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

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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.
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.

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

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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 outcomes[6] 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 score[2] 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 hypothermia[14] 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 score[13] 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/mm^2. Additional measurement without diffusion weighting (b = 0 s/mm^2) 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 – optical density_A*50). Fluctuations in rTHb reflect changes