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Cerebral Autoregulation and Conventional and Diffusion Tensor Imaging Magnetic Resonance Imaging in Neonatal Hypoxic-Ischemic Encephalopathy

Melisa Carrasco^{a,*}, Jamie Perin^b, Jacky M. Jennings^b, Charlamaine Parkinson^{c,d}, Maureen M. Gilmore^{c,d}, Raul Chavez-Valdez^{c,d}, An N. Massaro^e, Raymond C. Koehler^f, Frances J. Northington^{c,d}, Aylin Tekes^{c,g}, and Jennifer K. Lee^{c,f}

^aDepartment of Neurology, Division of Pediatric Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland ^bCenter for Child and Community Health Research (CCHR), Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, Maryland

^cNeurosciences Intensive Care Nursery, Johns Hopkins School of Medicine, Baltimore, Maryland

^dDivision of Neonatology, Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, Maryland ^eDepartment of Pediatrics, Children's National Medical Center, George Washington University School of Medicine, Washington, District of Columbia ^fDepartment of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland ^gDepartment of Radiology, Division of Pediatric Radiology and Pediatric Neuroradiology, Johns Hopkins University School of Medicine, Baltimore, Maryland

Abstract

Background—Deviation of mean arterial blood pressure (MAP) from the range that optimizes cerebral autoregulatory vasoreactivity (optimal MAP) could increase neurological injury from hypoxic-ischemic encephalopathy (HIE). We tested whether a global magnetic resonance imaging (MRI) brain injury score and regional diffusion tensor imaging (DTI) are associated with optimal MAP in neonates with HIE.

Methods—Twenty-five neonates cooled for HIE were monitored with the hemoglobin volume index. In this observational study, we identified optimal MAP and measured brain injury by qualitative and quantitative MRIs with the Neonatal Research Network (NRN) score and DTI mean diffusivity scalars. Optimal MAP and blood pressure were compared with brain injury.

*Corresponding author. mcarras6@jhmi.edu (M. Carrasco).

Dedication

We dedicate this manuscript to the Poretti family in loving memory of Dr. Andrea Poretti (AP).

Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.pediatrneurol.2018.02.004>.

Conflicts of interest

JKL, FJN, and RC-V received research support from Medtronic for a separate study. JKL was also a paid advisory board member for Medtronic. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies. Medtronic had no role in the current study's design, data collection and analysis, interpretation of the results, writing, or decision to submit our manuscript for publication.

Results—Neonates with blood pressure within optimal MAP during rewarming had less brain injury by NRN score ($P = 0.040$). Longer duration of MAP within optimal MAP during hypothermia correlated with higher mean diffusivity in the anterior centrum semiovale ($P = 0.008$) and pons ($P = 0.002$). Blood pressure deviation below optimal MAP was associated with lower mean diffusivity in cerebellar white matter ($P = 0.033$). Higher optimal MAP values related to lower mean diffusivity in the basal ganglia ($P = 0.021$), the thalamus ($P = 0.006$), the posterior limb of the internal capsule ($P = 0.018$), the posterior centrum semiovale ($P = 0.035$), and the cerebellar white matter ($P = 0.008$). Optimal MAP values were not associated with the NRN score.

Conclusions—The NRN score and the regional mean diffusivity scalars detected injury with mean arterial blood pressure deviations from the optimal MAP. Higher optimal MAP and lower mean diffusivity may be related because of cytotoxic edema and limited vasodilatory reserve at low MAP in injured brain. DTI detected injury with elevated optimal MAP better than the NRN score.

Keywords

Newborn; Brain hypoxia ischemia; Magnetic resonance imaging; Cerebrovascular circulation; Blood pressure

Introduction

Neuroprotective treatment for hypoxic-ischemic encephalopathy (HIE) has focused on therapeutic hypothermia, but this protection is incomplete as nearly half of hypothermia-treated survivors develop moderate to severe disabilities.^{1,2} Cerebral autoregulation maintains blood flow across fluctuations in blood pressure. Cerebral vasoreactivity describes the vasodilatory and vasoconstrictive responses to changes in blood pressure that mediate cerebral blood flow autoregulation. Dysfunctional vasoreactivity and autoregulation during resuscitation,³ hypothermia,⁴ and rewarming^{5,6} may contribute to secondary brain injury and poor neurological outcomes in HIE.

The blood pressure range with optimized autoregulatory vasoreactivity—the optimal mean arterial blood pressure (MAP)—can be identified using the hemoglobin volume index (HVx) from near-infrared spectroscopy.^{7–10} Conceptually, optimal MAP is located in the center of the blood pressure-cerebral blood flow autoregulation plateau. Vasoreactivity decreases and autoregulation becomes progressively more dysfunctional as blood pressure deviates from optimal MAP. Using optimal MAP as a hemodynamic goal to optimize autoregulatory vasoreactivity in individual neonates reflects a precision medicine approach that contrasts with using generalized blood pressure goals, such as those based on gestational age, that assume similar hemodynamic needs among all neonates. We previously demonstrated a relationship between blood pressure relative to optimal MAP and brain injury on magnetic resonance imaging (MRI)^{5,11,12} and neurodevelopmental outcomes⁶ in a small cohort of babies with HIE.

Both conventional MRI and diffusion tensor imaging (DTI) can map brain injury. The qualitative National Institute of Child Health and Human Development (NICHD) Neonatology Research Network (NRN) brain injury score analyzes conventional T1- and

T2-weighted images to combine subcortical, basal ganglia, thalamus, internal capsule, watershed, and cerebral injuries into one global injury score. A higher NRN score predicts death or disability.¹³ The NRN score is a standardized, reproducible, qualitative global brain injury scoring system that can be used across institutions in multicenter studies because it uses conventional sequences. Quantitative brain injury can be evaluated with DTI mean diffusivity (MD) scalars. MD identifies compromised microstructural integrity in brain parenchyma after hypoxic-ischemic injury. Region of interest (ROI) analysis can be performed in specific anatomic locations.

In the current study, we extend our prior work^{5,6,11,12} to validate the relationships between blood pressure, optimal MAP, and brain injury using qualitative and quantitative MRIs with the NRN brain injury score² and DTI MD scalars in neonates younger than 10 days. We hypothesized that both the NRN score and MD scalars would detect relationships between blood pressure deviation from optimal MAP and brain injury in newborns with HIE. We also hypothesized that absolute values of optimal MAP would be associated with brain injury severity.

Materials and Methods

This observational study was conducted in the Johns Hopkins University neonatal intensive care unit (NICU) with institutional review board approval. We sequentially screened all neonates with HIE admitted to the NICU between September 2010 and July 2015. Written informed consent was obtained from the parents until May 2013, when near-infrared spectroscopy (NIRS) monitoring became the standard of care for HIE treatment at our hospital. The institutional review board then granted a waiver of consent. Inclusion criteria, which included a diagnosis of moderate to severe HIE based on the National Institute of Child Health and Human Development clinical trial of hypothermia¹⁴ and gestational age 35 weeks, have been reported previously.^{5,6,11} Only neonates who underwent a brain MRI on a 1.5 Tesla (T) scanner before the tenth day of life were eligible for the study. Exclusion criteria included congenital anomalies that could make cooling unsafe, coagulopathy with active bleeding, and absence of an arterial blood pressure catheter. We reported autoregulation and MRI data from a subset of these neonates in our prior studies.^{5,6,11,12}

Therapeutic hypothermia

Neonates with HIE received whole-body hypothermia with a cooling blanket (Mul-T-Blanket and Mul-T-Pad; Gaymar Industries Inc, Orchard Park, NY) to a rectal temperature of 33.5 ° 0.5°C for 72 hours. Neonates were rewarmed at approximately 0.5°C/h to normothermia (36.5°C). Clinicians determined the hemodynamic goals and decided whether to initiate vasoactive support. Dopamine was the first-line vasopressor, followed by dobutamine, epinephrine, milrinone as needed. Hydrocortisone was given for adrenal insufficiency. Neonates were monitored with amplitude-integrated electroencephalography or full-montage electroencephalography throughout hypothermia, rewarming, and the first six hours of normothermia. Seizures were treated with phenobarbital followed by fosphenytoin, levetiracetam, pyridoxine, or topiramate if the seizures persisted. Neonates were sedated with morphine, lorazepam or midazolam, or clonidine as needed. An

investigator (RC-V) blinded to blood pressure, autoregulation, and MRI data obtained clinical data from the electronic medical record.

Brain MRI

MRI scans were obtained during natural sleep. Brain MRIs with sagittal T1-weighted, axial T2-weighted, axial DTI with diffusion tracer images and MD maps were obtained with a 1.5-T clinical scanner (Avanto; Siemens, Erlangen, Germany). A pediatric neuroradiologist and a pediatric neurologist experienced in neuroimaging for HIE (AT and AP)^{5,11} graded injury using the NRN score¹³ in consensus. The NRN score is a published, standardized score with injury categories 0: normal; 1A: minimal cerebral lesions only with no involvement of the basal ganglia, the thalamus, or the anterior limb of the internal capsule (ALIC) or the posterior limb of the internal capsule (PLIC) and no watershed infarction; 1B: more extensive cerebral lesions without the basal ganglia, the thalamus, PLIC or ALIC involvement or infarction; 2A: any basal ganglia, thalamus, ALIC, or PLIC involvement or watershed infarction without other cerebral lesions; 2B: lesions in the basal ganglia, the thalamus, ALIC or PLIC or area of infarction with additional cerebral lesions; and 3: cerebral hemispheric devastation.¹³

Single-shot, echo-planar axial DTI sequence with diffusion gradients along 20 noncollinear directions were obtained in each subject. Each diffusion-encoding direction had an effective high b value of 1000 s/mm². Additional measurement without diffusion weighting ($b = 0$ s/mm²) was also obtained. The DTI parameters were as follows: repetition time: 8500 milliseconds, time to echo: 86 milliseconds, section thickness: 2.0 mm, field of view: 192 × 192 mm, and matrix size: 96 × 96 (reconstructed as 192 × 192 with zero-filled interpolation). Vendor-specific software calculated the MD maps, and MD scalars were measured by ROI analysis on a picture archiving and communication system workstation. A pediatric neurologist (AP) experienced in neuroradiology and neuroanatomy manually drew ROIs in the left and the right thalami; the left and the right PLICs; the left and the right basal ganglia; the left and the right anterior centrum semiovale (ACS); the left and the right posterior centrum semiovale (PCS); the left and right cerebellar white matter; and the pons. Each ROI was measured in three contiguous axial slices, and the median value was used for statistical analysis. The investigators who analyzed the brain MRIs were blinded to the autoregulation and blood pressure data.

Autoregulation monitoring

Bilateral neonatal cerebral oximetry probes (INVOS; Medtronic, Minneapolis, MN) were placed on the neonate's forehead. A computer synchronously recorded the NIRS and arterial blood pressure data (Marquette MAC 500; GE Healthcare, Milwaukee, WI) with an analog-to-digital converter (DT9804; Data Translation, Marlboro, MA) at 100 Hz using ICM + software (Cambridge Enterprises, Cambridge, UK).

NIRS measures oxygenated and deoxygenated hemoglobin optical densities, and the sum is the relative total tissue hemoglobin (rTHb; $rTHb = 1 - \text{optical density}_A \times 50$). Fluctuations in rTHb reflect changes in cerebral blood volume during vasoconstriction and vasodilation with autoregulatory vasoreactivity across changes in blood pressure. Synchronous 10-second

mean values of MAP and rTHb were recorded in a low-pass filter step to remove oscillations from respiratory and pulse frequencies. Then, the hemoglobin volume index (HVx) was calculated by a correlation coefficient between rTHb and MAP in 300-second time windows that were updated every 10 seconds at 0.004 to 0.05 Hz (20 to 250 seconds). This frequency is where slow wave changes in cerebral blood volume occur during pressure autoregulation.⁸

When autoregulatory vasoreactivity is functional, MAP and rTHb (a surrogate measure of cerebral blood volume) are negatively correlated. This finding yields a negative HVx index that approaches -1 . As blood pressure deviates farther from optimal MAP and vasoreactivity becomes progressively more impaired, rTHb and MAP positively correlate and HVx approaches $+1$. HVx distinguishes functional from dysfunctional vasoreactivity during hypothermia and rewarming after neonatal brain hypoxia.⁷

After confirming that no neonates had a unilateral intracranial lesion, we averaged the right and the left HVx values for sorting into 5-mm Hg bins of MAP to generate bar graphs. Three investigators (JKL, FJN, and MMG) blinded to clinical histories and MRIs identified the optimal MAP at which autoregulatory vasoreactivity was most robust during hypothermia, rewarming, and the first six hours of normothermia in consensus. Optimal MAP was defined as the MAP bin with HVx nadir and an overall increase in HVx as MAP deviated from this nadir.⁶ If there was no apparent HVx nadir, the patient was coded as having an “unidentifiable” optimal MAP (Fig 1). We then determined blood pressure deviation from optimal MAP during three separate periods (hypothermia, rewarming, and the first six hours of normothermia) using three parameters: (1) maximal blood pressure deviation above or below optimal MAP; (2) percentage of the monitoring period with blood pressure within, below, or above optimal MAP; and (3) the area under the curve ($\text{min} \times \text{mm Hg/h}$) to combine time (minutes) and blood pressure deviation (mm Hg) below optimal MAP normalized by the monitoring duration (hours).^{10,11} To describe optimal MAP, we report the average MAP within the 5 mmHg bin of optimal MAP. For example, an optimal MAP of 50 mmHg represents the bin 47.5–52.5 mmHg. In addition, we calculated the duration of time spent with blood pressure below the neonate’s gestational age + 5.

Statistical analysis

Data are presented as medians with interquartile range (IQR) or means with standard deviations (SDs) as appropriate. Data were analyzed with Rv3.3 (Vienna, Austria). The associations between MRI and optimal MAP or blood pressure relative to optimal MAP were each analyzed separately three times (once for hypothermia, once for rewarming, and once for normothermia). The NRN score was analyzed for association with the predictors (optimal MAP, blood pressure in relation to optimal MAP, and time spent with MAP below gestational age + 5) with ordered polytomous regression for proportional increase in injury.¹⁵ MD scalars in each ROI were analyzed for association with the predictors by regression analysis. These analyses were adjusted for the minimum arterial partial pressure of carbon dioxide (PaCO_2) during autoregulation monitoring (encom-passing hypothermia, rewarming, and the first six hours of normothermia) because hypocarbia increases the risk of brain injury.¹¹ Wilcoxon signed-rank tests were used to compare right and left MD measurements in each ROI and the percentage of time spent with MAP below 45 mm Hg in each period. In

addition, we compared NRN scores and MD scalars in each ROI between babies with and babies without an identified optimal MAP using Wilcoxon signed-rank tests.

Results

We screened 122 neonates with HIE. Forty-seven (39%) did not meet eligibility criteria because of the following: unreliable arterial blood pressure tracing (16), parents did not consent to the study (nine), the patient was transferred out of the NICU for potential extracorporeal membrane oxygenation (six), technical difficulties (five), death before HVx monitoring could be started (five), inadequate resources (three), coagulopathy (one), complex cardiac disease (one), or parents did not speak English or Spanish (the languages available for the consent forms, one). Seventy-five (61%) neonates underwent autoregulation monitoring. Seven had motion artifact on the MRI and four had withdrawal of support before MRI was obtained. Thirty-nine underwent their MRI on a 3-T scanner or had their MRI on day of life less than ten and were excluded from the current study. Thus 25 neonates (15 males and 10 females) were included in the final analysis.

All neonates received morphine, four received clonidine, and one received a benzodiazepine for sedation. Seizures were treated with phenobarbital (7), levetiracetam (3), fosphenytoin (2), and pyridoxine (1). Dopamine was administered to 11 neonates during hypothermia, eight neonates during rewarming, and eight neonates during normothermia. Three received dobutamine, and none received epinephrine or milrinone. Six received hydrocortisone. The percentage of time spent with MAP < 45 mm Hg during rewarming was greater than that during hypothermia ($P = 0.005$) and normothermia ($P = 0.001$, Fig 2). Table 1 summarizes the neonates' clinical data.

Autoregulation and brain injury by qualitative MRI

Neonates underwent MRI on median day of life eight (range: four to nine). Brain injury severity ranged between NRN grade 0 and 2B (Table 1). All 25 neonates had HVx monitored during hypothermia and rewarming, and 24 were monitored during normothermia. HVx was stopped early in one because the NIRS stickers were removed after rewarming. We monitored HVx for a median of 53 hours (IQR: 41.8 to 67.5) during hypothermia, 6.2 hours (IQR: 5.0 to 7.3) during rewarming, and six hours (IQR: 6 to 6) during normothermia. Optimal MAP was identified in 22 of 25 neonates (88%) at 47.5 (SD: 8) mm Hg during hypothermia, in 22 of 25 neonates (88%) at 50 (SD: 9) mm Hg during rewarming, and in 23 of 24 neonates (96%) at 50 (SD: 10) mm Hg during normothermia. Optimal MAP was not identifiable in three neonates during hypothermia, three during rewarming, and one during normothermia. The NRN score and MD scalars in each ROI were similar between babies with and without an identified optimal MAP during hypothermia, rewarming, and normothermia ($P > 0.18$ for all comparisons).

The NRN score detected a relationship between brain injury and blood pressure relative to optimal MAP. More time with blood pressure within optimal MAP during rewarming was associated with less injury by NRN score ($\beta = -0.138$, $P = 0.040$; Table 2). The NRN score was not related to optimal MAP values (Table 3) or blood pressure deviation from optimal MAP during any period ($P > 0.05$ for all comparisons).

Autoregulation and brain injury by quantitative MRI

The left and right MD scalars were similar in the basal ganglia, the thalamus, the ACS, the PCS, and the cerebellar white matter. The left PLIC had lower MD than the right PLIC ($P=0.015$, Supplemental Table S1). Greater duration of blood pressure within optimal MAP during hypothermia was associated with higher MD in the right ACS ($\beta = 0.008$, $P=0.024$) and pons ($\beta = 0.006$, $P=0.002$; Table 2). Higher optimal MAP values during rewarming were associated with lower MD scalars in the right basal ganglia ($\beta = -0.005$, $P=0.021$), the bilateral thalami (left: $\beta = -0.005$, $P=0.006$; right: $\beta = -0.004$, $P=0.017$), the left PLIC ($\beta = -0.004$, $P=0.018$), the left PCS ($\beta = -0.005$, $P=0.035$), and the bilateral cerebellar white matter (left: $\beta = -0.006$, $P=0.008$; right: $\beta = -0.005$, $P=0.012$; Table 3).

Blood pressure regulation relative to optimal MAP and bilateral cerebellar white matter injury showed several significant relationships. Lower MD related to longer duration of blood pressure below optimal MAP (left: $\beta = -0.001$, $P=0.015$; right: $\beta = -0.001$, $P=0.022$), greater maximal blood pressure deviation below optimal MAP (left: $\beta = -0.005$, $P=0.018$; right: $\beta = -0.005$, $P=0.025$), and higher area under the curve below optimal MAP (left: $\beta = -0.0001$, $P=0.033$; right: $\beta = -0.0001$, $P=0.044$). Accordingly, higher MD scalars were associated with more time with blood pressure above optimal MAP (left: $\beta = 0.002$, $P=0.003$; right: $\beta = 0.002$, $P=0.006$) and maximal blood pressure deviation above optimal MAP (left: $\beta = 0.006$, $P=0.003$; right: $\beta = 0.006$, $P=0.001$). These relationships were specific for blood pressure relative to optimal MAP during rewarming but not hypothermia or normothermia (Table 2).

MAP below gestational age +5

Greater time with MAP below gestational age + 5 during normothermia was associated with lower NRN score ($\beta = -0.161$, $P=0.046$), but that during hypothermia or rewarming showed no association with NRN score ($P>0.05$). Time spent with MAP below gestational age + 5 in any period was unrelated to MD scalar in any region ($P>0.05$ for all comparisons).

Discussion

In an observational pilot study of newborns treated with hypothermia for HIE, we identified relationships between blood pressure regulation relative to optimal MAP and brain injury measured by the global NRN score and regional MD scalars. Greater duration of blood pressure within optimal MAP was related to less injury by NRN score and higher MD in the ACS and the pons. Blood pressure deviation below optimal MAP was associated with lower MD in cerebellar white matter. Higher optimal MAP values during rewarming were associated with lower MD scalars in the basal ganglia, the thalamus, the PLIC, the PCS, and the cerebellar white matter. These data support the relationship between blood pressure deviation from the range with optimized autoregulatory vasoreactivity and brain injury in HIE.

The associations between higher optimal MAP and lower MD scalars in the basal ganglia, the thalamus, the PLIC, the PCS, and the cerebellar white matter occurred specifically

during rewarming. Injured brain regions with cytotoxic edema might have limited vasodilatory capacity at lower blood pressures during rewarming that may manifest as higher optimal MAP. Preclinical and clinical studies of neonatal brain hypoxia suggest that rewarming may cause cytotoxic injury or otherwise may be detrimental to the brain.^{16–19} The longer duration of low blood pressure and greater blood pressure variability during rewarming may have improved sensitivity for detecting these relationships (Fig 2). These observations may also reflect the withdrawal of hypothermia and highlight a potential role for autoregulation monitoring in determining the need for continued therapy.

The association between cerebellar white matter integrity on DTI and autoregulatory vasoreactivity readings from frontal HVx suggests that blood pressure below optimal MAP measured in the frontal lobe might risk cerebellar white matter hypoperfusion. Although the cerebellum is not classically considered a highly vulnerable region in HIE, cerebellar injury is known to occur in HIE.^{20–23} Cerebellar injury may be difficult to detect in some situations because occult cerebellar white matter injury may be detectable by DTI but not conventional qualitative MRI. The incidence and specific characteristics of cerebellar injury that may predict adverse neurodevelopmental outcome in HIE deserve further study.

Optimal MAP measured in the frontal cortex may not reflect that of other regions. Autoregulatory vasoreactivity has prominent macrocirculatory involvement of large cerebral arteries and pial arterioles upstream from local parenchymal tissue. Vasoreactivity is primarily mediated by intrinsic myogenic responses to changes in transmural pressure. Global HIE would not be expected to cause large regional differences in optimal MAP. Prolonged and large deviations in blood pressure from optimal MAP in the frontal lobe are likely to affect perfusion throughout much of the brain. We suggest that identifying optimal MAP using frontal NIRS is a reasonable first approximation to guide hemodynamic management.

We evaluated qualitative and quantitative MRIs for pragmatic and scientific reasons. Conventional MRI is widely used in clinical care for newborns with HIE. We previously reported an association between autoregulatory vasoreactivity and regional brain injury on conventional MRI in HIE.^{11,12} In the current study, we used a reproducible and validated global NRN brain injury score that predicts neurodevelopmental outcomes in HIE.¹³ Although the NRN score provides global assessment from conventional MRI, it may miss detailed regional injuries that are detectable by quantitative MD scalars from DTI. Accordingly, we identified more relationships between auto-regulation and DTI mean diffusivity measurements and less of a robust relationship between autoregulation and qualitative MRI assessment (using the NRN). Quantitative MRI provides continuous measures of injury with high granularity. However, DTI is generally not as widely available as conventional MRI sequences or diffusion-weighted imaging. DTI-based measurements in multi-institutional studies would require harmonization of scanner type, magnetic field strength, and sequence parameters, which can be challenging. Nonetheless, future large-scale studies of autoregulation in HIE will likely need to include both conventional and advanced DTI sequences to enable qualitative and quantitative MRI assessments.

We previously reported an association between blood pressure deviation from optimal MAP and low MD scalars in a small cohort of neonates with HIE older than 10 days.⁵ Because clinical protocols have shifted toward obtaining MRIs earlier, we conducted the current study to examine more relevant brain MRI timing. Indeed, optimal MAP and blood pressure regulation relative to optimal MAP were related to regional MD scalars in newborns younger than 10 days. We only studied neonates who underwent imaging on a 1.5-T scanner before day of life 10 to ensure comparable MRIs and to account for pseudonormalization of the diffusivity signal after hypothermia.²⁴ The exclusion of neonates who underwent MRIs on 3T scanners or after the tenth day of life may have caused study bias.

MD scalars for the right and left ROIs were analyzed separately rather than using the lowest scalar to represent the region.⁵ Our findings that autoregulation is associated with bilateral injury in some regions emphasizes the important relationship between optimal MAP and brain injury.

We use NIRS rTHb, a surrogate measure of cerebral blood volume, to calculate HVx and optimal MAP. Because rTHb incorporates both oxygenated and deoxygenated hemoglobin, it should be less sensitive to the changes in oxygen supply and demand that occur during hypothermia, rewarming, and mechanical ventilation than metrics based solely on oxygenated hemoglobin. Coherence, gain, and wavelet coherence analyses of cerebral NIRS and MAP have also shown an association with neurological injury in HIE.^{4,25} Additionally, optimal MAP has been identified in premature neonates using correlation between slow waves of heart rate and NIRS tissue oxygenation index.²⁶ Whether one method or a combinative value is superior has not been fully studied.

Monitoring arterial blood pressure alone is not a reliable approach to avoid cerebral hypoperfusion. Blood pressure parameters based on gestational age were not consistently associated with brain injury. Generalized blood pressure goals based on gestational age are inferior to those determined by an individual's cerebral hemodynamics and physiology with autoregulation monitoring.

A causal relationship between blood pressure in relation to optimal MAP and brain injury in HIE cannot be inferred from this small observational study. It is possible that identifying and targeting optimal MAP as a hemodynamic goal could reduce the risk of secondary brain injury after birth asphyxia. However, it is also possible that the primary brain injury could cause poor autoregulatory function and poor cardiovascular regulation with large blood pressure deviations from optimal MAP. Multicenter studies on the relationships between autoregulation and neurological injury in HIE are needed. Future studies that randomize neonates with HIE to standard clinical care or optimal MAP-based hemodynamic goals may better define the therapeutic potential of autoregulation monitoring.

We did not correlate autoregulation or MRI findings to long-term neurodevelopmental outcome in the present study. However, several regions of injury identified by DTI in the present study are known to be associated with outcome. For instance, lower apparent diffusion coefficient values in the cerebellar vermis are associated with worse motor

outcome or death,²⁷ and lower fractional anisotropy in the PLIC and centrum semiovale correlate with poor neurodevelopmental outcomes²⁸ in HIE.

Our study had several limitations, including small sample size, which may underidentify relationships between brain injury and blood pressure relative to optimal MAP. The majority of neonates had mild to moderate HIE because the sickest neonates died before initiation of HVx monitoring, were transferred out of the NICU for potential extracorporeal membrane oxygenation, or were not given consent for study participation by their parents. Early postnatal abnormalities in autoregulation were not captured because HVx monitoring could only be initiated after arterial blood pressure monitoring was established and after consent was obtained. This finding likely impacted our ability to detect relationships during hypothermia as the first 24 to 36 hours of life is vulnerable to dysfunctional autoregulation after HIE.⁴ We identified optimal MAP during all of hypothermia, rewarming, or the first six hours of normothermia rather than using shorter time intervals as in adult brain trauma studies of optimal cerebral perfusion pressure.²⁹ We conservatively identified optimal MAP from the HVx versus MAP bar graphs only when there was an apparent nadir in HVx. Thus not all babies had an identifiable optimal MAP in this research study. Because of the small sample size, we were unable to adjust for potential confounders, such as etiology of the birth injury, seizures, and vasopressors. Finally, we conducted multiple testing of outcome data derived from single patients, which may introduce statistical limitations in the interpretation of the results.

Conclusions

We observed significant relationships between blood pressure deviation from the MAP range with most robust cerebral autoregulatory vasoreactivity and brain injury measured by qualitative and quantitative MRIs. MD scalars from DTI MRI identified detailed relationships between optimal MAP and regional injury that the NRN score did not. Higher optimal MAP and lower MD in multiple brain regions may be related to cytotoxic edema with limited vasodilatory reserve at low blood pressure. Future multicenter autoregulation studies should utilize both qualitative and quantitative MRIs as indicators of brain injury after HIE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Examples of identifying the optimal MAP with the most robust autoregulatory vasoreactivity. The arrows denote optimal MAP during hypothermia (A), rewarming (B), and normothermia (C) at the HVx nadir. When a nadir in HVx was not present, the neonate was coded as having an unidentifiable optimal MAP (D). HVx, hemoglobin volume index; MAP, mean arterial blood pressure.

FIGURE 2.

The distribution of time that neonates spent at each level of mean arterial blood pressure. Whiskers are fifth to ninety-fifth percentiles.

TABLE 1

Clinical Characteristics of the Neonates

Parameter	n	Data
Gender (male), n (%)	25	15 (60)
Gestational age, mean (wk)	25	38.7 (range: 34.9–41.4)
Birth weight, mean (g)	25	3201 (range: 2250–4195)
Vasopressor use, n (%) [*]	25	11 (44)
Seizures, n (%) [†]	25	7 (28)
PaCO ₂ (mm Hg), n (%) [‡]	25	
All (35–45)		3 (12)
Some <35, all <45		5 (20)
None <35, some >45		11 (44)
Some <35, some >45		6 (24)
Lowest PaCO ₂ (mm Hg), mean (SD) [§]		
10-min Apgar score, median (IQR)	22	5 (3–9)
Umbilical cord blood gas base deficit, median (IQR)	14	–13.5 (–19.5 to –10.3)
Umbilical cord pH, median (IQR)	17	6.9 (6.9–7.1)
Age at MRI (d), median (IQR)	25	8.0 (7–9)
NRN brain injury score, n (%)	25	
0		6 (24)
1A		1 (4)
1B		10 (40)
2A		6 (24)
2B		2 (8)
3		0 (0)
Regional cerebral oxygen saturation (%), mean (SD)		
Hypothermia	25	83 (6)
Rewarming	25	82 (9)
Normothermia	24	80 (11)

Abbreviations:

MRI = Magnetic resonance imaging

NRN = Neonatal Research Network

PaCO₂ = Partial pressure of arterial carbon dioxide

SD = Standard deviation

^{*} Among neonates who received a vasopressor, all received dopamine and three received dobutamine.[†] Clinical or subclinical and electrographic seizures.[‡] PaCO₂ category from the entire autoregulation monitoring period during hypothermia, rewarming, and the first six hours of normothermia.[§] Minimal PaCO₂ during autoregulation monitoring was used as a covariate in the analysis.

Blood Pressure in Relation to Optimal MAP and Magnetic Resonance Imaging Measures of Brain Injury

TABLE 2

Blood Pressure Parameter	Injury Score or Region of Diffusion Scalar	Period	n	β	95% CI
Time with blood pressure within optimal MAP (%)	NRN brain injury score	Hypothermia	22	-0.104	(-0.239 to 0.030)
		Rewarming	22	-0.138*	(-0.267 to -0.010)
		Normothermia	23	-0.107	(-0.233 to 0.020)
	Anterior centrum semiovale (right)	Hypothermia	22	0.008*	(0.002 to 0.014)
		Rewarming	22	0.000	(-0.004 to 0.005)
		Normothermia	23	0.000	(-0.003 to 0.004)
	Pons	Hypothermia	22	0.006*	(0.003 to 0.009)
		Rewarming	22	-0.001	(-0.003 to 0.002)
		Normothermia	23	0.000	(-0.002 to 0.002)
	Cerebellar white matter (left)	Hypothermia	22	0.000	(-0.001 to 0.001)
Rewarming		22	-0.001*	(-0.002 to -0.0001)	
Normothermia		23	0.000	(-0.001 to 0.001)	
Time with blood pressure below optimal MAP (%)	Cerebellar white matter (right)	Hypothermia	22	0.000	(-0.001 to 0.001)
		Rewarming	22	-0.001*	(-0.002 to -0.0001)
		Normothermia	23	0.000	(-0.001 to 0.000)
	Cerebellar white matter (left)	Hypothermia	22	0.000	(-0.001 to 0.001)
		Rewarming	22	-0.001*	(-0.002 to -0.0001)
		Normothermia	23	0.000	(-0.001 to 0.001)
	Cerebellar white matter (right)	Hypothermia	22	0.000	(-0.001 to 0.001)
		Rewarming	22	-0.001*	(-0.002 to -0.0001)
		Normothermia	23	0.000	(-0.001 to 0.001)
	Maximal blood pressure below optimal MAP (mm Hg)	Cerebellar white matter (left)	Normothermia	23	0.000
Hypothermia			22	0.000	(-0.004 to 0.004)
Rewarming			22	-0.005*	(-0.009 to -0.001)
Cerebellar white matter (right)		Normothermia	23	0.001	(-0.003 to 0.004)
		Hypothermia	22	-0.001	(-0.004 to 0.003)
		Rewarming	22	-0.005*	(-0.009 to -0.001)
Cerebellar white matter (left)		Normothermia	23	0.000	(-0.004 to 0.003)
		Hypothermia	22	0.000	(-0.001 to 0.001)

Blood Pressure Parameter	Injury Score or Region of Diffusion Scalar	Period	n	β	95% CI
AUC of blood pressure below optimal MAP (min $\times$ mm Hg/h)	Cerebellar white matter (left)	Hypothermia	22	0.000	(-0.0001 to 0.000)
		Rewarming	22	-0.0001*	(-0.0001 to -0.0001)
Cerebellar white matter (right)	Cerebellar white matter (right)	Normothermia	23	0.000	(-0.0001 to 0.000)
		Hypothermia	22	0.000	(-0.0001 to 0.000)
		Rewarming	22	-0.0001*	(-0.0001 to -0.0001)
		Normothermia	23	0.000	(-0.0001 to 0.000)
Time with blood pressure above optimal MAP (%)	Cerebellar white matter (left)	Hypothermia	22	0.000	(-0.001 to 0.001)
		Rewarming	22	0.002*	(0.001 to 0.003)
		Normothermia	23	0.000	(-0.001 to 0.001)
		Hypothermia	22	0.000	(-0.001 to 0.001)
Cerebellar white matter (right)	Cerebellar white matter (right)	Rewarming	22	0.002*	(0.001 to 0.003)
		Normothermia	23	0.000	(-0.001 to 0.001)
		Hypothermia	22	0.003	(-0.001 to 0.008)
		Rewarming	22	0.006*	(0.002 to 0.009)
Maximal blood pressure above optimal MAP (mm Hg)	Cerebellar white matter (left)	Normothermia	23	0.003	(-0.002 to 0.007)
		Hypothermia	22	0.004	(-0.0001 to 0.007)
		Rewarming	22	0.006*	(0.003 to 0.008)
		Normothermia	23	0.003	(-0.0001 to 0.007)

Abbreviations:

AUC = Area under the curve

CI = Confidence interval

NRN = Neonatal Research Network

MAP = Mean arterial blood pressure

Each β is a regression coefficient for the expected change in regional median mean diffusivity with a one-unit increase in the specified blood pressure measurement. For the NRN brain injury score, β is the log odds of an increase in brain injury level (0, 1A, 1B, 2A, or 2B) with a one-unit increase in the specified blood pressure measurement. Significant findings are designated in bold.

* $P < 0.05$. Analyses were adjusted for minimum arterial partial pressure of carbon dioxide during autoregulation monitoring.

TABLE 3

Optimal MAP Values and Magnetic Resonance Imaging Measures of Brain Injury

Injury Score or Region of Interest Mean Diffusivity Scalars	Period	n	β	95% CI
NRN brain injury score	Hypothermia	22	-0.100	(-0.235 to 0.036)
	Rewarming	22	-0.130	(-0.264 to 0.003)
	Normothermia	23	-0.106	(-0.238 to 0.025)
Mean diffusivity scalars				
Basal ganglia (left)	Hypothermia	22	0.002	(-0.004 to 0.007)
	Rewarming	22	-0.005	(-0.009 to 0.000)
	Normothermia	23	-0.001	(-0.005 to 0.004)
Basal ganglia (right)	Hypothermia	22	0.003	(-0.002 to 0.007)
	Rewarming	22	-0.005*	(-0.009 to -0.001)
	Normothermia	23	-0.001	(-0.005 to 0.003)
Thalamus (left)	Hypothermia	22	0.003	(-0.001 to 0.007)
	Rewarming	22	-0.005*	(-0.008 to -0.002)
	Normothermia	23	-0.001	(-0.005 to 0.002)
Thalamus (right)	Hypothermia	22	0.003	(-0.001 to 0.007)
	Rewarming	22	-0.004*	(-0.008 to -0.001)
	Normothermia	23	-0.001	(-0.004 to 0.002)
PLIC (left)	Hypothermia	22	0.002	(-0.002 to 0.005)
	Rewarming	22	-0.004*	(-0.007 to -0.001)
	Normothermia	23	0.000	(-0.003 to 0.002)
PLIC (right)	Hypothermia	22	0.002	(-0.002 to 0.005)
	Rewarming	22	-0.002	(-0.005 to 0.000)
	Normothermia	23	0.001	(-0.002 to 0.003)
Posterior centrum semiovale (left)	Hypothermia	22	-0.001	(-0.006 to 0.005)
	Rewarming	22	-0.005*	(-0.010 to -0.001)
	Normothermia	23	0.001	(-0.004 to 0.006)
Posterior centrum semiovale (right)	Hypothermia	22	-0.003	(-0.009 to 0.004)
	Rewarming	22	-0.004	(-0.010 to 0.001)
	Normothermia	23	-0.001	(-0.007 to 0.005)
Cerebellar white matter (left)	Hypothermia	22	-0.001	(-0.006 to 0.004)
	Rewarming	22	-0.006*	(-0.010 to -0.002)
	Normothermia	23	-0.001	(-0.005 to 0.003)
Cerebellar white matter (right)	Hypothermia	22	-0.002	(-0.007 to 0.002)
	Rewarming	22	-0.005*	(-0.009 to -0.002)
	Normothermia	23	-0.002	(-0.006 to 0.001)

Abbreviations:

MAP = Mean arterial blood pressure

NRN = Neonatal Research Network

PLIC = Posterior limb of the internal capsule

Each β is a regression coefficient for the expected change in regional median mean diffusivity with a 1 mm Hg increase in optimal MAP. For NRN brain injury score, β is the log odds of an increase in brain injury level (0, 1A, 1B, 2A, or 2B) with a 1 mm Hg increase in optimal MAP.

Significant findings are designated in bold.

* $P < 0.05$. Analyses were adjusted for minimum arterial partial pressure of carbon dioxide during autoregulation monitoring.