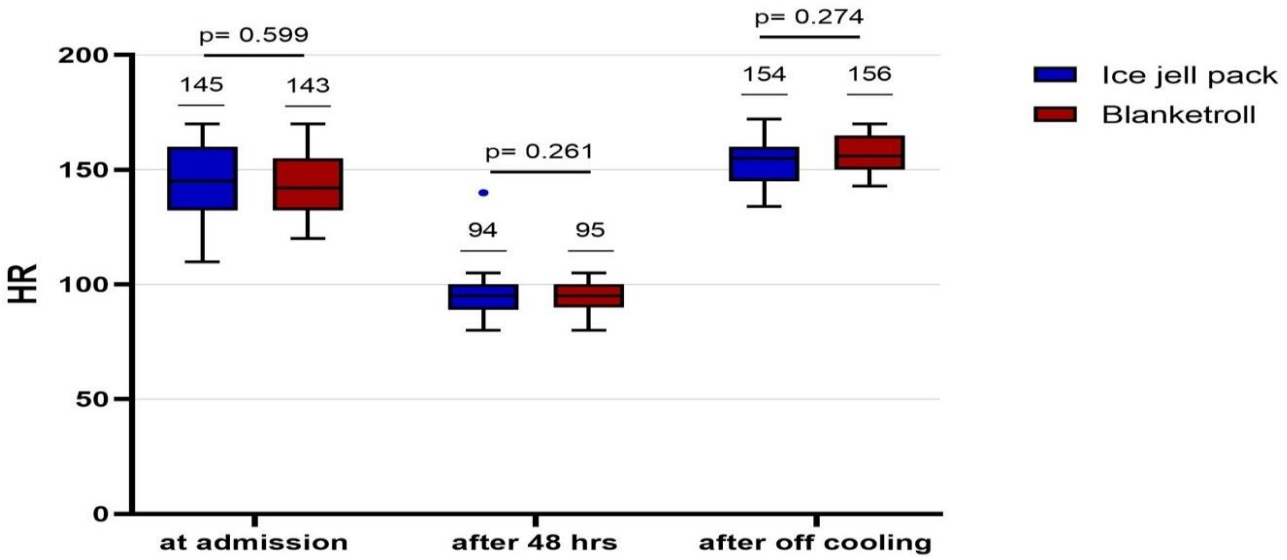

Figure 2: The pattern of heart rate changes (in beats/minute) before to after 48 hours to after off cooling of the Blanketrol III subgroup versus Ice jell pack subgroup.

Discussion

HIE is a public health problem in developing countries and many studies had reported the impaired cardiac performance in neonates with HIE [3, 5]. Although, TH has been established as the standard of care treatment for neuroprotection for neonates with HIE, still it is debatable for cardiac protection. Optimizing cardiovascular system (CVS) during TH may improve the long-term outcomes of these infants. It remains unclear whether TH promotes CVS recovery in these infants or contributes to progressive CVS dysfunction especially with associated sinus bradycardia. This challenged us to conduct this work to explore the immediate effect of TH on the cardiac function of neonates with HIE post cooling.

The cardiac performance of one hundred neonates with HIE (mean gestational age 38±1 weeks and birth weight 3.2±0.4 Kg) was initially evaluated by monitoring heart rate, BP, cardiac enzymes and echocardiography. Whole body cooling started within 6 hours after birth then

echocardiography was re-evaluated and compared during TH and after cooling.

In the current study, high troponin level sampled within the first 4 hours was found among 54% of the study population and this is explained by the severity of perinatal asphyxia and failure of adaptation of cardiovascular system to hypoxia thus, brain and myocardium develop ischemic lesions [10, 20]. Similarly found by Matter et al., who found significantly higher troponin I in neonates with HIE versus healthy controls. It is important to mention that sepsis involved only 13% of the cases while PPHN involved 19% [11].

The initial levels of heart rate and blood pressure before TH were subnormal values as being affected by perinatal hypoxia [21]. In consistent to Vergales et al., who conducted a study over 37 neonates and found depressed heart rate in first 24 hour after birth explained by autonomic dysfunction secondary to HIE [22]. In the present study, evaluation of RV function by conventional echo and TDI-derived MPI showed significant improvement along the clinical phases of TH (before cooling, after 48 hours of cooling and after rewarming). On the other side, LV had showed significant improvement in systolic function (EF, FS) at day 4 after rewarming but not yet normalized. While TDI-derived MPI of LV and diastolic function showed no significant changes along the three echo scans. That might need longer time for follow up.

In agreement with Giesinger et al., who studied fifty-three neonate with HIE with a mean gestation age of 38.8± 2.0 weeks and birthweight of 3.33±0.6 kg and reported that the measures of RV systolic performance (TAPSE and fractional area change) were initially lower than published normative data then increased significantly by time during cooling and after rewarming [23]. However, no change was identified over time in EF or FS among the cases. In contrast to our results of the LV. This might be explained by different severity of HIE among study

population as his study included 25% mild, 50% moderate and 25% severe HIE cases versus 43% mild, 51% moderate and 6% severe HIE cases in the current study.

Yajamanyam et al., conducted a study over 20 term infants receiving TH on days 1–3 and demonstrated that TDI-derived MPI of LV was higher in cases compared to controls before cooling [24]. After rewarming, MPI of LV has improved but not yet normalized. While FS and TDI-derived MPI of RV was similar between cases and controls all through. The study population included only moderate and severe HIE cases and he stated that LV dysfunction might persist for longer duration post cooling.

Also, Nestaas et al., showed impaired myocardial function in Forty-four infants with HIE by low strain-rate indices but it improved significantly at day 4 cooled for 72hours [25].

On the other hand, Rodriguez et al., 2022 found significant improvement of TD-LV-MPI after cooling and not for RV-MPI [26]. They also concluded that FS was not useful to determine systolic dysfunction as it was not changed and recommended the use of EF.

Furthermore, TR gradient, PAAT and IVC-CI were assessed to estimate PH. Initially the values were low, then worsened by cooling and finally improved after rewarming. Thus, TH regardless the method of cooling improves pulmonary hypertension parameters [27].

In light of the above mention studies, impact of TH on the cardiovascular system was evidenced through improving the hemodynamic of the neonate, (HR) to normal values, BP and the cardiac dysfunction regardless the used tool for identification and also PHT. This could be explained as hypothermia possibly decreases the ATP consumption, decreases oxygen free radicals and inflammatory mediators involved in tissue injury [28]. Comparing the subgroup, I and II, there was no statistically significant difference as regard mode of delivery, anesthesia, resuscitation data and also APGAR score at 1 minute or at 5 minutes,

but there was significant difference as regard APGAR score at 10 minutes. However, no significant difference was found between the two groups regarding patients scored below 7 or those scored above 7. No significant difference was found between the two groups regarding hypoxia parameters or cardiac enzymes. However, LDH, CRP, platelet count and AST were significantly different between the two groups but these are not specific for myocardial injury [29].

Surprisingly, the heart rates showed the same pattern of changes in both study subgroups. Also, insignificant difference was observed in echocardiographic variables of cardiac function between Blanketrol-III subgroup when compared to Ice/pack subgroup during the second and third scan phase respectively, except for EF, LV-MPI and TR gradient. In which, LV-MPI and TR were greater after rewarming of Ice/pack cooling rather than Blanket-Rol- III subgroup. However, longer-term follow up for larger scale study might show better improvement.

Up to our knowledge, this first study in literature demonstrating the comparable cardioprotective effect of the two cooling modalities.

Study limitation: This study has some limitation, First: short follow up time. Further longer follow up and larger scales studies are recommended to evaluate role of different cooling modality on the cardiac protection as well as on the other organs. Detailed Tissue Doppler and speckle tracking echocardiographic studies are recommended for further cardiac evaluation.

Conclusions

Therapeutic hypothermia might be cardioprotective in neonates with HIE proved by echocardiographic parameters especially MPI. It is possible for perinatal hypoxia to harm a newborn's myocardium, despite mild encephalopathy. Ice/pack cooling has a very close protective effect on heart of neonate with HIE, almost similar to Blanket-Rol III modality that’s highly

recommends its use especially in absence of device cooling modalities.

Lists of abbreviation:

- Hypoxic ischemic encephalopathy (HIE)
- Therapeutic hypothermia (TH)
- Tissue Doppler Echocardiography: TDE
- Myocardial Performance Index: MPI
- Ejection Fraction: EF.

Acknowledgements

The study group is grateful to the NICU team who supported this work

Author's contributions

The study conception and design were done by RW and MF. Echocardiography and were performed and analyzed by HM and RW. Data acquisition by HM and MF. Analysis and interpretation were performed by all members of the group. The drafting the manuscript was done by MF and HM. Critical review was carried out by RW and RN. The authors have read and approved the manuscript.

Conflict of interest

The authors declare that they have no known financial or non-financial competing of interest.

Funding

On behalf of authors, I declare that they have no competing interests.

Author's details

[1]Department of Pediatrics, Cardiology Unit, Faculty of Medicine, Alexandria University, Egypt

[2]Department of medical Biochemistry, faculty of Medicine, Alexandria university, Egypt

[3]Clinical demonstrator, pediatric department, Alexandria main children hospital, Alexandria, Egypt.

[4]Department of pediatrics, intensive care neonatology unit, faculty of Medicine, Alexandria university, Egypt

Date received: 1st August 2023, accepted 15th September 2023

References

1- Gupta S and Singh Y. Heamodynamics in the asphyxiated neonates and effect of thraputic hypothermia. in: Seri I, Kluckow M (editors).Heamodynamics and Cardiology. 3rd ed.Philadeilphia: Elsevier; 2019. 503-19.

2- Giesinger RE, Bailey LJ, Deshpande P, McNa- mara PJ. Hypoxic-ischemic encephalopathy and therapeutic hypothermia: the hemody- namic perspective. J Pediatr. 2017 Jan; 180: 22–e2.

3- Rakesh K, Vishnu Bhat B, Adhisivam B, Ajith P. Effect of therapeutic hypothermia on myocardial dysfunction in term neonates with perinatal asphyxia – a randomized controlled trial. J Mater Fetal Neonatal Med.

(2017) 31:2418–23. doi:10.1080/14767 058. 2017.1344633

4- E.M.W. Kooi et al. Cerebral autoregulation in sick infants Cur. Insights Clin. Perinatol (2020); 47(3):449-67.

5- Thoresen M, Whitelaw A. Cardiovascular changes during mild therapeutic hypothermia and rewarming in infants with hypoxic-ischemic encephalopathy. Pediatrics 2000; 106(1 Pt 1):92-9.

6- Johnston MV, Fatemi A, Wilson MA, Northington F. Treatment advances ineonatal neuroprotection and neurointensive care. Lancet Neurol 2011; 10(4):372-82.

7- Y. Celik, A. Atıcı, S. Gulası, C. Okuyaz, K. Makharoblıdze, M.A. SungurComparison of selective head cooling versus whole-body cooling Pediatr Int, 2016, 85:27-33. https://doi.org/10.1111/ped.12747.

8- Tagin M, Woolcott C, Vincer M, Whyte R, Stinson D. Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematice review and meta-analysis. Arch Pediatr Adolesc Med 2012; 166(6):558-66.

9- Robertson N.J, Kendall G.S, Thayyil S. Techniques for therapeutic hypothermia during transport and in hospital for perinatal asphyxial encephalopathy. Semin Fetal Neonatal Med, 15 (2010), 276-286. 15(5): 276-86.

10- Costa S, Zecca E, De Rosa G, De Luca D, Barbato G, Pardeo M, et al. Is serum troponin T a useful marker of myocardial damage in newborn infants with perinatal asphyxia? Acta Paediatr 2007; 96(2):181-4.

11- 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(5):634-42.

12- Executive summary: Neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. Obstet Gynecol 2014; 123(4):896-901.

13- Conway JM, Walsh BH, Boylan GB, Murray DM. Mild hypoxic ischaemic encephalopathy and long-term neurodevelopmental outcome - A systematic review. Early Hum Dev 2018; 120:80-7. https://doi.org/10.1016/j.earlhumdev.2018.02.007.

14- Queensland Clinical Guideline. Hypoxic-ischaemic encephalopathy (HIE). No. MN21.11-V11-R26. Queensland Health. 2021. Available from: https://www.health.qld.gov.au/data/assets/pdf_file/0014/40162/g-hie. pdf. [Accessed in: Aug 2023].

15- Howard LS, Grapsa J, Dawson D, Bellamy M, Chambers JB, Masani ND, et al. Echocardiographic assessment of pulmonary hypertension: standard operating procedure. Eur Respir Rev 2012; 21(125):239-48.

16- Vonk MC, Sander MH, van den Hoogen FH, van Riel PL, Verheugt FW, van Dijk AP. Right ventricle Tei-index: a tool to increase the accuracy of non-invasive detection of pulmonary arterial hypertension in connective tissue diseases. Eur J Echocardiogr 2007; 8(5):317-21. https:// doi.org/ 10.1016/j.euje.2006.06.002

17- Wei Y, Xu J, Xu T, Fan J, Tao S. Left ventricular systolic function of newborns with asphyxia evaluated by tissue Doppler imaging. Pediatr Cardiiol. 2009; 30:741–6. doi: 10.1007/s00246-009-9421-6

18- 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(9):1002-9.

19- Bussmann N, El-Khuffash A, Breatnach CR, McCallion N, Franklin O, Singh GK, et al. Left ventricular diastolic function influences right ventricular - Pulmonary vascular coupling in premature infants. Early Hum Dev. (2019) 128:35–40.

20- Sehgal A, Wong F, Mehta S. Reduced cardiac output and its correlation with coronary blood flow and troponin in asphyxiated infants treated with therapeutic hypothermia. Eur J Pediatr. (2012) 171:1511–7. doi: 10.1007/s00431-012-1764

21- Vrancken SL, van Heijst AF, de Boode WP. Neonatal hemodynamics: from developmental physiology to comprehensive monitoring. Front Pediatr. (2018) 6:87. doi: 10.3389/fped.2018.00087

22- Vergales BD, Zanelli SA, Matsumoto JA, Goodkin HP, Lake DE, Moorman JR, et al. Depressed heart rate variability is associated with abnormal EEG, MRI, and death in neonates with hypoxic ischemic encephalopathy. Am J Perinatol 2014; 31(10):855-62.

23- Giesinger RE, El Shahed AI, Castaldo MP, Breatnach CR, Chau V, Whyte HE, et al. Impaired Right Ventricular Performance Is Associated with Adverse Outcome after Hypoxic Ischemic Encephalopathy. Am J Respir Crit Care Med 2019; 200(10):1294-305.

24- Yajamanyam PK, Negrine RJ, Rasiah SV, Plana MN, Javier Zamora J, K. Ewer AK. Left Ventricular Dysfunction Persists in the First Week after Re-Warming following Therapeutic Hypothermia for Hypoxic-

Ischaemic Encephalopathy Neonatology 2022; 119:510–516

25- Nestaas E, Skranes JH, Støylen A, Brunvand L, Fugelseth D. The myocardial function during and after whole-body therapeutic hypothermia for hypoxicischemic encephalopathy, a cohort study. Early Hum Dev. 2014; 90:247–52.

26- Rodriguez MJ, Martinez-Orgado J, Corredera A, Serrano I and Arruza L (2022) Diastolic Dysfunction in Neonates With Hypoxic-Ischemic Encephalopathy During Therapeutic Hypothermia: A Tissue Doppler Study. Front. Pediatr. 10:880786. doi: 10.3389/fped.2022.880786.

27- Ryan .J. Right ventricular Adaptation and failure in pulmonary hypertention. Can J Cardiol 2015; 31(4):391-406.

28- Thomsen JH, Nielsen N, Hassager C, Wanscher M, Pehrson S, Kober L, et al. Bradycardia during targeted temperature management: an early marker of lower mortality and favorable neurologic outcome in comatose out-of-hospital cardiac arrest patients. Crit Care Med 2016; 44:308- 18.

29- Special Report. Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. Circulation 1979; 59(3):607-9.

Citation: Wagdy, R., Nassra, R., El-Morsy, H., Farag, M. The Immediate Impact of Therapeutic Hypothermia on Cardiac Function of Neonates with Hypoxic Ischemic Encephalopathy. *Annals of Neonatology*, 2024; 6(1): 37-56. doi: 10.21608/anj.2023.232256.1073