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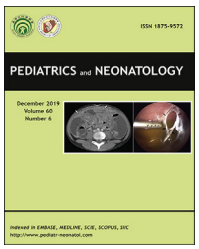

Original Article

Gastrointestinal hemodynamic changes during therapeutic hypothermia and after rewarming in neonatal hypoxic-Ischemic encephalopathy

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Background: Hypoxic-ischemic encephalopathy (HIE) is associated with disturbances in visceral blood flow velocities. Therapeutic Hypothermia (TH) is a standard of care; however, its impact on gastrointestinal blood flow in infants with HIE is unknown. The objective of this study was to assess gastrointestinal (GI) blood flow and left ventricle output (LVO) in infants with hypoxic-ischemic encephalopathy during whole body TH and after rewarming.
Methods: Serial echocardiography and Doppler evaluation of intestinal blood flow (celiac (CA) and superior mesenteric (SMA) arteries) were prospectively performed in a cohort of 20 newborn infants with HIE at 4 time points during hypothermia and after rewarming. Demographic, clinical and biochemical data were collected and analyzed for their relevance.
Results: Median gestational age and birth weight was 40 weeks (37–41) and 3410 g (2190–4950) respectively. Celiac and mesenteric artery flow remained low during hypothermia and rose significantly after rewarming [peak systolic velocity in CA (0.63 m/s to 0.77 m/s, $p = 0.004$) and SMA (0.43 m/s to 0.55 m/s, $p = 0.001$)]. This increase was temporally associated with increased left ventricular output (106 ml/kg/min to 149 ml/kg/min, $p < 0.0001$).

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Median age to reach 25% of the feeds was 5 days (1—7 days). All patients survived.
Conclusions: CA and SMA blood flow velocity and LVO did not vary during hypothermia but rose after rewarming. This may suggest protective effect of therapeutic hypothermia on gastrointestinal system. The association of these physiological changes with neonatal outcome needs further assessment.

1. Introduction

Hypoxic-ischemic encephalopathy (HIE) is the major cause of neonatal mortality worldwide with an incidence of approximately 0.7—1.2 million annually.[1] Although insult to the central nervous system is the most common outcome (70%), multiorgan dysfunction including renal (40%), pulmonary (25%), cardiac (30%), and/or gastrointestinal (30%) compromise is not infrequent.[2,3] There is evidence of altered visceral (celiac (CA), superior mesenteric (SMA) and renal artery) blood flow velocities post HIE.[4] In addition, it has been suggested that asphyxiated infants may be at risk for feeding intolerance and necrotizing enterocolitis (NEC).[5] Therapeutic Hypothermia (TH) improves neurological outcomes in asphyxiated neonates and is now a standard of care.[4] The physiologic and clinical impact of TH and rewarming on intestinal (CA and SMA) blood flow velocity is unknown. There is an association between abnormal intestinal ultrasonographic findings like reduced or absent peristalsis, increased bowel wall echogenicity and mucosal sloughing with severity of HIE in infants receiving TH treatment.[7] These changes may have relevance to the method, time of initiation and rate of enteral feed escalation. Targeted neonatal echocardiography (TNE), a term proposed for focused neonatal echocardiography in NICU, allows non-invasive estimation of cardiac function and assessment of visceral arterial flow velocities with good reproducibility.[8,9] We aimed to assess the blood flow changes in the SMA and CA and the relation of these changes to the LVO during whole body TH treatment for HIE and after rewarming and to explore its clinical relevance.

2. Methods and participants

We studied a cohort of 20 outborn newborn infants with HIE who received TH at the Hospital for Sick Children NICU, a referral center, over 2 years. Approval from the Institutional Research Ethics Board and written informed parental consent were obtained before recruiting the participants. All infants were outborn and transported to the NICU by the Acute Care Transport Service team.

2.1. Therapeutic hypothermia protocol

Moderate whole-body TH (33°C-34 °C) was initiated at the referral hospital within 6 h of birth and up to 12 h at consultant's discretion if all of the following criteria were met as defined in the ICE trial.[10]

1. Evidence of intrapartum hypoxia (**2 or more** of the following criteria)
   a. Apgar score of 5 or less at 10 min
   b. Need for mechanical ventilation or resuscitation at 10 min
   c. Cord or blood gas within one hour of birth with pH $\leq$ 7.00, OR with base deficit $\geq$16
2. Neonate $\geq$35 weeks gestational age
3. Evidence of moderate or severe encephalopathy as defined by modified Sarnat staging.

During patient transport core body temperature was maintained between 33 °C and 34 °C by removing all sources of external heat and applying ice packs if necessary.[10]

The parents of infants with HIE receiving TH treatment in NICU were approached for consent within 24 h of admission.

Exclusion criteria included presence of congenital heart disease, chromosomal anomaly, severe HIE with high likelihood of mortality, or lack of parental consent. TH involved maintaining core temperature between 33 °C and 34 °C for 72 h using the Blanketrol III TM machine. Rewarming was achieved gradually by increasing core body temperature by 0.5 °C/h over 6 h.

2.2. Demographic/biochemical/clinical data

Data included gender, gestational age, birth weight, mode of delivery, Apgar scores, need for cardiopulmonary resuscitation, duration of cardiac compression, age at the beginning of TH (hours of life), Sarnat score at initiation of TH, presence of seizures and need for anticonvulsant treatment, presence of umbilical arterial or venous lines, need for inhaled nitric oxide treatment, need for inotropic support, type and duration of total mechanical ventilation, development of NEC before NICU discharge, time taken to achieve 25% of enteral feeds, total duration of hospital stay in days, and survival to NICU discharge.

Patients were followed through their NICU course to record indices of cardiorespiratory stability, biochemical tests of end-organ performance, and medical interventions. Only invasive arterial pressure measurements, obtained from an umbilical artery catheter, were recorded. Continuous cerebral electrical activity was monitored on all babies using amplitude-integrated electroencephalography. Laboratory monitoring, electrophysiological studies [EEG, visual evoked potentials] and radiological studies [cranial ultrasound and magnetic resonance imaging (MRI)] were in accordance with a standardized clinical protocol for

neonates receiving TH. Infants received low-dose morphine infusion for sedation where required. All the patients were discharged back to the referral hospital when stable and the survival to NICU discharge was confirmed over the telephone from the referral hospital.

2.3. Hemodynamic assessments

Hemodynamic evaluation was performed using the Vivid 7 or Vivid 9 machine (GE Medical) using a 7–12 Hz multi-frequency sector probe. Neonatologists accredited in TNE[9] conducted the evaluations at 4 time points as follows: (Hypothermia I) within 24 h of starting TH; (Hypothermia II) between 48 and 72 h of starting TH; (Rewarming I) within 24 h of rewarming to normothermia and (Rewarming II) after 24 h of starting feeds. All infants were examined in a quiet state. Sucrose was used whenever restlessness occurred.

The epigastrium was examined in a longitudinal plane to locate the origin of the SMA and the CA from the aorta color Doppler imaging.[8] The sample volume was adjusted to 2 mm and the angle of insonation was less than 20°. The average of three spectral traces estimated for peak systolic blood flow velocity (BFV) (Vs), end diastolic peak BFV (Vd) and time-averaged maximum velocity (TAMV).[8] The primary outcome was the gastrointestinal BFV changes (in SMA and CA) during TH and after rewarming. The left ventricle output (LVO) was measured using the standard formula and the measurements were averaged over 5 beats.[8]

2.4. Feeding

As per unit protocol, enteral feeds were withheld during the cooling period. Feeds were started upon restoration of normothermia and increased as per protocol. Signs of feed intolerance were vomiting, abdominal distension and gastric aspirates >25% of the previous feed.

2.5. Statistical analysis

Statistical analyses were done using SPSS 22.0 (Chicago, IL, USA). Descriptive statistics were used to characterize neonatal demographics and outcomes, and hemodynamic parameters. The Shapiro-Wilk test was applied to test for normality. Wilcoxon-Signed Rank test/Friedman's two-way analysis of variance (ANOVA) was performed to compare serial changes over time, as appropriate. Mann–Whitney tests were used to compare medians of parameters that were not normally distributed. The Chi-square test or Fisher's exact test was performed to compare proportions, as appropriate.

3. Results

Twenty outborn neonates with median (range) gestation of 40 weeks (37–41) and birth weight of 3410 g (2190–4950) were studied (Table 1). Only one baby was less than 2.5 kg. Seven patients had 10-min Apgar score of <5 (range: 4–10). Six patients also received chest compressions. The median (range) age at initiation of TH was 2.5 h (0–8) and time to achieve the target temperature range was 4 h (0–12). Fourteen (70%) of the patients had moderate HIE at the time of admission, and 6 (30%) of the infants had improved to a mild stage of HIE and none were severe. All patients survived and there were no cases of NEC. The mean (±SD) length of stay was 11 ± 6 days.

Table 1 Demographics of the study population.

Characteristic	N (%)
Male gender	14 (70%)
Normal vaginal delivery	5 (25%)
Instrumental delivery	8 (40%)
Cesarean section	7 (35%)
Meconium stained liquor at delivery	8 (42.1%)
Mechanical ventilation at 10 min	14 (70%)
Cord pH	6.9 (6.6–7.2)
Base deficit	−17 (-8–29)
Seizures	11 (55%)
Hypotension (use of inotropes)	7 (35%)
Use of iNO	2 (10%)
NEC	0
Survival	20 (100%)

3.1. Hemodynamics

Blood flow velocity measurements are shown in Table 2. Hemodynamic changes in SMA and CA were depicted by comparing the blood flow velocity measurements at different time points during hypothermia and after rewarming. There was no significant difference in blood flow velocity in CA and SMA, either between Hypothermia I scan and Hypothermia II scan during the period of hypothermia or between Rewarming I scan and Rewarming II scan after rewarming. A significant increase in Vs of CA ($p = 0.004$) and SMA ($p = 0.001$) was noted between the period of hypothermia and after rewarming during the period of normothermia (Table 2). The heart rate (HR), blood pressure (BP) and Left ventricular output (LVO) remained stable during hypothermia (Hypothermia I & II scans) and rose significantly after rewarming [HR($p < 0.001$), BP ($p = 0.004$) and LVO ($p < 0.001$)] with no significant increase in LV ejection fraction ($p = 0.245$) (Fig. 1).

3.2. Feeding

Once the feeds were started the median (range) time to reach 25% of total feeds was 5 (1–7) days. Eight infants needed >5 days to tolerate 25% of feeds. They were characterized by higher birth weight [median 4146 g (range: 2820–4950 g) vs. 3150 g (range: 2190–4100 g), $p = 0.02$] and had higher Vs (0.63 vs. 1.02 m/s, $p = 0.008$) and TAMV (0.32 vs. 0.48; $p = 0.03$) in CA within 24 h of rewarming (Fig. 2). Flow patterns in SMA and LVO were not different between the two groups.

4. Discussion

We found that in newborn infants with HIE, intestinal blood flow did not change during the period of

Table 2 Celiac Artery and Superior Mesenteric Artery Doppler velocity during cooling and rewarming (TAMV: Time-averaged maximum velocity).

Echo parameter	Intervention	Time points	Median (range)	p-value	*p-value*
Superior Mesenteric Artery (SMA)					
SMA Vs (m/s)	Hypothermia	Hypothermia I	0.40 (0.22—0.67)	0.287	0.001
		Hypothermia II	0.47 (0.27—0.83)		
	Rewarming	Rewarming I	0.54 (0.34—0.86)	0.586	
		Rewarming II	0.57 (0.21—0.94)		
SMA TAMV	Hypothermia	Hypothermia I	0.22 (0.14—0.34)	0.754	0.003
		Hypothermia II	0.21 (0.14—0.43)		
	Rewarming	Rewarming I	0.25 (0.17—0.43)	0.906	
		Rewarming II	0.26 (0.10—0.36)		
Celiac Artery (CA)					
CA Vs (m/s)	Hypothermia	Hypothermia I	0.62 (0.17—1.06)	0.235	0.004
		Hypothermia II	0.64 (0.32—1.09)		
	Rewarming	Rewarming I	0.83 (0.33—2.10)	0.088	
		Rewarming II	0.71 (0.41—1.75)		
CA TAMV	Hypothermia	Hypothermia I	0.37 (0.12—0.68)	0.432	0.07
		Hypothermia II	0.36 (0.18—0.98)		
	Rewarming	Rewarming I	0.46 (0.15—1.50)	0.438	
		Rewarming II	0.41 (0.29—1.25)		

hypothermia but rose significantly after rewarming. The rewarming period was temporally associated with a major rise in intestinal flow predominantly due to increased heart rate and left ventricular output, without any rise in the left ventricular ejection fraction. To the best of our knowledge this is the first study to report the effects of

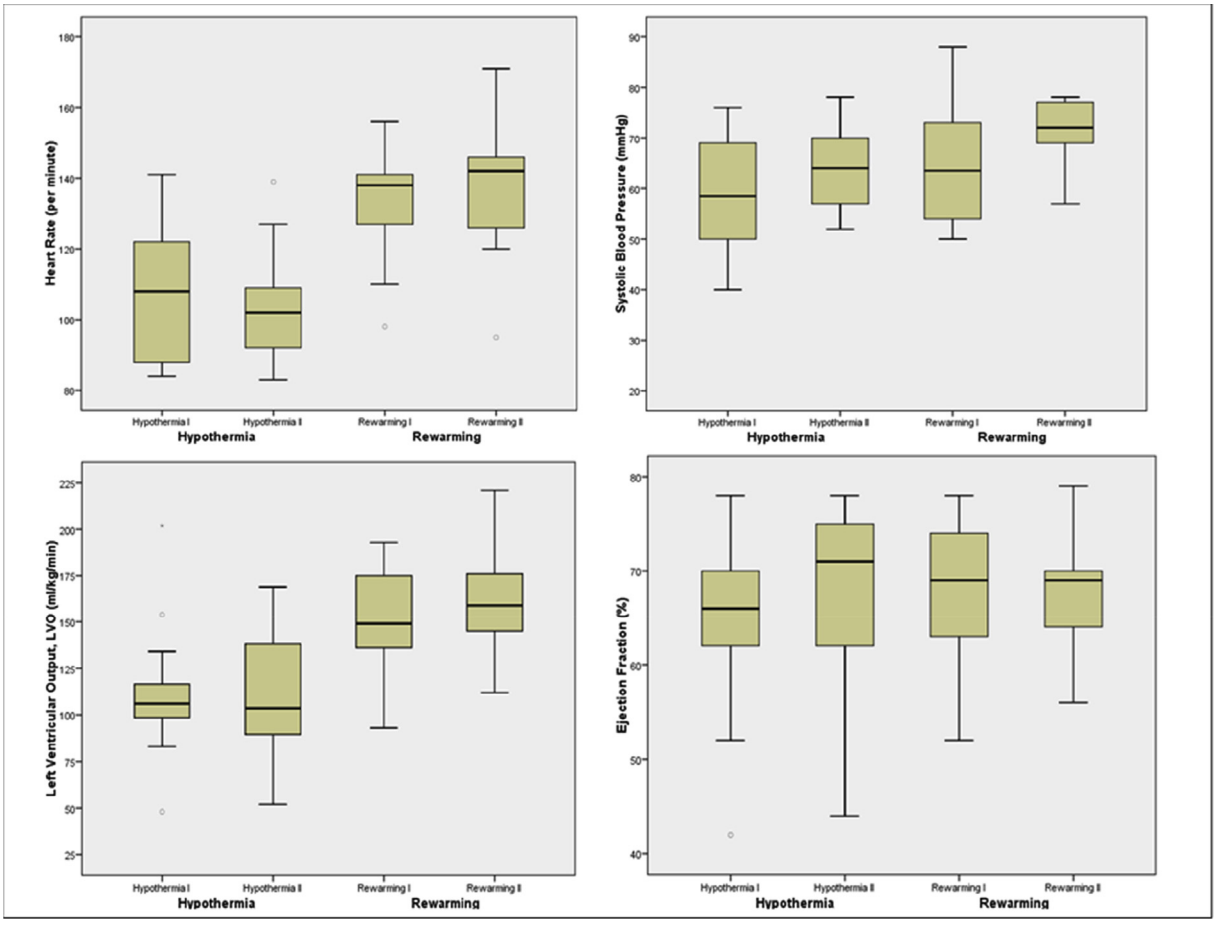

Figure 1 Effect of cooling and rewarming on Heart Rate, Left Ventricular Output, Systolic BP and Ejection Fraction.

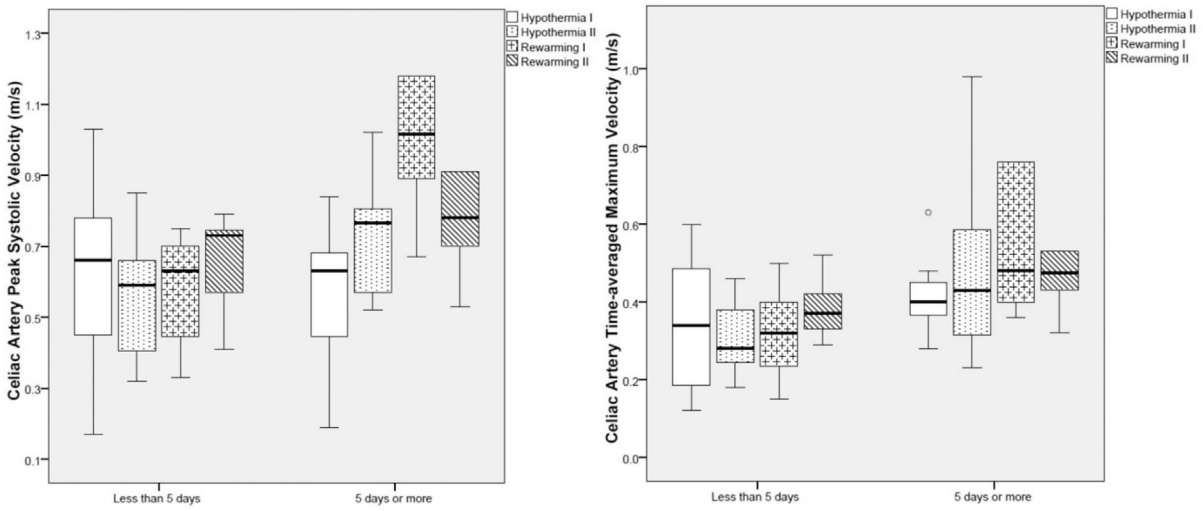

Figure 2 Celiac artery time-averaged maximum and peak systolic velocities during hypothermia and rewarming in the two feeding groups.

cooling and subsequent rewarming on intestinal hemodynamics in infants with HIE.

Normally, in healthy babies, there is an increase in the intestinal BFV throughout infancy, with visceral BFV also being affected by blood pressure changes during the first days of life.[11,12] The SMA and CA blood flow in healthy term infants rise during the first three days with significant increase during first 24 h of life.[13] Birth asphyxia is known to be associated with visceral hemodynamic disturbances with increases in the SMA and CA velocities in non-cooled infants with mild to moderate HIE and with very low BFV in cases of severe HIE as compared to control infants in the studies from pre-TH era. These changes often persisted for up to three days.[4] Reperfusion is the main mechanism of injury after ischemia. It has been shown in animal studies that reperfusion of ischemic viscera is characterized by an initial phase of hyperemia which later leads to mucosal repair.[14] One could argue that the increase in blood flow in the SMA and CA during the first day of life in mild — moderate HIE infants either reflects normal physiology or a reperfusion process due to the body's compensatory mechanism to restore the blood flow of the viscera. Poor BFV in severe HIE infants may reflect a very severe insult leading to loss of compensatory physiology to restore blood flow in the visceral arteries.

The unaltered intestinal blood flow during therapeutic hypothermia in our study population is in contrast to the reported normal physiological rise or that seen in mild—to—moderate HIE infants studied in the pre-hypothermia era as described above. The intestinal blood flow in our cohort increased once normothermia was restored after rewarming. It is unclear whether this was just a gradual physiological improvement following HIE or the effect of rewarming per se. We believe that the increase in intestinal BFV after rewarming of the infants was brisk and likely due to the restoration of normothermia. The effect was evident on Rewarming I scans which were done within 24 h after rewarming. These were significantly different from the Hypothermia II scans done while the infants were still hypothermic between 48 and 72 h after starting TH. Hypothermia I scans done within 24 h of starting TH and Hypothermia II scans done at least 24 h after Hypothermia I scans, both during the period of hypothermia, were not significantly different, suggesting that in addition to preventing reperfusion injury of the brain, cooling is also preventing reperfusion injury of the GI tract.

In the precooling era, NEC was recognized in the full-term infant with birth asphyxia and withholding of enteral feeds for up to 7 days of life was commonplace. Birth asphyxia was shown to decrease intestinal motor activity and reduce intestinal perfusion, thus increasing the risk of feeding intolerance and NEC in term infants, as compared to non-asphyxiated infants.[15] In infants with HIE receiving TH treatment where the prevalence of intestinal involvement is high, the ultrasound findings of sloughed intestinal mucosa and increased bowel wall echogenicity in all four quadrants indicate greater severity of hypoxic ischemic insult.[7] Similar to our findings, data from animal and adult human studies suggest that intestinal blood flow either remains unchanged or decreases during induced hypothermia.[16] Animal studies have shown that the injury is proportional to the duration and severity of total ischemia and moderate hypothermia may be protective against reperfusion injury following intestinal ischemia.[17,18] Researchers have also investigated the benefit of hypothermia in the treatment of infants with NEC.[19]

The median time to achieve 25% of the feeds in our cohort was 5 days. Infants who took more than 5 days to tolerate 25% of feeds had higher birth weights and higher Vs and TAMV in CA within 24 h of rewarming. The implication of this findings is unclear, but anecdotally feeding intolerance remains common post HIE. None of the hypothermia trials were designed to examine the incidence of feeding intolerance in this population. Most of the trials withheld enteral feeding during hypothermia as part of the protocol and reported a low rate of NEC, 1—2% for both groups.[4,6,10,20,21] As in the TH trials, our unit practice is to start enteral feeds once normothermia is established. In a retrospective cohort study whole-body hypothermia was shown to have beneficial effects on GI morbidity and

feeding tolerance for infants with moderate—to—severe HIE as compared to historical controls who did not undergo TH; however, the median time to reach full enteral feeds was 11 days.[22] The Scandinavian protocols and some authors from the USA allow minimal enteral feeding throughout the hypothermia period, and they show reduced time to full feeds and shorter hospital stay without increased risk of complications.[23,24]

We also found a significant change in the systemic hemodynamic parameters after rewarming such as increase in the HR, systolic BP and LVO with no significant difference in the LVEF over the various time points during hypothermia and after rewarming. These findings are consistent with other hemodynamic studies on infants with HIE undergoing therapeutic hypothermia that have focused on cardiac and cerebrovascular hemodynamics.[25,26] They showed that whole-body hypothermia was associated with a reduction in heart rate and left ventricular cardiac output with subsequent increase in the cardiac output and systolic blood pressure during rewarming phase. In keeping with our results, a recent study showed that the increase in LVO was related to the rise in HR rather than stroke volume.[27]

4.1. Limitation

Some caution is warranted in interpreting the results of our study considering it is a small observational study and there is no control group for comparison. However as TH is now a standard of care it is not possible to find a non-cooled cohort of HIE infants. Nevertheless, unchanged flow during hypothermia and the magnitude of the hemodynamic changes in GI arteries after rewarming warrant more detailed investigation of the relevance of these changes in a larger population of high-risk neonates. There was no case of severe HIE and none of the patients died, which may suggest a less compromised population. However, all infants had a significant hypoxic-ischemic insult and met established criteria for therapeutic hypothermia.

For logistical reasons (all the infants were outborn), we were unable to study intestinal blood flow velocities before the start of TH in this study.

Secondly, we could only collect complete data on time to achieve 25% of the feeds rather than the time to establish full feeds; due to variability in discharge patterns as being a quaternary referral unit the babies were discharged back to the local unit once stable and before reaching full feeds.

5. Conclusion

It is known that HIE is associated with hemodynamic changes in the visceral arteries and gastrointestinal morbidities in term infants, but no previous data exists on visceral blood flow velocity during hypothermia treatment in infants with HIE. The effect of hypothermia on GI blood flow velocities in HIE infants is studied for the first time. We have been able to show that in a cohort of infants with mild—to—moderate HIE, Celiac and Superior mesenteric artery blood flow velocities and left ventricular output remained stable during hypothermia but rose significantly after rewarming. The unchanging GI hemodynamics during hypothermia may indicate a favorable effect of cooling against reperfusion injury of the GI tract and merit further investigation, perhaps combined with measures of intestinal oxygenation saturation. Moreover, as hypothermia therapy for HIE is standard of care, it will be important to look at the potentially beneficial effects of hypothermia on other systems, such as the gastrointestinal tract in addition to the central nervous system. The relationship of these physiologic changes to initiation of feeds and other neonatal outcomes also require further evaluation.

Conflict of interest

The authors report no conflict of interest.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2019.04.003.