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Cerebrovascular autoregulation and neurologic injury in neonatal hypoxic-ischemic encephalopathy

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Abstract

Background—Neonates with hypoxic-ischemic encephalopathy (HIE) are at risk of cerebral blood flow dysregulation. Our objective was to describe the relationship between autoregulation and neurologic injury in HIE.

Methods—Neonates with HIE had autoregulation monitoring with the hemoglobin volume index (HVx) during therapeutic hypothermia, rewarming, and the first 6 h of normothermia. The 5-mmHg range of mean arterial blood pressure (MAP) with best vasoreactivity (MAP_{OPT}) was identified. The percentage of time spent with MAP below MAP_{OPT} and deviation in MAP from MAP_{OPT} were measured. Neonates received brain MRIs 3–7 days after treatment. MRIs were coded as no, mild, or moderate/severe injury in five regions.

Results—HVx identified MAP_{OPT} in 79% (19/24), 77% (17/22), and 86% (18/21) of neonates during hypothermia, rewarming, and normothermia, respectively. Neonates with moderate/severe injury in paracentral gyri, white matter, basal ganglia, and thalamus spent a greater proportion of time with MAP below MAP_{OPT} during rewarming than neonates with no or mild injury. Neonates with moderate/severe injury in paracentral gyri, basal ganglia, and thalamus had greater MAP deviation below MAP_{OPT} during rewarming than neonates without injury.

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Conclusion—Maintaining MAP within or above MAP_{OPT} may reduce the risk of neurologic injuries in neonatal HIE.

INTRODUCTION

Neonatal hypoxic ischemic encephalopathy (HIE) affects approximately 3 in 1000 births (1) and causes significant neurologic morbidity despite therapeutic hypothermia (2). Identifying modifiable factors and additional interventions may improve outcomes. The healthy brain maintains constant cerebral blood flow (CBF) across changes in blood pressure through cerebrovascular autoregulation. This physiologic mechanism functions within a specific hemodynamic range, and the term optimal mean arterial blood pressure (MAP_{OPT}) refers to the range of MAP where cerebral vasoreactivity is most robust. That is, MAP_{OPT} is the blood pressure range in which the cerebral vasculature has maximal pressure reactivity (3,4). Neonates with HIE may be at risk of CBF dysregulation with shifts in the limits of autoregulation, particularly with intracranial hypertension (5). The hemodynamic goals that conform to the limits of autoregulation are unknown in neonatal HIE. Moreover, traditional blood pressure goals based on gestational age have not been tested against neurologic outcomes in HIE.

Traditionally, autoregulation has been monitored with transcranial Doppler (TCD) or intracranial pressure (ICP) (6,7). However, continuous TCD monitoring requires expertise and equipment that are not widely available, and ICP is not routinely monitored in neonates. We developed a method to monitor cerebrovascular reactivity using near-infrared spectroscopy (NIRS): the hemoglobin volume index (HVx) (8). HVx represents the relationship between relative tissue hemoglobin (rTHb; a surrogate measure of cerebral blood volume (CBV) obtained by NIRS) and MAP. The rTHb is a trend of total hemoglobin measurements obtained by NIRS using light with a wavelength of 805 nm. Because the 805 nm wavelength is isobestic to both oxyhemoglobin and deoxyhemoglobin, rTHb is not affected by fluctuations in oxygen saturation. HVx is based on the premise that autoregulatory vasoconstriction and vasodilation induce changes in CBV that are proportional to changes in rTHb (8). In a neonatal swine model of HIE, HVx accurately identified the lower limit of autoregulation (9,10). We sought to translate our laboratory work to neonates with HIE.

The goal of this pilot study was to describe the relationship between autoregulation and neurologic injury on MRI in neonates with HIE who receive therapeutic hypothermia. First, we determined whether HVx would identify MAP_{OPT}. Second, we investigated whether neonates who spent more time with blood pressure below MAP_{OPT} and who had greater blood pressure deviation below MAP_{OPT} would have more severe neurologic injury than neonates whose blood pressure remained within or above MAP_{OPT}. Third, we assessed whether measurements based on HVx and MAP_{OPT} would be more strongly associated with injury than regional cerebral oxygen saturation (rSO_2) or hemodynamic goals based on gestational age.

RESULTS

Forty-four neonates with HIE were identified. Seven families did not consent to enroll, and one family did not speak English or Spanish. Eight neonates were not eligible, including five who did not have arterial cannulae, and three who died or had support withdrawn. Two neonates had intracranial hemorrhages or congenital heart disease, which precluded the use of hypothermia. Twenty-six neonates were enrolled in the study. Autoregulation monitoring could not be accomplished with one patient due to technical problems, and one neonate's MRI had motion artifact. Thus, results were analyzed on 24 neonates (15 males, 9 females).

Of these 24 neonates, autoregulation monitoring was carried out during hypothermia in all patients, during rewarming in 22 patients, and during normothermia in 21 patients. Reasons for early cessation of monitoring included technical failure (1 patient), early removal of the arterial cannula (1 patient), and transfer to the pediatric ICU for extracorporeal membranous oxygenation (1 patient).

Patient Descriptions

The mean gestational age was 39.2±1.5 (standard deviation (SD)) weeks with birth weight 3353±596 g. Seventeen neonates (71%) were born by caesarean section, and eight (33%) required chest compressions after delivery. The umbilical cord gases had a mean pH of 6.98±0.13 (n=19) and base deficit of −13±3 (n=17). Blood gases obtained within 1±0.5 h of birth had a mean pH of 7.11±0.17 (n=24) and base deficit of −18±6 (n=21). Sixteen neonates (67%) had moderate encephalopathy, and eight (33%) had severe encephalopathy. Median Apgar scores were 2 (range: 0–7), 4 (range: 0–8), and 6 (range: 2–9) at 1, 5, and 10 min of life. Fourteen patients (58%) had seizures diagnosed clinically or electrographically, and all were treated with phenobarbital. Six neonates also received fosphenytoin, levetiracetam, or topiramate. Head ultrasounds were abnormal in 18 patients (75%): all 18 had cerebral edema, one had a germinal matrix hemorrhage, and another had cystic white matter changes. None of the neonates had an intraventricular hemorrhage. Eight neonates (33%) received opiate infusions; 16 (67%) received vasoactive infusions, including dopamine (16/24), dobutamine (15/24), epinephrine (1/24), and milrinone (2/24); and 22 (92%) had respiratory compromise. Eighteen neonates (75%) were mechanically ventilated with a mean oxygenation index of 3.7±3 at the beginning of the study. One neonate had a positive bacterial blood culture. The patients' physiologic and laboratory variables are shown in Table 1. All enrolled neonates survived to NICU discharge.

Neurologic Injury

Brain MRIs were obtained 3–7 days after treatment on day of life 9±3 (range: 4–14). Three neonates had no injuries in any region. Twenty-one had injury in at least one region, and four had moderate/severe injury in all regions. Moderate/severe injury was more common in the white matter than in paracentral gyri, basal ganglia, thalamus, or brainstem (Table 2). No infants had selective, unilateral brain injury.

Blood Pressure and Autoregulation

The median duration of HVx monitoring was 30.9 h (22.6, 42.6 (interquartile range, IQR); n=24), 6.5 h (5.4, 7.9; n=22), and 6 h (6, 6; n=21) during hypothermia, rewarming, and normothermia, respectively. Figure 1 illustrates the neonates' range of MAP. MAP_{OPT} was identified in 19/24 (79%), 17/22 (77%), and 18/21 (86%) neonates during hypothermia, rewarming, and normothermia. The median MAP_{OPT} bin was 45 mmHg (45, 55 (IQR); n=19), 50 mmHg (45, 50; n=17), and 50 mmHg (45, 55; n=18) during hypothermia, rewarming, and normothermia. In some individual patients, the MAP_{OPT} differed between time periods. Neonates with no or mild brain injuries had no or minimal change in MAP_{OPT} as they progressed from hypothermia to rewarming in comparison to neonates with moderate/severe injuries (Figure 2).

Patients with moderate/severe injuries in paracentral gyri, white matter, basal ganglia, thalamus, and brainstem spent a greater proportion of time with blood pressure below MAP_{OPT} during rewarming than uninjured neonates. Injury severity in paracentral gyri, white matter, basal ganglia, and thalamus correlated with the percentage of time spent below MAP_{OPT} during rewarming. Neonates with no or mild injuries in all brain regions spent a greater proportion of time with blood pressure within the MAP_{OPT} bin than patients with moderate/severe injuries (Figure 3; Table 3).

During normothermia, neonates with injuries in white matter and brainstem spent a greater proportion of time with blood pressure below MAP_{OPT} than neonates without injuries in these regions. Injury severity in the white matter increased with more time below MAP_{OPT}. Neonates with no or mild injuries in all regions spent a greater proportion of time with blood pressure above MAP_{OPT} than neonates with moderate/severe injuries. Injuries in the paracentral gyri, white matter, basal ganglia, and thalamus were less severe in neonates who spent more time above MAP_{OPT} (Figure 4; Table 4).

Neurologic injury and the percentages of time spent with blood pressure below, within, or above MAP_{OPT} were not consistently associated during hypothermia (Table 5). Furthermore, time spent below the MAP threshold of gestational age + 5 did not correlate with injury severity in any brain region (Table 6). Patients spent little time with MAP below their gestational age (data not shown).

Brain injury was also associated with maximal deviation in blood pressure from MAP_{OPT} during rewarming. Neonates with no, mild, or moderate/severe injury in paracentral gyri had median MAP deviations below MAP_{OPT} of 10 mmHg (5, 10 (IQR)), 15 mmHg (15, 20), and 15 mmHg (5, 15), respectively. For neonates with no, mild, or moderate/severe injury in basal ganglia, the median MAP deviations below MAP_{OPT} were 10 mmHg (5, 15), 12.5 mmHg (10, 15), and 15 mmHg (5, 15). Patients with no, mild, or moderate/severe injury in thalamus had median MAP deviations below MAP_{OPT} of 10 mmHg (5, 15), 10 mmHg (10, 15), and 15 mmHg (5, 15).

Neonates with no or mild injury in all brain regions had greater blood pressure deviation above MAP_{OPT} during rewarming than patients with moderate/severe injury. During normothermia, neonates with no or mild injury in paracentral gyri, white matter, basal

ganglia, and thalamus also had greater blood pressure deviation above MAP_{OPT} than patients with moderate/severe injury (data not shown). No complications were associated with the autoregulation monitoring.

Among neonates with an identified MAP_{OPT} during hypothermia, rewarming, and normothermia, the rates of moderate/severe injury in paracentral gyri, basal ganglia, thalamus, and brainstem were similar or greater than the rates of moderate/severe injury in these regions in neonates without an identified MAP_{OPT}. The proportions of neonates with moderate/severe white matter injury were similar between those with and without an identified MAP_{OPT} during rewarming (data not shown.) Of neonates with an MAP_{OPT} during hypothermia (n=19), 74% had moderate/severe white matter injury, whereas 100% of neonates without an MAP_{OPT} during hypothermia (n=5) had moderate/severe white matter injury. During normothermia, the rate of moderate/severe white matter injury was 83% in neonates with an MAP_{OPT} (n=18) and 100% in neonates without an MAP_{OPT} (n=3).

Cerebral Oximetry

Patients with moderate/severe injuries had slightly higher rSO_2 values than patients with no or mild injuries (Table 7). Phenobarbital was administered to 14 neonates during hypothermia, two neonates during rewarming, and five neonates during normothermia. Compared to those with no or mild injuries, a higher proportion of neonates with moderate/severe injuries received phenobarbital during hypothermia or rewarming and received a second anti-epileptic (fosphenytoin, levetiracetam, or topiramate) during hypothermia, rewarming, or normothermia. Neonates with moderate/severe injuries had median PaO_2 values of 82–122 mmHg, and those with no or mild injuries had PaO_2 levels of 39–155 mmHg during hypothermia, rewarming, and normothermia. $PaCO_2$, arterial oxygen saturation, hemoglobin levels, the administration of opiate infusions, and the incidence of red blood cell transfusions were not associated with injury or rSO_2 (data not shown).

DISCUSSION

The results of this pilot study suggest that continuous autoregulation monitoring with HVx may identify blood pressures associated with reduced risk of neurologic injury in neonatal HIE. HVx successfully identified MAP_{OPT} during therapeutic hypothermia, rewarming, and normothermia. Descriptive analyses identified an association between neurologic injury and blood pressure in relation to MAP_{OPT}. By contrast, MAP goals based on the gestational age + 5 were not associated with brain injury. Greater severity of brain injury in neonates was associated with more time spent with blood pressure below MAP_{OPT} during rewarming. Conversely, neonates with no or mild injury spent more time with blood pressure within or above MAP_{OPT}. Moreover, patients with no injury or only mild injury had minimal shift in MAP_{OPT} when moving from hypothermia to rewarming.

Because this was an observational study, we do not know if maintaining MAP within or above MAP_{OPT} provides neuroprotection or is the result of better cardiovascular regulation in those with less injury. However, the data suggest that maintaining blood pressure within or above MAP_{OPT} may be safer than maintaining blood pressure below MAP_{OPT}. Clinicians use many techniques to maintain cerebral perfusion, including selecting a minimal tolerable

MAP of gestational age + 5 or monitoring rSO_2. Thresholds of MAP based on gestational age did not correlate with neurologic injury in this study. Absolute rSO_2 values depend on cerebral metabolic rate, which varies with temperature, sedation, anti-epileptic treatment, oxygen saturation, and hematocrit. Because these variables change frequently in neonates with HIE, interpretation of rSO_2 is challenging and is unlikely to define optimal cerebral perfusion pressure as a single measure. Alternatively, HVx is calculated from MAP and rTHb, a surrogate measure of CBV (8). HVx is less affected by cerebral oxygenation and primarily reflects changes in cerebral vasoconstriction/vasodilation during autoregulatory responses to changing perfusion pressure. We theorized that identifying MAP_{OPT} with HVx would be a more reliable method of guiding hemodynamic management to support cerebral perfusion. Indeed, neonates who had no neurologic injury or only mild injury spent more time with blood pressures within or above MAP_{OPT} than neonates with moderate/severe injuries.

The association between time spent within MAP_{OPT} and less neurologic injury was strongest during the rewarming period for the paracentral gyri and white matter. NIRS measures superficial cortex, and cortical measurements of rTHb would most closely reflect vasoreactivity in the paracentral gyri. The white matter, posterior limb of the internal capsule (PLIC), basal ganglia, thalamus, and brainstem are also vulnerable to hypoxic injury. In neonatal HIE, early MRI evidence of basal ganglia and thalamic injury are associated with future motor impairments, and brainstem injury is associated with death (11). The association between basal ganglia and thalamic injury and MAP_{OPT} suggests that cortical autoregulation measurements reflect vascoreactivity in deeper regions and that MAP_{OPT} may be similar in all brain regions. Alternatively, injury to deep brain structures may cause cardiovascular instability and poor autoregulatory function measured in the cortex. Because brainstem injury may induce hemodynamic instability and impaired autoregulation could cause brainstem injury, we expected a complex association between autoregulation and brainstem injury.

Related findings have been reported in adults. In adults with traumatic brain injury, mortality increased as cerebral perfusion pressure (CPP) decreased below optimal CPP (CPP_{OPT}) (4). Spending more time with CPP below CPP_{OPT} was associated with severe disability, vegetative state, or death in adults with aneurysmal subarachnoid hemorrhage (12). Neonates with no or mild injury had greater maximal blood pressure deviation above MAP_{OPT} than those with moderate/severe injury in our study. In contrast, a greater difference in median CPP above CPP_{OPT} was associated with severe disability in adult traumatic brain injury (4). We evaluated the maximal deviation in MAP above MAP_{OPT}, and neonates spent little time at higher blood pressures (Figure 1). Additional studies are needed to evaluate the effects of higher blood pressures in HIE.

In several patients, the MAP_{OPT} value changed between the hypothermic and rewarming periods. Neonates with no or mild injury had no or minimal change in MAP_{OPT}. The lower limit of autoregulation shifts to a higher CPP with intracranial hypertension (5). Theoretically, if ICP increased during rewarming in the more severely injured patients (13), a shift in the autoregulation curve could also shift MAP_{OPT}. Variation in MAP_{OPT} among

patients and changes in MAP_{OPT} within patients emphasize the importance of using continuous, real-time autoregulation monitoring to individualize hemodynamic goals.

We did not identify a correlation between neurologic injury and MAP_{OPT} during hypothermia. Hypothermia may preserve the cerebral vasodilatory response to hypotension. In a swine model of neonatal HIE, hypothermia acutely decreased the lower limit of autoregulation (9). If the lower limit of autoregulation was decreased during hypothermia in our patients, the adverse effect of blood pressure below MAP_{OPT} would be diminished.

Neonates with moderate/severe neurologic injuries had slightly higher rSO_2. Compared to their counterparts, these patients more often received phenobarbital, which suppresses cerebral metabolism and increases rSO_2. Whether more severe neurologic injury is consistently associated with higher rSO_2 requires additional studies. Nonetheless, in situations with frequent changes in cerebral metabolism, we propose that autoregulation monitoring with HVx would be better than rSO_2 alone to guide hemodynamic management. Additional studies are needed to evaluate this theory.

Metabolic acidosis (14), prostaglandins (15), and altered adenosine homeostasis (16,17) after hypoxia may affect CBF regulation (17–19). Autoregulation monitoring was initiated once study consent was obtained and after an arterial cannula was placed. It is possible that before monitoring was established, some neonates may have had severe metabolic derangements with altered autoregulatory function. Moreover, rewarming may increase lactate, adenosine, and prostaglandin production in injured regions of brain and limit myogenic reactivity and the range of autoregulation. Because the brain was not imaged early after rewarming, the timing of the injury and alterations in vasoreactivity cannot be linked on an individual basis.

An association between impaired autoregulation and mortality in neonatal HIE has been suggested previously. Using Xenon techniques 2–3 times over a 2-h period in neonates with asphyxia, Pryds et al. (20) reported an association between pressure-passive CBF and death. Our findings expand upon the relationship between autoregulation and neurologic outcomes. We obtained autoregulation measurements continuously over days and across a wide hemodynamic range. In individual patients, HVx identified MAP_{OPT} and distinguished this MAP from levels with poorer autoregulation. Neonates with moderate/severe brain injury displayed an increase in MAP_{OPT} when transitioning from hypothermia to rewarming despite similar blood pressure distributions between these periods, which suggests a rightward shift in the autoregulation curve. Deviation in blood pressure below MAP_{OPT} was associated with worse neurologic injury. Therefore, we suggest that neonates with HIE and poor neurologic outcomes do not have completely impaired autoregulation. Rather, the blood pressure range within the confines of autoregulation may shift, necessitating an adjustment in hemodynamic management to maintain pressure-reactive CBF. This possibility emphasizes the importance of continuous autoregulation monitoring to individualize hemodynamic goals as injury evolves and therapeutic conditions change.

Our pilot study had limitations. First, monitoring duration differed among patients during hypothermia because monitoring was started after obtaining consent. The durations of

monitoring during rewarming and normothermia were more consistently 6 h. We analyzed the data using the percentage of time of the monitoring period to account for the different absolute monitoring durations. Second, tests for reproducibility in MRI interpretation were not performed in this single-institution study. MRI analyses were qualitative, which is generally considered to be less sensitive than quantitative analyses. Specific MRI findings as a function of postnatal age were not evaluated. It is possible that neurologic injury on MRI reflected prenatal insults and that cardiovascular regulation was worse in these patients than in those with less injury. Third, MRIs were obtained within the first 2 weeks of life. Although early MRI evidence of brain injury correlates to poor motor outcomes or death (11), long-term outcome data were not available for our study. Fourth, the effects of vasoactive infusions or seizures on autoregulation were not examined. The impact of vasopressors on autoregulation in neonatal HIE is unclear, although phenylephrine did not affect autoregulation in a neonatal swine model of HIE (10). Finally, an alternative measure of CBF, such as TCD, was not used to validate HVx, because continuous Doppler over 3–4 days is not feasible in neonates. Nonetheless, HVx correlates with ICP-derived autoregulation measurements in patients (3), HVx identified the limits of autoregulation determined by laser-Doppler in a swine model of HIE (9,10), and HVx was validated against TCD in identifying MAP_{OPT} during cardiopulmonary bypass (21).

In conclusion, blood pressure maintenance within or above MAP_{OPT} was associated with decreased neurologic injuries in neonates with HIE. HVx monitoring could enable clinicians to target optimal hemodynamic ranges for individual patients to support autoregulation and prevent secondary brain injury. Future clinical studies are indicated to further evaluate the utility of HVx in neonatal HIE.

METHODS

This study was approved by the Johns Hopkins University Institutional Review Board, and written informed consent was obtained from the parents. Between September 2010–April 2012, neonates with HIE who were admitted to the Johns Hopkins Neonatal Intensive Care Unit (NICU) for therapeutic hypothermia were screened. To be eligible for the study, the patient's parent had to speak English or Spanish (the languages available for the consent forms), and the attending neonatologist had to agree to enroll the neonate. Eligibility criteria included gestational age ≥35 weeks, birth weight ≥1800 g, initiation of cooling before 6 h of age, and an arterial blood pressure cannula. Criteria for HIE were based on the National Institute of Child Health and Human Development Neonatal Research Network's clinical trial of hypothermia in neonatal HIE (22) and included a blood gas obtained from the umbilical cord or in the first hour of life with pH <7.15 or base deficit >10 mmol/l, and moderate to severe encephalopathy. If a blood gas was unavailable, an acute perinatal event, 10-min Apgar score <5 or assisted ventilation for ≥10 min after birth, and moderate to severe encephalopathy were required to diagnose HIE. Neonates without arterial blood pressure cannulae or who had congenital anomalies or coagulopathy with active bleeding that could make cooling unsafe were ineligible for the study.

Clinical Care

Clinical care was determined by the clinical team and per NICU protocol. Neonates received whole-body hypothermia with a cooling blanket (Mul-T-Blanket Hyper/Hypothermia Blanket and Mul-T-Pad Temperature Therapy Pad; Gaymar Medi-Therm III; Gaymar Industries Inc., Orchard Park, NY) to maintain a rectal temperature of 33.5±0.5°C for 72 h. Neonates were rewarmed over 6 h (goal 0.5°C/h) to normothermia (36.5°C). Hemodynamic goals were determined by the clinical team. Neonates who required vasoactive medications were given dopamine followed by dobutamine, epinephrine, or milrinone infusions as necessary. Sedation was provided with morphine, fentanyl, or hydromorphone infusions and boluses. Neonates received full montage electroencephalograms (EEG) during hypothermia and after rewarming, and continuous amplitude-integrated EEG monitoring (Brainz BRM3 Monitor or CFM Olympic Brainz Monitor, Natus Medical Inc., San Carlos, CA) during hypothermia, rewarming, and the first 6 h of normothermia. Phenobarbital was administered for electrographic or clinical seizures. Fosphenytoin, levetiracetam, or topiramate were added for persistent seizures. Head ultrasounds were obtained upon NICU admission and after rewarming. Clinicians could view the blood pressure and rSO_2, but they were blinded to HVx. Clinical variables, including vital signs and laboratory measurements, were extracted from a replicated database of the electronic medical record. Clinical histories were obtained by chart reviews.

Autoregulation Monitoring

Bilateral, adhesive, neonatal cerebral oximetry probes (INVOS; Covidien, Boulder, CO) were placed on the patients' foreheads. Arterial blood pressure from the patient monitor (GE Marquette, Garnerville, NY) and NIRS signals were synchronously sampled at 100 Hz and processed with an analog-to-digital converter (DT9804, Data Translation, Marlboro, MA) and bedside computer using ICM+ software (Cambridge Enterprises, Cambridge, UK) (8–10,23,24). Artifacts in the NIRS and MAP signals (e.g., arterial line flushes) were manually removed, and data comprising less than 1% of the recording period were excluded as an additional measure to remove artifacts (23).

HVx was calculated with a continuous, moving correlation coefficient between MAP and rTHb (a surrogate measure of CBV obtained by NIRS) (8–10). Consecutive, paired, 10-s averaged values from 300-s duration were incorporated into each calculation, utilizing 30 data points for each HVx calculation (24). HVx ranges from −1 to +1. Negative or near-zero HVx represents functional vasoreactivity (and therefore intact autoregulation) because MAP and CBV are either negatively correlated or are not correlated. When blood pressure decreases and vasoreactivity becomes impaired, HVx becomes positive and approaches +1 because MAP and CBV positively correlate (8–10). HVx values for the right and left sides were averaged and sorted into 5-mmHg bins of MAP to generate bar graphs. The MAP_{OPT} in each time period (hypothermia, rewarming, and first 6 h of normothermia) was identified as the bin with the most negative HVx when the bar graph showed a trend of increasing index values as MAP deviated from this nadir (3) (Figure 5). Two physicians (JKL and MMG), who were blinded to the patient's history and MRI results, independently interpreted the HVx bar graph. Both physicians had to agree on a patient's MAP_{OPT} to include the patient in the analysis of MAP_{OPT} and neurologic injury.

MRI

Neonates received brain MRIs 3–7 days after completion of hypothermia on a 1.5-Tesla Magnetom Avanto (Siemens AG, Erlangen, Germany). All neonates received sequences with T1-weighted (T1-W), T2-weighted (T2-W), and diffusion tensor imaging (DTI). Two pediatric neuroradiologists (AT and TH) with 5 and 15 years of dedicated pediatric neuroradiology experience evaluated the MRIs in consensus. Injury was graded as none, mild, moderate, or severe in paracentral gyri, white matter (including PLIC), basal ganglia, thalamus, and brainstem. These regions are associated with motor impairment or death in HIE (11). Qualitative evaluation for injury grading was based on the severity of signal alterations on T1-W, T2-W, and diffusion-weighted imaging (derived from the DTI data) (25). Increasing T1 and T2 signals in the cortex, basal ganglia, PLIC, and thalami represented more severe injury. Increased T2 signal and loss of gray-white matter differentiation identified greater white matter injury. Increased signal in the apparent diffusion coefficient (ADC) maps confirmed the presence of injury (Figure 6). The radiologists were blinded to the patients' HVx, blood pressures, and clinical histories.

Statistical Analysis

Descriptive summary statistics were conducted with SAS v9.2 (SAS Institute Inc., Cary, NC), and graphs were generated with GraphPad Prism (v5.03, GraphPad Software Inc., La Jolla, CA). Data are reported as means with SD or medians with IQR when appropriate. Neurologic outcomes in each anatomic region were categorized as no, mild, or moderate/severe injury. Right and left rSO_2 values were averaged to analyze the relationship between rSO_2 and injury. Time was analyzed as the percentage of the autoregulation monitoring period obtained during hypothermia, rewarming, or normothermia.

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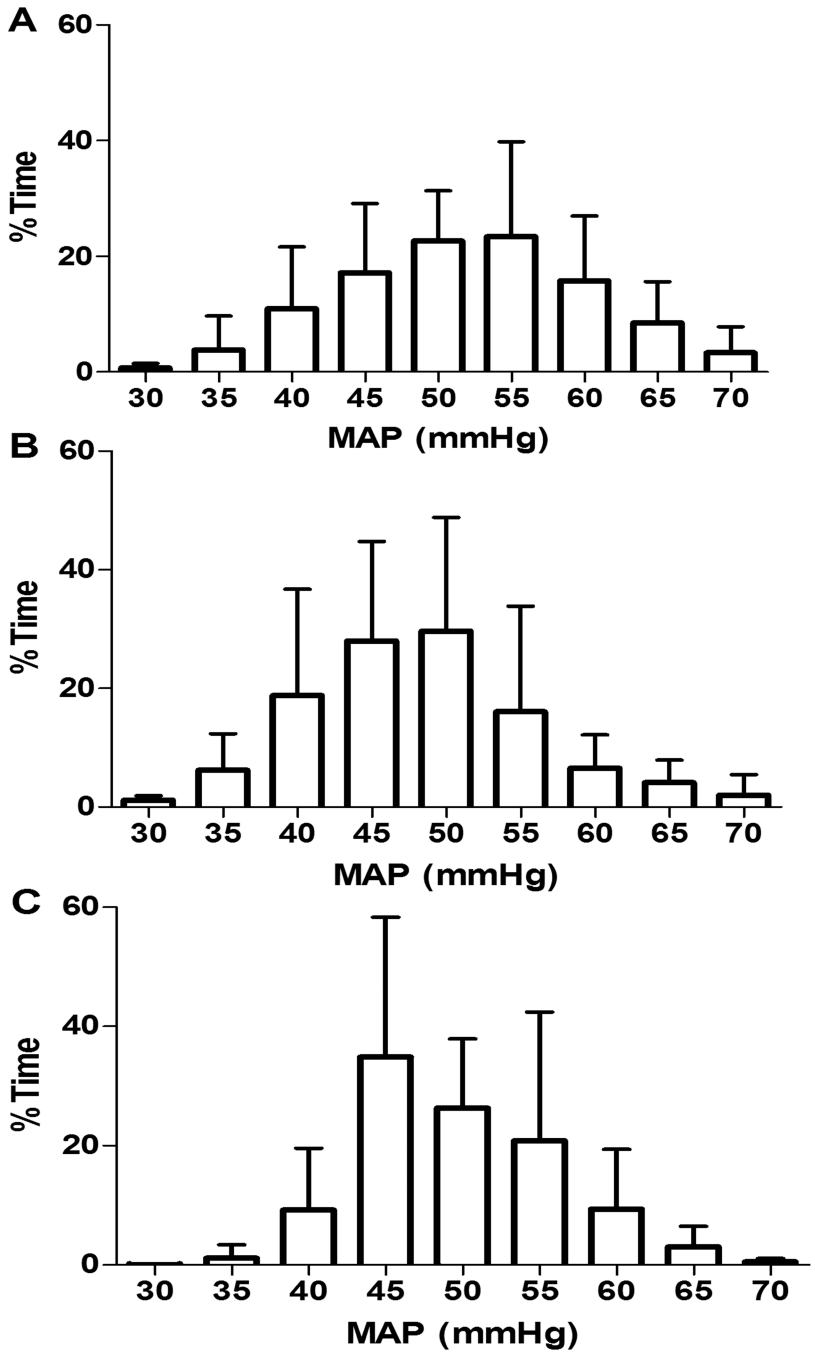

Figure 1.

The percentage of time during (A) hypothermia (n=24), (B) rewarming (n=22), and (C) normothermia (n=21) that neonates spent at each mean arterial blood pressure (MAP). Data are shown as means with SDs.

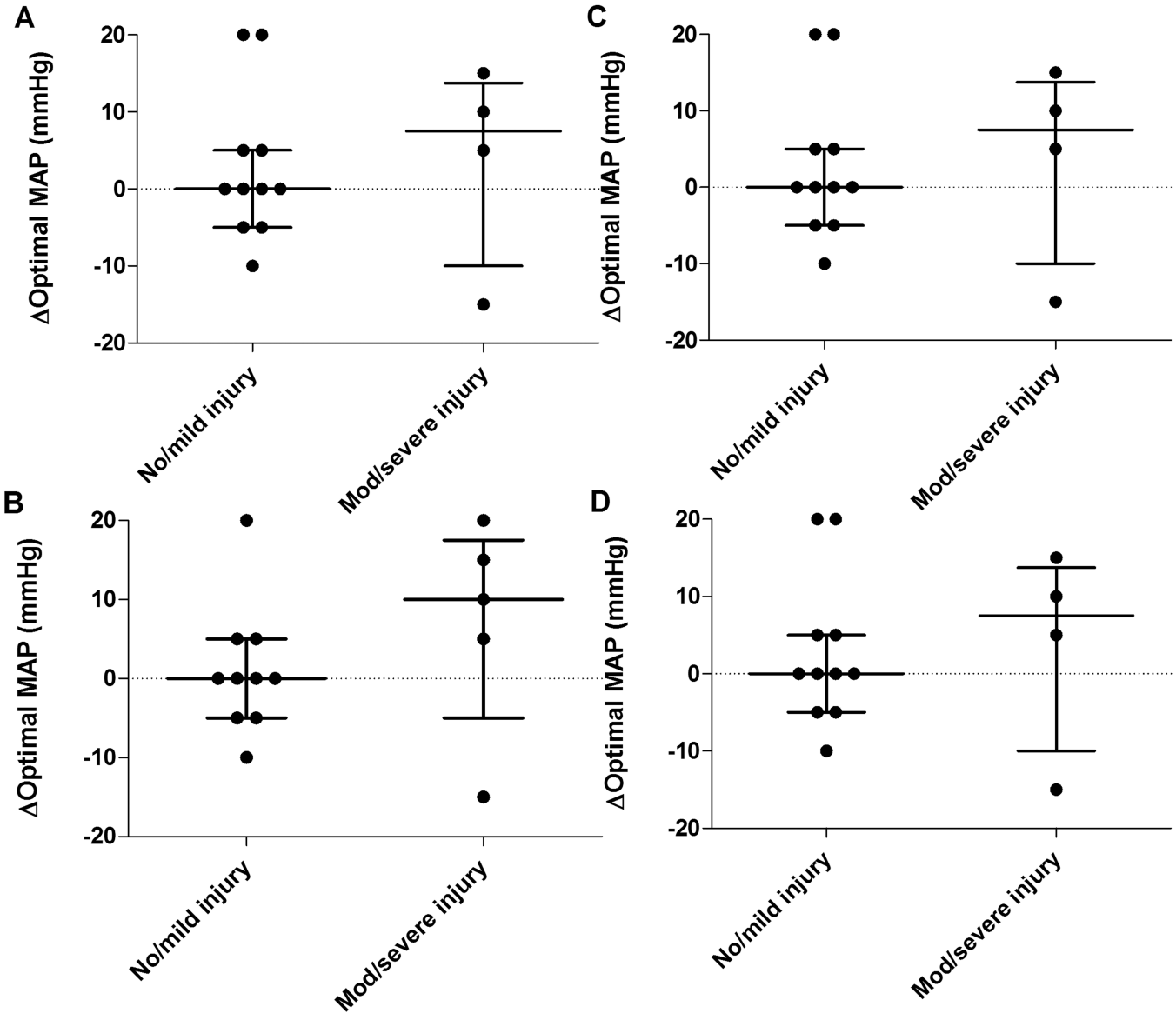

Figure 2.

Fifteen neonates had an identifiable optimal mean arterial blood pressure (MAP_{OPT}) during both hypothermia and rewarming. When progressing from hypothermia to rewarming, some individuals had a shift in MAP_{OPT}. This shift is represented on the y-axis. For instance, a value of 5 indicates the MAP_{OPT} increased by 5 mmHg as the patient moved from hypothermia to rewarming. A value of 0 represents no shift. Patients with no or mild injury in (A) paracentral gyri, (B) white matter, (C) basal ganglia, and (D) thalamus had no or minimal shift in MAP_{OPT} when moving from hypothermia to rewarming. Data are shown as medians and interquartile ranges.

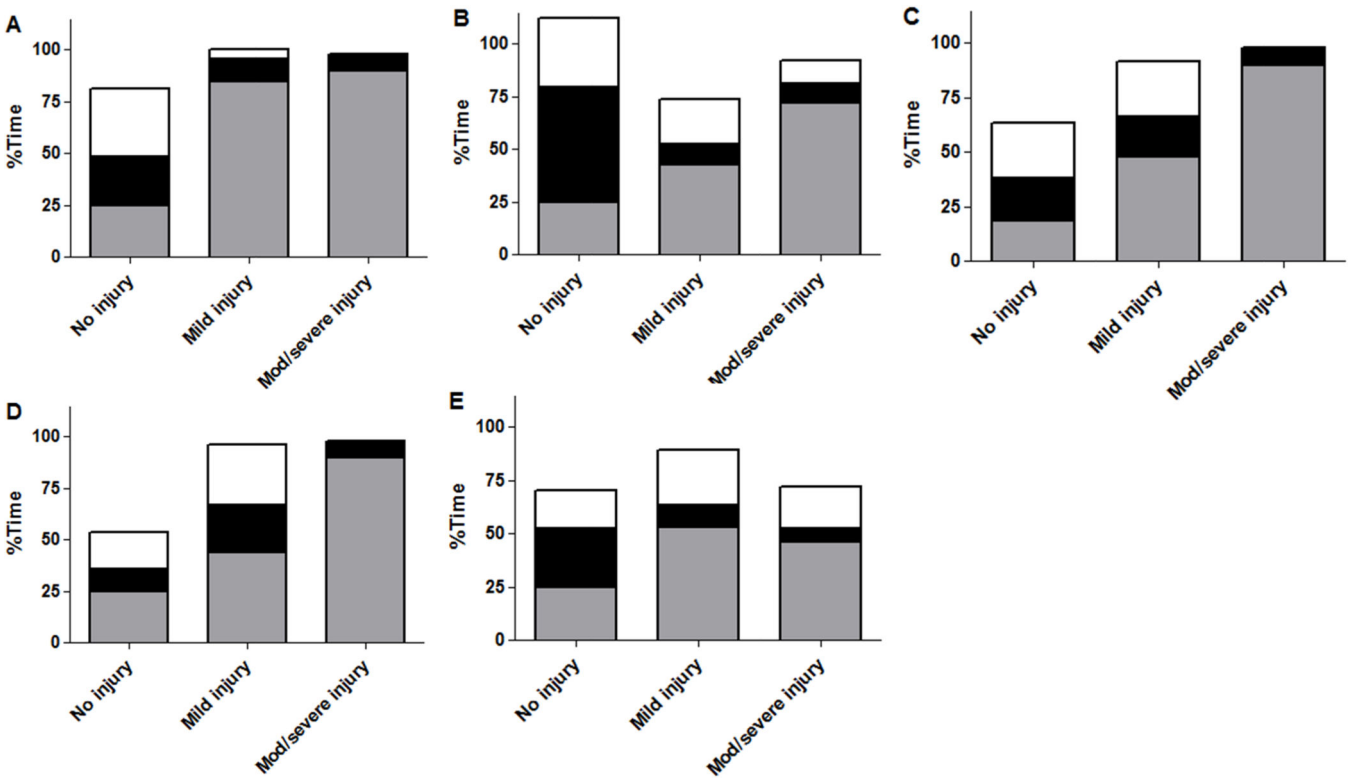

Figure 3.

The percentage of time neonates (n=17) spent below, within, or above the optimal mean arterial blood pressure bin (MAP_{OPT}) during rewarming in relation to injury in (A) paracentral gyri, (B) white matter, (C) basal ganglia, (D) thalamus, and (E) brainstem. Gray represents the percentage of time spent with blood pressure below MAP_{OPT}. Black represents the percentage of time spent with blood pressure within MAP_{OPT}. White represents the percentage of time spent with blood pressure above MAP_{OPT}. Neonates with injuries in all regions spent more time with blood pressure below MAP_{OPT} than patients without injury. The degree of injury in paracentral gyri, white matter, basal ganglia, and thalamus increased with greater time below MAP_{OPT}. Neonates with no or mild injury spent a greater proportion of time with blood pressure within the MAP_{OPT} bin than patients with moderate/severe injury. Data are displayed as medians.

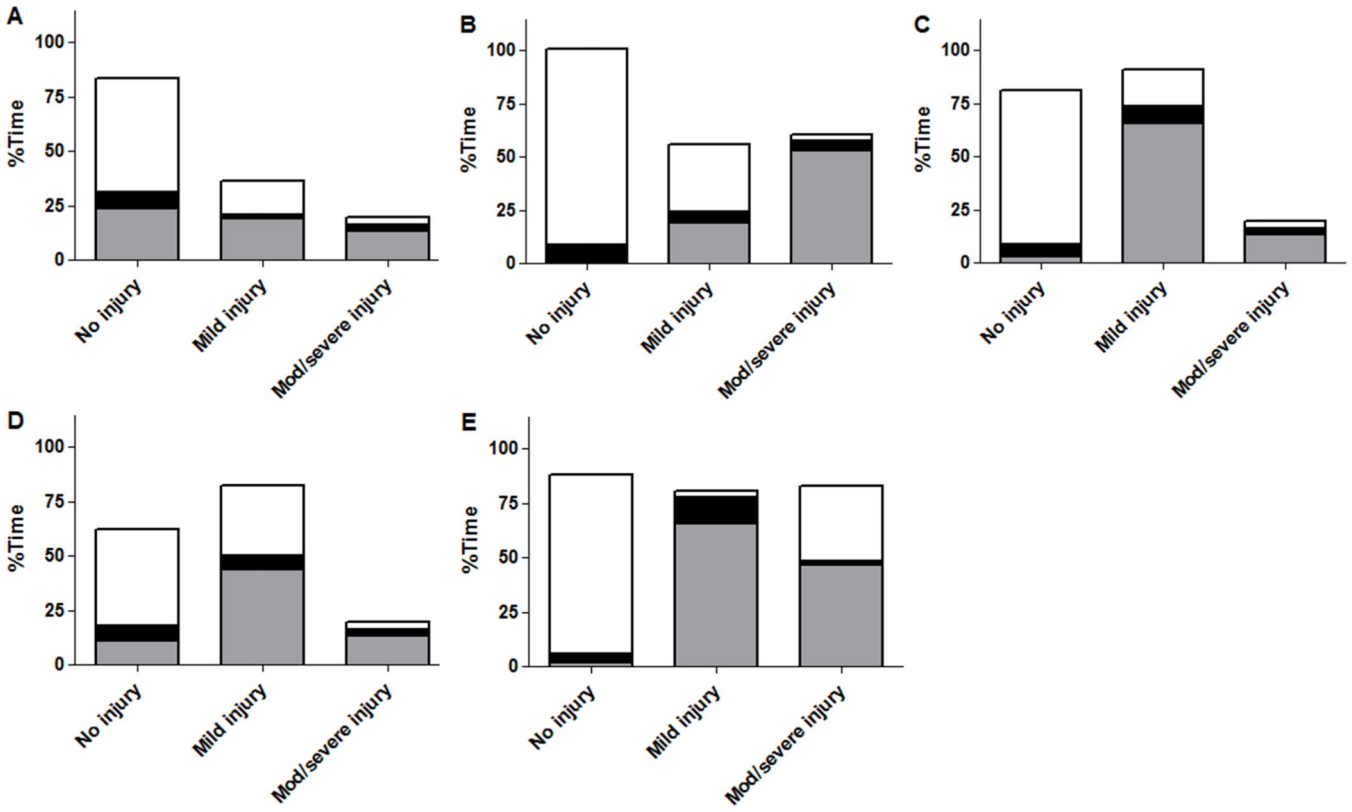

Figure 4.

The percentage of time neonates (n=18) spent below, within, or above the optimal mean arterial blood pressure bin (MAP_{OPT}) during normothermia in relation to injury in (A) paracentral gyri, (B) white matter, (C) basal ganglia, (D) thalamus, and (E) brainstem. Gray represents the percentage of time spent with blood pressure below MAP_{OPT}. Black represents the percentage of time spent with blood pressure within MAP_{OPT}. White represents the percentage of time spent with blood pressure above MAP_{OPT}. Patients with injury in white matter and brainstem, and patients with more severe injury in white matter spent more time with blood pressure below MAP_{OPT}. Neonates with no or mild injury in all regions spent more time with blood pressure above MAP_{OPT} than patients with moderate/severe injury. Injury severity was lower in paracentral gyri, white matter, basal ganglia, and thalamus with greater time spent above MAP_{OPT}. Data are displayed as medians.

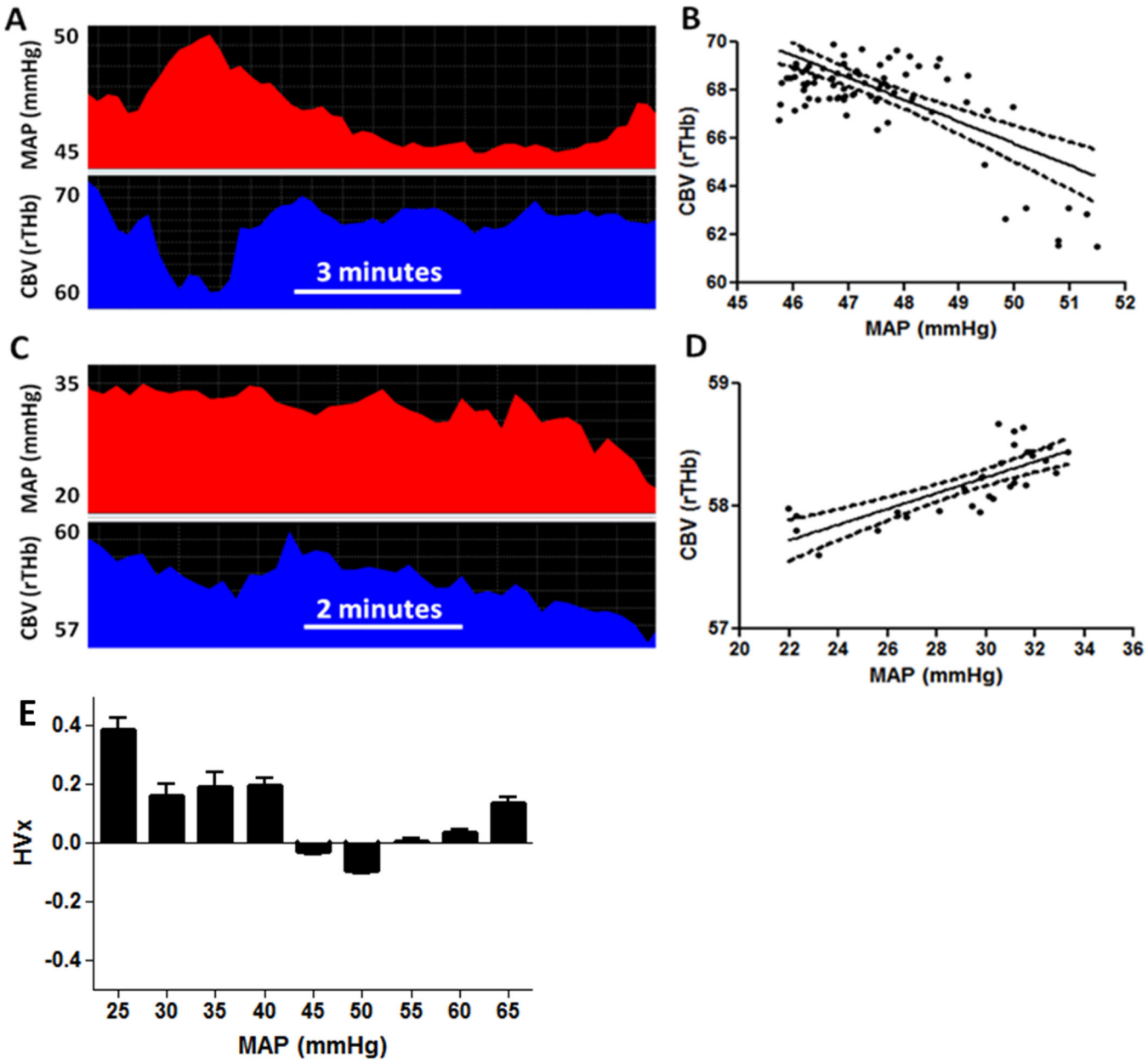

Figure 5.

Hemoglobin volume index (HVx) calculation in a neonate with hypoxic-ischemic encephalopathy. (A, B) When mean arterial blood pressure (MAP) exceeded 45 mmHg, MAP negatively correlated with cerebral blood volume (CBV, or the relative total hemoglobin (rTHb) measured by near-infrared spectroscopy). This negative correlation yielded an HVx of −0.29, indicating pressure-reactive vasoreactivity with functional autoregulation. The linear regression line is illustrated (E(Y)=111.5−0.91X; 95% confidence interval for slope: −1.18, −0.66; $p<0.0001$). (C, D) When MAP was less than 35 mmHg, MAP and CBV positively correlated. This resulted in an HVx of 0.12, indicating pressure-passive vasoreactivity with impaired autoregulation. The linear regression line is illustrated (E(Y)=56.3+0.06X; 95% confidence interval for slope: 0.04, 0.08; $p<0.0001$). (E) Six hours

of HVx monitoring. HVx was sorted into 5-mmHg bins of MAP. Optimal MAP (MAP_{OPT}) was identified at the HVx nadir and represents the range of MAP with most robust vasoreactivity. This patient's MAP_{OPT} was 50 mmHg. Data in panels B and D are shown with linear regression lines and 95% confidence intervals. Data in panel E are shown as means with SDs.

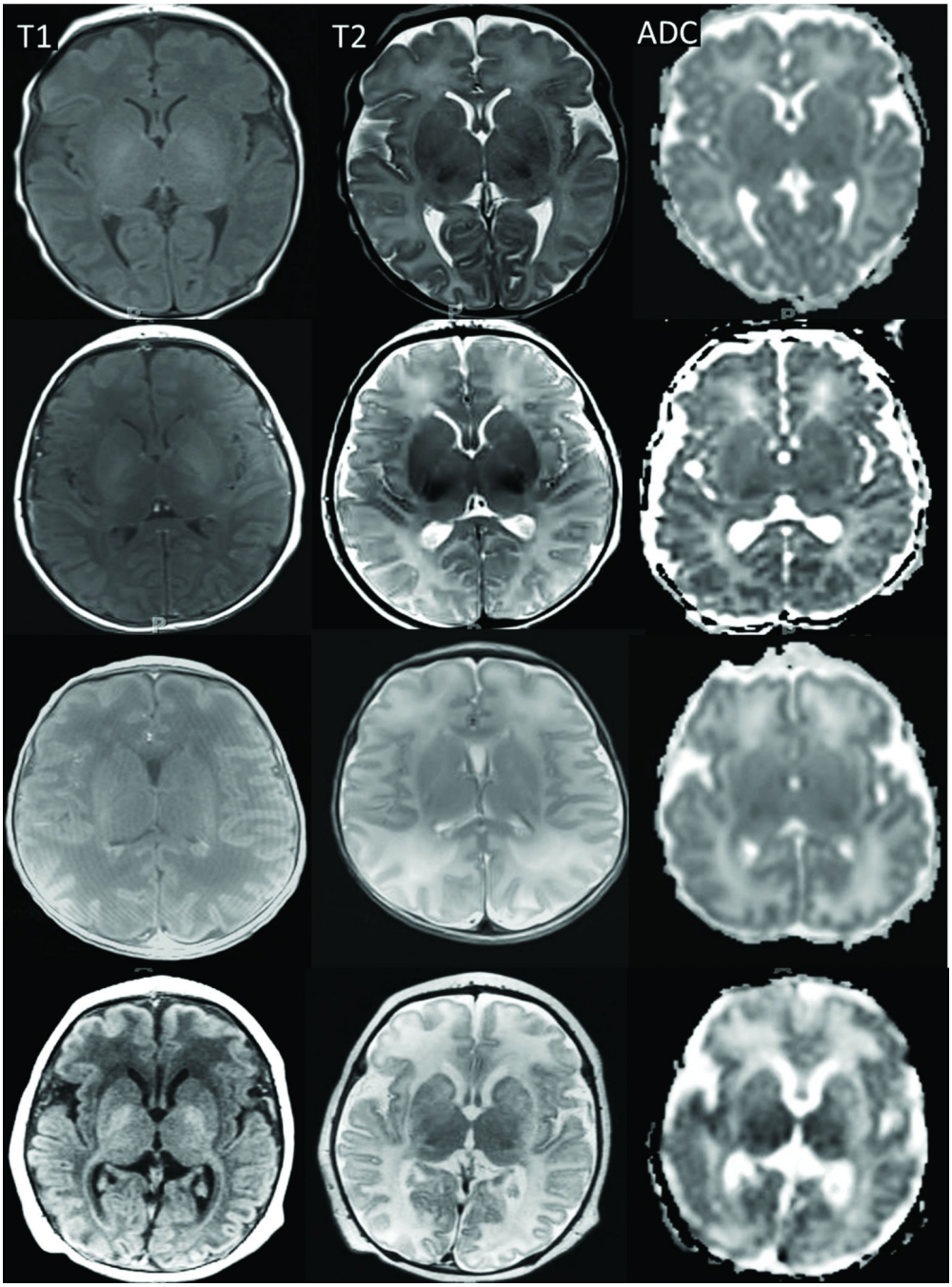

Figure 6.

Axial T1-weighted (first column) and T2-weighted (second column) images and ADC maps (third column) of four neonates with no (first row), mild (second row), moderate (third row), or severe (fourth row) injury. T1 and T2 signals increased in the cortex, basal ganglia, thalami, and posterior limb of the internal capsule with greater injury. With worsening white matter injury, the T2 signal increased and the gray-white matter differentiation became less

distinct. ADC maps confirmed the injuries, particularly in the white matter, as signal increased with greater injury.

Table 1

Physiologic variables and laboratory measurements during the study period (n=24)

Parameter	Hypothermia	Rewarming	Normothermia
Temperature (°C)	33.5 (0.3)	35.2 (0.4)	36.9 (0.3)
Heart rate (bpm)	108 (12)	117 (13)	135 (17)
MAP (mmHg)	52 (5)	49 (4)	50 (4)
pH	7.37 (0.04)	7.37 (0.06)	7.37 (0.05)
$PaCO_2$ (mmHg)	43 (6)	48 (9)	48 (7)
PaO_2 (mmHg)	115 (47)	94 (29)	105 (48)
Hemoglobin (g/dl)	15.2 (1.2)	13.7 (0.7)[a]	13.4 (0.6)[b]
WBC (no./mm^3)	10,032 (3,156)	8,315 (3,646)[a]	9,566 (1,423)[b]
Sodium (mEq/l)	138 (3)	138 (3)[a]	141 (3)[b]

Data are shown as means with SD. Bpm, beats per minute; WBC, white blood count.

[a] Laboratory measurements were taken in 9 patients.

[b] Laboratory measurements were taken in 11 patients.

Table 2

Summary of anatomical and diffusion MRI findings

Brain region	No. of Patients
Paracentral gyri	
No injury	14
Mild injury	4
Moderate/severe injury	6
White matter[a]	
No injury	5
Mild injury	7
Moderate/severe injury	12
Basal ganglia	
No injury	11
Mild injury	7
Moderate/severe injury	6
Thalamus	
No injury	10
Mild injury	8
Moderate/severe injury	6
Brainstem	
No injury	12
Mild injury	7
Moderate/severe injury	5

[a]Includes the posterior limb of the internal capsule.

Table 3

Brain injury and percent of time spent in relation to optimal MAP during rewarming

Brain region	Below optimal MAP (%, median, IQR)	At optimal MAP (%, median, IQR)	Above optimal MAP (%, median, IQR)
Paracentral gyri			
No injury	25 (9, 52)	24 (5, 28)	33 (22, 63)
Mild injury	85 (41, 89)	11 (9, 44)	4 (2, 14)
Moderate/severe injury	90 (2, 92)	8 (2, 10)	0 (0, 39)
White matter			
No injury	25 (13, 52)	54 (13, 58)	33 (18, 35)
Mild injury	42 (5, 84)	10 (3, 27)	22 (8, 80)
Moderate/severe injury	72 (2, 92)	9 (2, 24)	11 (0, 39)
Basal ganglia			
No injury	19 (9, 85)	19 (9, 54)	25 (4, 63)
Mild injury	48(41, 54)	18 (5, 26)	26 (14, 35)
Moderate/severe injury	90 (2, 92)	8 (2, 10)	0 (0, 39)
Thalamus			
No injury	25 (13, 25)	11 (9, 11)	18 (4, 18)
Mild injury	44 (9, 44)	24 (5, 24)	29 (14, 29)
Moderate/severe injury	90 (2, 90)	8 (2, 8)	0 (0, 0)
Brainstem			
No injury	25 (9, 85)	28 (9, 54)	18 (4, 63)
Mild injury	53 (44, 84)	11 (5, 24)	26 (12, 35)
Moderate/severe injury	46 (1, 94)	6 (2, 34)	20 (0, 69)

Table 4

Brain injury and percent of time spent in relation to optimal MAP during normothermia

Brain region	Below optimal MAP (%, median, IQR)	At optimal MAP (%, median, IQR)	Above optimal MAP (%, median, IQR)
Paracentral gyri			
No injury	24 (0, 93)	8 (3, 14)	52 (1, 92)
Mild injury	19 (1, 99)	2 (1, 65)	16 (0, 98)
Moderate/severe injury	13 (0, 93)	3 (2, 33)	4 (2, 67)
White matter			
No injury	1 (0, 87)	8 (3, 10)	92 (3, 97)
Mild injury	19 (2, 94)	5 (2, 23)	32 (1, 84)
Moderate/severe injury	53 (0, 93)	5 (2, 33)	2 (2, 67)
Basal ganglia			
No injury	3 (0, 94)	5 (2, 24)	73 (0, 97)
Mild injury	66 (2, 93)	8 (2, 14)	17 (1, 84)
Moderate/severe injury	13 (0, 93)	3 (2, 33)	4 (2, 67)
Thalamus			
No injury	11 (1, 94)	7 (3, 24)	44 (0, 92)
Mild injury	44 (1, 93)	7 (2, 14)	32 (1, 98)
Moderate/severe injury	13 (0, 93)	3 (2, 33)	4 (2, 67)
Brainstem			
No injury	2 (0, 57)	4 (2, 16)	82 (8, 97)
Mild injury	66 (13, 93)	12 (7, 23)	3 (1, 32)
Moderate/severe injury	47 (0, 95)	2 (2, 18)	34 (2, 82)

Table 5

Brain injury and percent of time spent in relation to optimal MAP during hypothermia

Brain region	Below optimal MAP (%, median, IQR)	At optimal MAP (%, median, IQR)	Above optimal MAP (%, median, IQR)
Paracentral gyri			
No injury	11 (1, 43)	12 (6, 19)	78 (26, 90)
Mild injury	47 (0, 96)	2 (1, 3)	50 (1, 99)
Moderate/severe injury	1 (0, 16)	27 (3, 27)	73 (57, 96)
White matter			
No injury	55 (1, 64)	12 (11, 19)	26 (13, 87)
Mild injury	5 (0, 41)	4 (2, 12)	90 (46, 98)
Moderate/severe injury	1 (0, 16)	27 (3, 27)	73 (57, 96)
Basal ganglia			
No injury	5 (1, 55)	6 (2, 12)	87 (26, 90)
Mild injury	41 (0, 43)	14 (3, 24)	7 (21, 97)
Moderate/severe injury	1 (0, 16)	27 (3, 27)	73 (57, 96)
Thalamus			
No injury	11(1, 75)	8 (3, 12)	78 (14, 89)
Mild injury	20 (0, 43)	8 (2, 24)	71 (21, 98)
Moderate/severe injury	1 (0, 16)	27 (3, 27)	73 (57, 96)
Brainstem			
No injury	3 (0, 55)	5 (2, 12)	88 (26, 98)
Mild injury	41 (22, 43)	24 (14, 35)	44 (21, 46)
Moderate/severe injury	1 (0, 8)	15 (3, 27)	84 (65, 97)

Table 6

Brain injury and percentage of time spent with mean arterial blood pressure below the gestational age + 5

Brain region	Hypothermia (%, median, IQR)	Rewarming (%, median, IQR)	Normothermia (%, median, IQR)
Paracentral gyri			
No injury	14 (3, 20)	25 (9, 44)	3 (0, 31)
Mild injury	17 (8, 2)	53 (3, 62)	19 (2, 31)
Moderate/severe injury	15 (3, 22)	5 (2, 21)	5 (2, 33)
White matter			
No injury	11 (8, 13)	21 (15, 34)	3 (0, 39)
Mild injury	16 (3, 20)	39 (2, 53)	2 (0, 31)
Moderate/severe injury	16 (3, 28)	8 (2, 53)	5 (2, 33)
Basal ganglia			
No injury	13 (2, 20)	25 (9, 44)	3 (0, 25)
Mild injury	16 (3, 25)	39 (3, 54)	16 (1, 60)
Moderate/severe injury	15 (3, 22)	5 (2, 21)	5 (2, 33)
Thalamus			
No injury	16 (5, 20)	33 (6, 48)	3 (0, 31)
Mild injury	12 (3, 20)	28 (6, 49)	9 (2, 41)
Moderate/severe injury	15 (3, 22)	5 (2, 21)	5 (2, 33)
Brainstem			
No injury	12 (2, 20)	19 (3, 44)	2 (0, 19)
Mild injury	16 (8, 25)	44 (17, 54)	22 (1, 62)
Moderate/severe injury	14 (3, 16)	3 (2, 8)	4 (2, 5)

Table 7

Brain injury and absolute regional cerebral oxygen saturation (right and left averaged)

Brain region	Hypothermia (%, median, IQR)	Rewarming (%, median, IQR)	Normothermia (%, median, IQR)
Paracentral gyri			
No injury	83 (78, 86)	80 (79, 90)	83 (71, 89)
Mild injury	90 (85, 92)	90 (78, 94)	89 (78, 91)
Moderate/severe injury	90 (86, 94)	94 (90, 95)	92 (89, 94)
White matter			
No injury	86 (81, 89)	86 (79, 93)	92 (76, 94)
Mild injury	83 (73, 88)	80 (78, 90)	81 (67, 89)
Moderate/severe injury	91 (86, 94)	94 (87, 95)	91 (87, 94)
Basal ganglia			
No injury	84 (79, 89)	82 (79, 92)	85 (72, 92)
Mild injury	84 (73, 90)	80(74, 90)	81 (74, 89)
Moderate/severe injury	90 (86, 94)	94(90, 95)	92 (89, 94)
Thalamus			
No injury	85 (79, 89)	86 (79, 93)	85 (78, 92)
Mild injury	83 (73, 90)	79 (76, 89)	79 (70, 89)
Moderate/severe injury	90 (86, 94)	94 (90, 95)	92 (89, 94)
Brainstem			
No injury	85 (80, 90)	86 (79, 92)	85 (78, 91)
Mild injury	84 (73, 91)	80 (74, 91)	81 (74, 90)
Moderate/severe injury	87 (86, 93)	94 (90, 95)	91 (89, 94)