Original Article

Middle cerebral artery velocity is associated with the severity of MRI brain injury in neonates received therapeutic hypothermia☆

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ABSTRACT

Background: No previous study has investigated the relationship between middle cerebral artery (MCA) flow velocity and the severity of hypoxic ischemic encephalopathy (HIE) evaluated by magnetic resonance imaging (MRI). The aim of this study was to assess the correlation between cerebral blood flow as assessed by transcranial Doppler sonography and the severity of MRI brain injury in asphyxiated neonates with clinical HIE who received therapeutic hypothermia.
Methods: This retrospective cohort study was conducted in the neonatal intensive care unit at Chang Gung Memorial Hospital between April 2011 and May 2014. All neonates with HIE who received therapeutic hypothermia, transcranial Doppler examinations, and brain MRI

were eligible. Brain MRI was performed at 11 days of age (interquartile range: 8.5–15 days) and the severity of MRI brain injuries was evaluated using the MR scoring system proposed by Barkovich et al. Serial transcranial Doppler examinations were performed in pre-hypothermia, hypothermia, and post-hypothermia phases.

Results: Twenty-six neonates met the eligibility criteria for this study. Neonates with an abnormal MCA mean flow velocity (MFV) during the hypothermia phase had a higher risk of brain MRI abnormalities (77.8% vs. 22.2%, $p = 0.017$) and neonates with abnormal high MFV of MCA had higher MR scores of basal ganglia ($p = 0.022$). However, there were no statistical differences between abnormal MFV of MCA and brain MRI abnormalities during pre- and post-hypothermia phases.

Conclusions: During therapeutic hypothermia, mean cerebral blood flow velocity of the MCA was associated with the severity of MRI brain injury in the neonates with clinical HIE.

At a glance commentary

Scientific background on the subject

Studies predicting the severity of hypoxic ischemic encephalopathy (HIE) via transcranial Doppler sonography (TCD) are limited in therapeutic hypothermia (TH) era. This study aim to compare the correlation between cerebral blood flow assessed by TCD and the severity of brain MRI in neonates with clinical HIE who received TH.

What this study adds to the field

Our results support that mean cerebral blood flow velocity of the MCA was associated with the severity of MRI brain injury in the neonates with clinical HIE.

Alterations in cerebral blood flow (CBF) are common after perinatal asphyxia. Prolonged hypoxemia induces the loss of cerebral autoregulation with significant cerebral circulatory changes. Hypercapnia, hypoxemia, acidemia, and energy depletion [1] following asphyxia has also been reported to alter cerebral regulation [1,2]. The loss of autoregulation disturbs constant CBF, and this seems to be a major factor causing brain damage [2,3]. Several methods are used to assess CBF, including transcranial Doppler sonography (TCD), Xe-based computed tomography, positron emission tomography, and near-infrared spectroscopy (NIRS) [4–7]. Even though monitoring CBF and regional cerebral oxygenation with NIRS has the potential to guide clinical management, NIRS is not widely available in neonatal intensive care units (NICUs). Bedside TCD is a real-time, reproducible, and easily applicable tool to monitor CBF, pulsatility index (PI) and resistance index (RI) in the NICU. It can also be used during therapeutic hypothermia (TH) or other medical interventions.

Magnetic resonance imaging (MRI) is a validated and well-accepted biomarker of the severity of hypoxic ischemic encephalopathy (HIE) and neurological outcomes, and most studies have reported the use of MRI at 5–30 days of age [8–10]. However, the early recognition of hypoxic ischemic brain injury is important in the NICU, and it is difficult to perform MRI in critically ill neonates during the very early stage due to hemodynamic instability.

Therapeutic hypothermia has become the standard care for asphyxiated neonates with HIE. In pre-TH era, most previous studies have focused on anterior cerebral artery (ACA) parameters and their correlation with the prognosis in neonates with moderate to severe HIE [11,12]. The middle cerebral artery (MCA) supplies 80% of the cerebral hemisphere; however, no previous study investigated the correlation between TCD findings and the severity of HIE on MRI in the TH era. Hence, the aim of this study is to test the hypothesis that CBF evaluated by serial TCD can predict the severity of MRI brain injury in asphyxiated neonates with clinical HIE undergoing TH.

Materials and methods

Population

This is a retrospective cohort study of asphyxiated neonates with HIE who received TH in the NICU at Chang Gung Memorial Hospital between April 2011 and May 2014 [Fig. 1]. This study was approved by the Chang Gung Memorial Hospital Institutional Review Board (IRB#201900607B0). Patients were enrolled for this study if they met the following criteria: (1) gestational age ≥ 35 weeks; (2) commenced TH within 6 h after asphyxia; and (3) clinical evidence of moderate-to-severe HIE, defined as meeting one of the following criteria: (a) severe acidosis (pH ≤ 7.00 or base deficit ≥ 16 mmol/L) within 1 h after acute perinatal asphyxia; (b) Apgar score ≤ 5 at 10 min, or (c) resuscitation ≥ 10 min after acute perinatal asphyxia. We excluded neonates with major congenital anomalies, severe intracranial hemorrhage, 1st hour blood gas with pH > 7.15 and base deficit <10, no available TCD or MRI data, and those whose parents refused to provide consent.

Patient management

Affected neonates were placed on a thermal blanket which was controlled using a Blanketrol II cooling system (Cincinnati Sub-Zero Products, Inc., Cincinnati, OH, USA) or an Arctic Sun
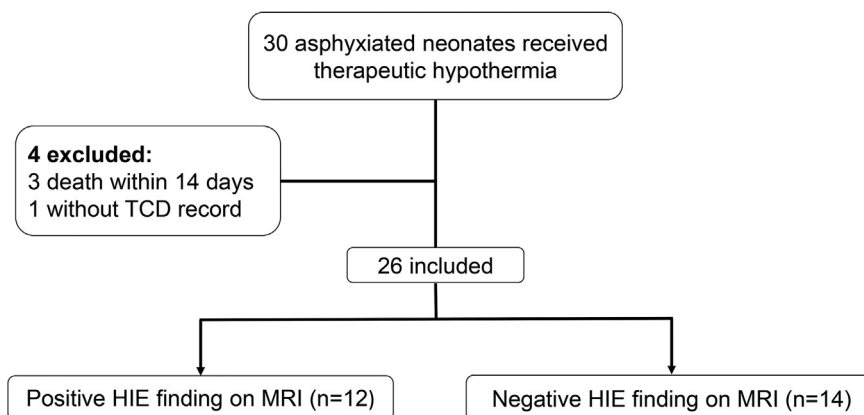
Fig. 1 A total of 30 neonates with perinatal asphyxia who received therapeutic hypothermia were identified. We excluded four neonates. In a total, 26 asphyxiated neonates were enrolled, including 12 with positive HIE finding on MRI and 14 with negative HIE findings on MRI. (HIE = hypoxic ischemic encephalopathy; MRI = magnetic resonance imaging; TCD = transcranial Doppler sonography).

Temperature Management System (C.R. BARD, Inc., Louisville, CO, USA). An esophageal probe was inserted to monitor the target core temperature, which was maintained within the range of 33–34 °C for 72 h. After 72 h of cooling, the patients were rewarmed slowly ($\leq$0.5 °C/h) to 36.5 °C. In terms of respiratory support, we aimed to maintain $PaCO_2$ 40–50 mmHg and SpO_2 94–98% or PaO_2 60–80 mmHg. Mean blood pressure was maintained at 40–60 mmHg. A peripheral or umbilical arterial catheter was used to monitor blood pressure in all patients. We maintained the hemoglobin level of all neonates above 12 g dL^{-1} with blood transfusions to maintain essential oxygen delivery. Sequential TCD examinations of the ACA and bilateral MCAs were performed using a 2 MHz probe (128XP; Acuson, Mountain View, CA, USA). TCD was performed in three distinct phases: pre-hypothermia (pre-TH) phase, hypothermia (TH) phase (12–24 h after the body temperature had reached 33–34 °C), and post-hypothermia (post-TH) phase (12–48 h after the body temperature had reached 36.5 °C). One experienced investigator (Lin JJ) performed all measurements. The probe was positioned over the anterior fontanelle in the sagittal plane for ACA data collection, and over the temporal bone window for MCA data collection. For each TCD investigation, the value of mean flow velocity (MFV) was recorded. The PI (peak systolic minus end diastolic velocity/time-averaged mean of the maximal velocities) and RI (peak systolic minus end diastolic velocity/peak systolic velocity) were calculated. The normal and abnormal values for MFV, PI, and RI in the ACA and MCA used in this study are summarized in Table 1 [13]. Abnormal data were defined as a twofold standard deviation below or above the mean of normal neonates. If the data were different in bilateral MCAs, the most severely abnormal MFV or the highest PI/RI was chosen. We recorded blood pressure every 2 h, arterial blood gas every 4 h and complete blood cell counts as well as biochemical data daily during these three phases. Measures of cardiovascular pharmacologic support were presented as Vasoactive-Inotropic Score proposed by Gaies and colleagues

[14]. Vasoactive-Inotropic Score was calculated with the following formula:

Vasoactive-Inotropic Score = Dopamine dose (mcg/kg/min) + Dobutamine dose (mcg/kg/min) + 10 × Milrinone dose (mcg/kg/min) + 100 × Epinephrine dose (mcg/kg/min) + 100 × Norepinephrine dose (mcg/kg/min) + 10,000 × Vasopressin dose (units/kg/min).

Outcome measures

Brain MRI was performed at 11 days of age (interquartile range: 8.5–15 days) in this study. The severity of HIE on MRI was assessed using the MR scoring system proposed by Barkovich et al. [15]. We used basal ganglia (BG) scores to represent the ACA and MCA territories, with scores ranging from 0 to 4, where 0 = normal or isolated focal cortical infarct, 1 = an abnormal signal in the thalamus, 2 = an abnormal signal in the thalamus and lentiform nucleus, 3 = an abnormal signal in the thalamus, lentiform nucleus, and perirolandic cortex, and 4 = more extensive involvement. Watershed scores were used to represent the ACA territory, with scores ranging from 0 to 5, where 0 = normal, 1 = single focal infarction, 2 = an abnormal signal in the anterior or posterior watershed white matter, 3 = an abnormal signal in the anterior or posterior watershed cortex and white matter, 4 = an abnormal signal in both anterior and posterior watershed zones, and 5 = more extensive cortical involvement [15]. MRI abnormalities (positive findings of HIE on MRI) were interpreted by a neuroradiologist, while MR scoring was performed by a pediatric neurologist, both of whom were blinded to all clinical parameters and outcome.

Each patient was classified with regards to: (1) MRI findings (negative findings or positive findings of HIE on MRI), and (2) predominant patterns of injury on MRI (normal, watershed, or BG/thalamus). A watershed pattern was defined as a watershed score higher than the BG score, and a BG/thalamus

Table 1 The normal values and abnormal values for transcranial Doppler sonography in this study.

	Normal	Abnormal
Mean velocity (cm s^{-1})		
ACA	22.1 (±4.0)	>30.1 or <14.1
MCA	26.7 (±7.9)	>42.5 or <10.9
Pulsatility index (PI)		
ACA	1.1 (±0.18)	>1.46 or <0.74
MCA	1.2 (±0.23)	>1.66 or <0.74
Resistance index (RI)		
ACA	0.7 (±0.06)	>0.82 or <0.58
MCA	0.7 (±0.07)	>0.84 or <0.56 (including reversal flow or undetectable flow)

This table was modified from the data in Ref. [13].
Abbreviations: ACA: anterior cerebral artery; MCA: middle cerebral artery.
Data are expressed as means (±standard deviation).

pattern was defined as a BG score equal to or higher than the watershed score [16].

Data analysis

The patients' demographic data in each study group were analyzed as descriptive statistics, and the data are presented as median with interquartile range. The TCD values during the three distinct phases and MRI findings were analyzed. All statistical analyses were conducted using SPSS statistical software, version 23.0 (IBM, Inc., Chicago, IL). Differences between groups were analyzed using the chi-square test or Fisher's exact test for categorical variables, and the Mann—Whitney test (U test) or Kruskal—Wallis test (H test) was used for between-group comparisons. Univariate logistic regression models were fit for the binary outcomes. A p value of less than 0.05 was statistically significant.

Results

Demographic data

During the 4-year study period, 30 asphyxiated neonates were identified, of whom 26 met the study inclusion criteria. We excluded four patients, including three who died within 14 days, and one without available TCD records. With regards to the pattern of brain injury on MRI, 53.9% had normal results, 26.9% had a BG/thalamus pattern, and 19.2% had a watershed pattern. The demographic data of these 26 patients are summarized in Table 2. There were no significant differences in birth weight, gender, gestational age, Apgar score, lactate (day 1, day 3), pH value and base deficit of blood gas analysis, and age for performing brain MRI between the neonates with negative (n = 14) and positive (n = 12) HIE lesions on MRI [Table 2]. We used hemoglobin, pH, PaCO$_2$, PaO$_2$, Vasoactive-Inotropic Score, and mean blood pressure measurements recorded closest to the time of performing TCD in the pre-TH, TH, and post-TH phases, and there were no significant differences in these values between the groups with negative and positive findings of HIE on MRI.

Table 2 The demographic data of the neonates with negative and positive hypoxic ischemic encephalopathy lesions on magnetic resonance imaging.

Characteristic	Negative HIE findings on MRI (n = 14)	Positive HIE findings on MRI (n = 12)	p value
Gestational age (weeks)	39 [37—40]	39 [37—40]	0.60
Gender (male; %)	71.4%	41.7%	0.13
Body weight (g)	2793 [2395—3160]	3450 [2877—3675]	0.07
Apgar scores			
1 min	2 [1—3]	1 [0—4]	0.27
5 min	4 [3—7]	4 [2—6]	0.64
Age at first MRI (days)	11.6 ± 7.9	10.8 ± 7.8	0.58
Lactate (mg/dL)			
Day 1	147.7 [45.0—191.7]	100.8 [64.3—121.4]	0.24
Day 3	18.6 [13.2—30.9]	25.3 [16.8—43.4]	0.20
pH[a]	7.19 [7.06—7.33]	7.02 [6.87—7.23]	0.96
Base defect[a] (mmol/L)	15.3 [11.4—23.3]	18.1 [9.8—22.2]	0.91
pH			
Pre-hypothermia	7.24 [7.13—7.32]	7.31 [7.28—7.38]	0.29
Hypothermia	7.38 [7.33—7.45]	7.40 [7.34—7.41]	0.41
Post-hypothermia	7.48 [7.44—7.53]	7.45 [7.44—7.47]	0.12
PaO2 (mmHg)			
Pre-hypothermia	107.5 [58.3—142.4]	88.2 [67.6—101.7]	0.34
Hypothermia	67.7 [51.6—83.3]	83.6 [76.5—90.9]	0.78
Post-hypothermia	70.7 [57.1—97.0]	71.0 [60.8—83.3]	0.36
PaCO2 (mmHg)			
Pre-hypothermia	26.8 [23.6—38.0]	36.0 [26.2—39.0]	0.60
Hypothermia	44.3 [39.1—49.9]	46.2 [38.2—47.0]	0.35
Post-hypothermia	41.6 [31.9—44.7]	43.1 [37.0—48.0]	0.32
Hemoglobin (g/dL)			
Pre-hypothermia	14 [11.2—18.4]	16.8 [15.7—17.5]	0.46
Hypothermia	13.9 [12.7—17]	17.7 [14.2—19.1]	0.09
Post-hypothermia	11.8 [11.0—13.5]	12.0 [10.7—12.5]	0.81
Vasoactive-Inotropic Score			
Pre-hypothermia	0.0 [0.0—7.0]	0.0 [0.0—6.0]	1.00
Hypothermia	10.0 [6.0—21.0]	9.5 [6.0—24.9]	0.87
Post-hypothermia	6.0 [0.0—21.0]	10.0 [4.5—14.0]	0.65
MBP (mmHg)			
Pre-hypothermia	41.0 [32.8—46.0]	41.9 [34.8—55.7]	0.92
Hypothermia	50.5 [44.2—53.7]	46.5 [43.4—49.6]	0.13
Post-hypothermia	45.7 [39.2—54.4]	50.7 [41.2—60.8]	0.71

Abbreviations: MBP: mean blood pressure; HIE: hypoxic ischemic encephalopathy; MRI: magnetic resonance imaging. The data are presented as median with 25th and 75th percentiles.
[a] The first data of pH and base defects after admission.

Outcomes

All 26 patients received sequential TCD examinations of the ACA [Table 3] and bilateral MCAs [Table 4]. Except for one patient whose TCD record was not available in the TH phase, remaining 25 patients with abnormal MFV of the MCA in the TH phase had a higher risk of positive findings of HIE on MRI than negative findings of HIE on MRI (77.8% vs. 22.2%, $p = 0.017$). Among patients with abnormal MFV of the MCA in the TH phase and positive findings of HIE on MRI, 42.9% (3/7) had abnormal high MFV, 42.9% (3/7) had undetectable flow, and 14.2% (1/7) had abnormal low MFV. There were no significant differences in MFV of the MCA in the pre-TH or post-TH phases between the groups with negative and positive

Table 3 Data of transcranial Doppler sonographic examinations of the anterior cerebral artery in three distinct phases.

Sonographic data	Negative HIE findings on MRI	Positive HIE findings on MRI	p value
Mean flow velocity			
Pre-hypothermia phase (n = 17)			0.28
Normal	3 (50%)	3 (50%)	
Abnormal	9 (81.8%)	2 (18.2%)	
Hypothermia phase (n = 25)			0.21
Normal	7 (77.8%)	2 (22.2%)	
Abnormal	7 (43.8%)	9 (56.3%)	
Post-hypothermia phase (n = 22)			0.40
Normal	7 (63.6%)	4 (36.4%)	
Abnormal	4 (36.4%)	7 (63.6%)	
Pulsatility index (PI)			
Pre-hypothermia phase (n = 17)			1.00
$0.74 \leq PI \leq 1.46$	3 (75%)	1 (25%)	
$PI < 0.74$ or >1.46	9 (69.2%)	4 (30.8%)	
Hypothermia phase (n = 25)			1.00
$0.74 \leq PI \leq 1.46$	7 (58.3%)	5 (41.7%)	
$PI < 0.74$ or >1.46	7 (53.8%)	6 (46.2%)	
Post-hypothermia phase (n = 23)			0.68
$0.74 \leq PI \leq 1.46$	8 (57.1%)	6 (42.9%)	
$PI < 0.74$ or >1.46	4 (44.4%)	5 (55.6%)	
Resistance index (RI)			
Pre-hypothermia phase (n = 17)			0.59
$0.58 \leq RI \leq 0.82$	4 (57.1%)	3 (42.9%)	
$RI < 0.58$ or >0.82	8 (80.0%)	2 (20.0%)	
Hypothermia phase (n = 25)			0.43
$0.58 \leq RI \leq 0.82$	8 (66.7%)	4 (33.3%)	
$RI < 0.58$ or >0.82	6 (46.2%)	7 (53.8%)	
Post-hypothermia phase (n = 23)			0.68
$0.58 \leq RI \leq 0.82$	8 (57.1%)	6 (42.9%)	
$RI < 0.58$ or >0.82	4 (44.4%)	5 (55.6%)	

Abbreviations: HIE: hypoxic ischemic encephalopathy; MRI: magnetic resonance imaging.

Table 4 Data of transcranial Doppler sonographic examinations of the middle cerebral artery performed during three distinct phases.

Sonographic data	Negative HIE findings on MRI	Positive HIE findings on MRI	p value
Mean flow velocity			
Pre-hypothermia phase (n = 16)			1.00
Normal	6 (66.7%)	3 (33.3%)	
Abnormal	5 (71.4%)	2 (28.6%)	
Hypothermia phase (n = 25)			0.017*
Normal	12 (75%)	4 (25%)	
Abnormal	2 (22.2%)	7 (77.8%)	
Post-hypothermia phase (n = 19)			0.66
Normal	6 (60%)	4 (40%)	
Abnormal	4 (44.4%)	5 (55.6%)	
Pulsatility index (PI)			
Pre-hypothermia phase (n = 16)			1.00
$0.74 \leq PI \leq 1.66$	3 (60%)	2 (40%)	
$PI < 0.74$ or >1.66	8 (72.7%)	3 (27.3%)	
Hypothermia phase (n = 25)			1.00
$0.74 \leq PI \leq 1.66$	7 (58.3%)	5 (41.7%)	
$PI < 0.74$ or >1.66	7 (53.8%)	6 (46.2%)	
Post-hypothermia phase (n = 19)			0.65
$0.74 \leq PI \leq 1.66$	5 (45.5%)	6 (54.5%)	
$PI < 0.74$ or >1.66	5 (62.5%)	3 (37.5%)	
Resistance index (RI)			
Pre-hypothermia phase (n = 16)			1.00
$0.56 \leq RI \leq 0.84$	5 (62.5%)	3 (37.5%)	
$RI < 0.56$ or >0.84	6 (75%)	2 (25%)	
Hypothermia phase (n = 25)			0.43
$0.56 \leq RI \leq 0.84$	8 (66.7%)	4 (33.3%)	
$RI < 0.56$ or >0.84	6 (46.2%)	7 (53.8%)	
Post-hypothermia phase (n = 19)			1.00
$0.56 \leq RI \leq 0.84$	5 (50%)	5 (50%)	
$RI < 0.56$ or >0.84	5 (55.6%)	4 (44.4%)	

Abbreviations: HIE: hypoxic ischemic encephalopathy; MRI: magnetic resonance imaging.
*$p < 0.05$.

findings of HIE on MRI. MFV of the ACA, as well as PI and RI levels of the ACA and MCA in all three phases were not associated with the outcome results shown on MRI.

Furthermore, MFV in the MCA in the three phases were analyzed and compared with their MR scores (BG score and watershed score) as outcome prediction [Table 5]. In the TH phase, neonates with abnormal MFV in the MCA had higher BG scores (p = 0.043). In terms of MR outcome, compared with neonates with normal MVF, neonates with abnormal high MFV in the TH phase had the highest BG scores (4.0 vs. 0.0, $p = 0.022$).

Discussion

The relationship of hemodynamics and the care of brain remains incompetently understood in the TH era. Though brain

MRI has been utilized for predicting neurodevelopmental outcomes in asphyxiated neonates, an earlier bedside TCD assessment for decision-making and cerebral resuscitation may be valuable in the initial critical days. Taking advantage of real-time bedside assessment tools, such as TCD and echocardiography, bedside TCD may enhance the brain health in caring asphyxiated neonates with HIE. In this retrospective study, we reviewed and analyzed sequential measurements of TCD parameters and MRI findings during pre-TH, TH, and post-TH phases in neonates with clinical HIE. Our main finding was that an undetectable cerebral flow or abnormal MFV of the MCA during TH was associated with the severity of brain MRI in neonates with HIE. In the pre-TH era, MFV of cerebral blood vessels at an age of 12–120 h has been reported

Table 5 Magnetic resonance imaging scores[a] vs. mean flow velocity of the middle cerebral artery in three distinct phases.

	BG score	p value	W score	p value
Mean flow velocity of MCA				
Pre-hypothermia phase (n = 16)		0.97		0.64
Normal	0.0 (0.0, 3.0)		0.0 (0.0, 2.0)	
Abnormal high	0.0 (0.0, 3.0)		0.0 (0.0, 3.8)	
Abnormal low	0.0 (0.0, 1.0)		0.0 (0.0, 0.0)	
Hypothermia phase (n = 25)		0.043*		0.09
Normal	0.0 (0.0, 0.8)		0.0 (0.0, 0.0)	
Abnormal high[b]	4.0 (1.0, 4.0)		4.0 (1.0, 4.8)	
Abnormal low	2.0 (0.5, 2.0)		0.0 (0.0, 2.0)	
Post-hypothermia phase (n = 19)		0.62		0.24
Normal	0.0 (0.0, 2.0)		0.0 (0.0, 0.0)	
Abnormal high	1.0 (0.0, 4.0)		2.0 (0.0, 5.0)	
Abnormal low	—		—	

Abbreviations: MCA: middle cerebral artery; BG: basal ganglia; W: watershed.

*$p < 0.05$.

[a] Magnetic resonance imaging scores are presented as median and interquartile range.

[b] Compare with normal mean flow velocity group; $p = 0.022$.

to be significantly higher in neonates with moderate to severe HIE [17]. In our study, neonates with an abnormal MFV of the MCA during the TH phase (12—24 h after initiating TH) had a higher risk of HIE abnormalities on MRI and higher MR scores of basal ganglia. Patients who had both abnormal high MFV of the MCA in the TH phase and HIE abnormalities on MRI had the highest BG scores ($p = 0.022$). Our findings imply that rapid increased CBF may cause severe reperfusion injury due to severe impairment of cerebral autoregulation. Though TH induces decreased cardiac output, significant cerebral redistribution indicates autoregulatory failure in patients with severe HIE on MRI [18]. The remaining patients with no detectable flow (42.9%) or abnormal low MFV of the MCA (14.2%) also had HIE abnormalities on MRI ($p = 0.017$), and this result suggested that brain ischemia initiates a cascade of cellular destruction and no detectable CBF has been confirmed as a lethal sign of cerebral circulatory arrest [19]. Not only had we found that neonates with an abnormal high MFV of the MCA during the TH phase had higher MR scores of basal ganglia. In this study, we also found a trend that neonates with an abnormal MFV of the MCA during the TH phase had higher MR scores of watersheds ($p = 0.09$). The reason why there was no significant difference in terms of abnormal MFV of the MCA during the TH phase and MR scores of watershed is that it may be due to the high proportion (26.9%) of brain injuries with a BG/thalamus pattern in this study. In contrast, there were no interrelationships between MFV and subsequent MRI brain injury during pre-TH and post-TH phases. Like previous studies [4,20], we noted that MFV during the pre-TH phase was not a suitable predictor of the severity of HIE on MRI. During rewarming, these CBF changes are likely to be further amplified. The results regarding MFV of the MCA during the TH phase in this study suggest that

commencement of interventions in the TH phase with a real-time and applicable biomarker for monitoring such as TCD parameters may have the potentials to decrease brain injuries in asphyxiated neonates in the future.

Most previous studies have focused on ACA parameters and their correlation with the prognosis in neonates with moderate to severe HIE in the pre-TH era [11,12], but we did not observe the same predictive value in this study. The MCA supplies 80% of the cerebral hemisphere. The lesions with BG/thalamus pattern on MRI, including the deep gray nuclei, perirolandic cortex, and total cortex, are supplied mainly by the MCA, and represents severe acute perinatal asphyxia with alteration of cerebral hemodynamics to deep nuclear structures [16]. Our findings indicate that in asphyxiated neonates with TH, the hemodynamic parameters in the MCA as evaluated by TCD are associated with the severity of HIE on MRI, while the ACA parameters are not. It is possible that TH alters cerebral hemodynamics and the prognosis in neonates with moderate to severe HIE, and that the change in flow velocity may be more sensitive and predictive than RI [17,20—22].

In the pre-TH era, abnormal higher or lower RI in the ACA and MCA measured within 72 h after birth has been reported to be significantly associated with neonates with moderate to severe HIE and poor outcomes compared to healthy neonates [11,23]. However, Elstad et al. reported that a lower RI in the ACA was less predictive of poor neurodevelopmental outcomes or death during the TH phase [21]. They concluded that hypothermia prevents hyperemia by affecting the cardiovascular system and protecting the brain at a cellular level. Another possible explanation of their findings is that the wider application of inotropic agents increased the unpredictability of the cerebrovascular system. In our study, PI and RI in the ACA and MCA during pre-TH, TH and post-TH phases could not predict the severity of HIE on MRI. There was also no significant difference between Vasoactive-Inotropic Score and the binary outcomes of parameters of the ACA and MCA during distinct phases in our study.

There are some limitations to this study. First, this was a retrospective cohort study and we only included a small sample size of neonates. However, there is no previous study investigating the relationship between MFV in the MCA and HIE lesions on MRI in the TH era. Second, some missing data of MCA were noted. Finally, it is difficult to investigate every possible confounder separately, such as the use of strategy of ventilator support, sedation, and anesthesia. Due to the retrospective design of this study, presence of confounding bias is inevitable. However, we tried our best to treat all the enrolled patients with standard protocol to maintain optimal blood pressure, ventilation, and hemodynamic status during TH. Future prospective studies with a larger group of neonates are needed to minimize such bias.

Conclusions

During therapeutic hypothermia, MFV in the MCA was associated with the severity of MRI brain injury in the neonates with HIE. Most of the patients with undetectable cerebral flow or abnormal MFV in the MCA as revealed by TCD had evidence

of HIE lesions on MRI. TCD examinations has the potential to serve as a predictive tool during the first critical days in asphyxiated neonates undergoing therapeutic hypothermia.

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Conflicts of interest

All authors declare no conflicts of interest.

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