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Optimizing cerebral autoregulation may decrease neonatal regional hypoxic-ischemic brain injury

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Abstract

Background—Therapeutic hypothermia provides incomplete neuroprotection for neonatal hypoxic-ischemic encephalopathy (HIE). We examined whether hemodynamic goals that support autoregulation are associated with decreased brain injury and whether these relationships are affected by birth asphyxia or vary by anatomic region.

Methods—Neonates cooled for HIE received near-infrared spectroscopy autoregulation monitoring to identify the mean arterial blood pressure with optimized autoregulatory function (MAP_{OPT}). Blood pressure deviation from MAP_{OPT} was correlated to brain injury on MRI after adjusting for the effects of arterial carbon dioxide, vasopressors, seizures, and birth asphyxia severity.

Results—Blood pressure deviation from MAP_{OPT} related to neurologic injury in several regions independent of birth asphyxia severity. Greater duration and deviation of blood pressure below MAP_{OPT} were associated with greater injury in the paracentral gyri and white matter. Blood pressure within MAP_{OPT} related to lesser injury in the white matter, putamen and globus pallidus, and brainstem. Finally, blood pressures that exceeded MAP_{OPT} were associated with reduced injury in the paracentral gyri.

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Conclusions—Blood pressure deviation from optimal autoregulatory vasoreactivity was associated with MRI markers of brain injury that, in many regions, were independent of the initial birth asphyxia. Targeting hemodynamic ranges to optimize autoregulation has potential as an adjunctive therapy to hypothermia for HIE.

Keywords

Brain injury; Cerebral blood flow; Hypoxia; Neonatal

INTRODUCTION

Therapeutic hypothermia offers only partial neuroprotection for neonates with hypoxic-ischemic encephalopathy (HIE). Even with hypothermia, neurologic disabilities persist in 35–55% of survivors at 6–7 years. [1, 2] Ensuring robust cerebrovascular autoregulation might improve outcomes. In pilot studies, we showed that blood pressure deviations from the optimal mean arterial blood pressure (MAP_{OPT}) at which autoregulation is most robust are associated with brain injury on MRI [3, 4] and 2-year neurodevelopmental outcomes [5] after HIE. However, these studies were too small to control for confounders that affect autoregulation, such as the arterial partial pressure of carbon dioxide ($PaCO_2$) [6] and vasopressors. [7, 8] Here, we studied a larger cohort to evaluate autoregulation independent of $PaCO_2$, vasopressors, perinatal insult severity, and seizures.

Autoregulation can be measured indirectly with near-infrared spectroscopy (NIRS). [3–5, 9, 10] NIRS measures deoxy- and oxyhemoglobin optical densities from regional cortex, and the sum of these densities – the relative total tissue hemoglobin (rTHb) – is as a surrogate measure of regional cerebral blood volume. NIRS rTHb measurements reflect the fluctuations in cerebral blood volume that occur during autoregulatory vasoactive responses to changes in arterial blood pressure. The hemoglobin volume index (HVx) is calculated as the correlation coefficient between rTHb and MAP. [11]

Because NIRS interrogation focuses on the frontal cortex, whether autoregulation measurements can gauge injury risk in other anatomic regions is unclear and must be studied to determine the relevance for HIE. Our objective was to measure autoregulation with HVx and brain injury with MRI in neonates w ho received therapeutic hypothermia for HIE to test the hypotheses that 1) HVx identifies the blood pressure range with optimal autoregulatory vasoreactivity; 2) autoregulation affects brain injury independent of perinatal insult severity; and 3) these relationships vary by anatomic region.

METHODS

This observational, prospective study was approved by the Johns Hopkins University School of Medicine Institutional Review Board. Written informed consents were obtained until May 2013, when NIRS became standard of care for HIE treatment at our hospital. After that we were granted a waiver of consent. We sequentially screened all neonates admitted for HIE between September 2010 and July 2015 using HIE diagnosis criteria from the NICHD Neonatal Research Network's trial of therapeutic hypothermia in HIE [12] and the eligibility criteria from our prior studies. [3–5] The neonates reported here include those from our pilot

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studies [3–5] with an additional 36 neonates. We excluded neonates who received extracorporeal membrane support (ECMO).

Clinical Care

Neonates received therapeutic hypothermia for 72 hours per previously described protocols. [3–5] We examined HVx during hypothermia, rewarming, and the first 6 hours of normothermia. Clinicians determined the neonates' blood pressure goals and could view the NIRS regional cerebral oximetry (rSO_2) but were blinded to HVx. When necessary, dopamine was initiated followed by dobutamine and epinephrine. Seizures were diagnosed by electroencephalogram and treated with phenobarbital. Hydrocortisone was initiated for adrenal suppression or persistent hypotension refractory to vasopressors when needed.

Clinical data were obtained from the medical record by investigators (RC-V, MO) blinded to the autoregulation and brain MRI data. $PaCO_2$ levels were classified into four categories: [13] (1) all $PaCO_2$ levels 35–45 mmHg; (2) some <35 mmHg but none >45 mmHg; (3) none <35 mmHg but some >45 mmHg; and 4) some <35 mmHg and some >45 mmHg. An investigator blinded to the autoregulation and MRI data (RC-V) created a perinatal insult score to grade the birth asphyxia severity. (Table 1)

Autoregulation Monitoring

Neonates received bilateral forehead NIRS monitoring with an INVOS 5100 (Medtronic, Minneapolis, MN). HVx was calculated from the NIRS and arterial blood pressure signals as previously described during hypothermia, rewarming (defined as rectal temperature 34.1–36.5°C), and the first six hours of normothermia. [3–5, 11] Briefly, HVx is calculated from deoxygenated and oxygenated hemoglobin optical densities, [11] which decreases this index's sensitivity to changes in systemic oxygenation when compared to metrics based solely on oxyhemoglobin. We synchronously sampled MAP from the arterial blood pressure catheter and NIRS signals using ICM+ software (Cambridge Enterprises, Cambridge, UK). HVx is calculated by a continuous, moving correlation coefficient between MAP and the NIRS rTHb (rTHb=1-optical density_A*50), a surrogate measure of cerebral blood volume, [11] after removal of signal artifacts and high-frequency waves from respiration and pulse. [3–5, 14] When autoregulatory vasoreactivity is functional, rTHb and MAP have negative or near-zero correlation, and HVx is negative or near-zero. During periods of dysfunctional autoregulation, rTHb and MAP become positively correlated, and HVx approaches +1 with progressive impairments in autoregulation. [11] We verified that neonates did not have unilateral intracranial lesions and averaged the right and left HVx values for sorting into 5-mmHg bins of MAP. The most negative HVx identified the MAP_{OPT} at which autoregulation was most robust with maximal vasoreactivity to changes in MAP during hypothermia, rewarming, and normothermia. The neonate was coded as "unidentifiable MAP_{OPT}" if a nadir in HVx could not be identified. [3–5] An investigator (JKL) blinded to outcomes and medical histories identified the MAP_{OPT} values with corroboration by additional investigators (FJN, MG). Blood pressure was analyzed as the (1) maximal blood pressure deviation below or above MAP_{OPT}; (2) duration with blood pressure below, within, or above MAP_{OPT} analyzed as a percentage of the autoregulation monitoring period; and (3) area under the curve (AUC; min* mmHg/h) to combine time (min) spent with blood

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pressure below MAP_{OPT} and blood pressure deviation (mmHg) below MAP_{OPT} normalized for the monitoring duration (h) in each period. [4, 15] We also calculated the percentage of the hypothermia, rewarming, and normothermia periods that neonates spent with MAP below gestational age (weeks)+5, a common clinical guide for neonatal hemodynamic goals. [16]

Brain MRI

Neonates received brain MRIs after completing hypothermia and autoregulation monitoring according to our published protocol. [3] MRI studies were performed on a 1.5T clinical scanner (Avanto; Siemens, Erlangen, Germany) by using a standard neonatal 8-channel head coil under natural sleep (without general anesthesia). Standard neonatal brain MRI with sagittal T1-weighted, axial T2-weighted, and axial SWI was obtained. A single-shot, spin-echo, echo-planar axial DTI sequence with diffusion gradients along 20 noncollinear directions was acquired. Trace of diffusion images and ADC maps were automatically calculated by the vendor-specific software in the MRI scanner. Image analysis was performed on the PACS (picture archiving and communication system) workstation. [4] Two experienced pediatric neuroradiologists (AT and TH) categorized the brain injury as none, mild, moderate, or severe [3] in the paracentral gyri, white matter, posterior limb of the internal capsule (PLIC), putamen and globus pallidus, thalamus, and brainstem. These regions are associated with adverse neurologic outcomes from HIE. [17–21] The radiologists were blinded to the neonates' HVx, blood pressures, and clinical history.

Statistical Analysis

Data were analyzed with Rv3.2 (Vienna, Austria) and presented as means with standard deviations (SD) or medians with interquartile ranges as appropriate. Associations between brain injury on MRI and the blood pressure autoregulation parameters were analyzed separately for each period (hypothermia, rewarming, or normothermia). Classifications of regional brain injury on MRI were analyzed for their associations with the predictors (MAP_{OPT}; blood pressure in relation to MAP_{OPT} [the percentage of time spent with MAP below, within or above MAP_{OPT}; the maximal MAP deviation above or below MAP_{OPT}; and the AUC of MAP below MAP_{OPT} in each period]; the percentage of time spent with MAP below gestational age+5 in each period; and the mean rSO_2 averaged between the right and left sides across each period) with ordered polytomous regression for proportional increase in injury. [22] Each analysis was adjusted for $PaCO_2$ category, presence of seizures, receipt of a vasopressor, and perinatal insult score. These covariates were selected due to their potential influence on cerebral autoregulation and neurologic injury. [6–8, 23–25] Relationships between perinatal insult score and brain injury were estimated with polytomous regression for ordered categorical outcomes. Finally, we examined the neonates' blood pressures in relation to MAP_{OPT} as they progressed through hypothermia, rewarming, and normothermia using a Pearson's correlation coefficient to compare the percentages of the autoregulation monitoring period with blood pressure below, within, or above MAP_{OPT} between hypothermia vs. rewarming; hypothermia vs. normothermia; and rewarming vs. normothermia.

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RESULTS

We screened 122 newborns with HIE. Forty-seven (39%) were ineligible for the study because of an unreliable arterial catheter blood pressure tracing (16), parents' refusal to consent for the study (9), transfer for ECMO (6), death before initiation of HVx monitoring (5), technical difficulties (5), inadequate resources (3), complex heart disease (1), coagulopathy (1), or parents' inability to speak English or Spanish (1). Therefore, 75 (61%) neonates with HIE were monitored with HVx. Eleven did not have diagnostic brain MRI for evaluation because of motion artifact (7) or withdrawal of support before MRI acquisition (4).

The final sample size was 64 neonates (38 boys, 26 girls), and data were analyzed among those with an identifiable MAP_{OPT} (see below). All 64 neonates with brain MRI data had HVx monitoring during hypothermia (mean duration 46.5 hours [SD, 19.8]), 59 during rewarming (duration 6.3 hours [SD, 2.6]), and 57 during normothermia (duration 5.3 hours [SD, 1.6]). HVx monitoring was stopped after hypothermia in two neonates because of technical problems and in three who were transferred to another unit; these three neonates underwent the therapeutic hypothermia protocol, did not receive ECMO, and had brain MRI data analyzed in the study. Two neonates had HVx monitoring stopped after rewarming because of early removal from NIRS (1) or arterial blood pressure catheter (1). Patient descriptions are in Table 2. The hemoglobin levels were 15.5 g/dL (SD, 2.0) during HVx monitoring. Twelve neonates received hydrocortisone.

The neonates' blood pressure distributions are shown in Figure 1. We identified MAP_{OPT} values in 55/64 neonates (86%; 32 boys, 23 girls) during hypothermia, 54/59 (92%; 31 boys, 23 girls) during rewarming, and 55/57 (97%; 35 boys, 20 girls) during normothermia. The mean MAP_{OPT} values were 50 mmHg (SD, 10) in each period. (Figure 2A) The neonates who were coded as having an unidentifiable MAP_{OPT} did not display a clear HVx nadir in the bar graph of MAP vs. HVx. The neonates' blood pressures in relation to MAP_{OPT} are shown in figures 2B–F.

We also compared neonates who did not have brain MRI (and were excluded from the study) with those who did. The perinatal injury scores among neonates who did or did not receive an MRI were 6 (SD, 1.3) and 6 (SD, 1.5), respectively. The MAP_{OPT} values between neonates with or without MRI were 50 mmHg (SD, 10; n=55) and 45 (SD, 10; n=10) during hypothermia (p>0.10) and 50 mmHg (SD, 10; n=54) and 45 mmHg (SD, 10; n=4) during rewarming (p>0.10), respectively. However, MAP_{OPT} during normothermia was lower in neonates without MRI (mean, 40 mmHg; SD, 10; n=5) than in those with MRI (mean, 50 mmHg; SD, 10; n=55; p=0.026). Blood pressure in relation to MAP_{OPT} during hypothermia and rewarming was similar between neonates with and without MRI (p>0.05; data not shown). Neonates without MRI had greater duration (p=0.018) and deviation (p=0.017) in blood pressure above MAP_{OPT} during normothermia than neonates with MRIs.

Autoregulation and Brain Injury on MRI

MRIs were obtained at 8.5 days of life (SD, 2.5; range, 4–16), and brain injury was graded in all 64 neonates. (Table 3) The perinatal insult score was not associated with injury in the

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white matter, PLIC, putamen and globus pallidus, thalamus, or brain stem (p>0.05; n=64). However, more severe perinatal insult was related to greater injury in the paracentral gyri (p=0.009; n=64).

In the analysis adjusted for $PaCO_2$, seizures, vasopressors, and perinatal insult severity, greater AUC below MAP_{OPT} during rewarming (β=0.002; p=0.047, n=54) was associated with more severe injury in the white matter. More time with blood pressure within the 5-mmHg range of MAP_{OPT} during rewarming related to less white matter injury (β= −0.044, p=0.017, n=54). (Supplemental Table 1) The autoregulatory parameters were not associated with PLIC injury. (p>0.05 for all comparisons; data not shown)

Both perinatal insult severity (p=0.009; n=64) and blood pressure affected paracentral gyri injury. The analyses therefore included adjustments for perinatal insult severity. Among neonates with an identified MAP_{OPT}, greater duration (β=0.041; p=0.007; n=55), deviation (β=0.104; p=0.012; n=55), and AUC (β=0.005; p=0.020; n=55) of blood pressure below MAP_{OPT} during hypothermia correlated with more severe injury in the paracentral gyri. In addition, greater duration (β= −0.027, p=0.020, n=55) and deviation (β= −0.069, p=0.038, n=55) of blood pressure above MAP_{OPT} during hypothermia related to decreased paracentral gyri injury. (Supplemental Table 2)

Spending more time with blood pressure within MAP_{OPT} during normothermia was associated with less injury in putamen and globus pallidus (β= −0.034, p=0.040, n=55). (Supplemental Table 3) Finally, greater duration of blood pressure within MAP_{OPT} during normothermia was related to less brainstem injury (β= −0.035, p=0.027, n=55). (Supplemental Table 4) Blood pressure relative to MAP_{OPT} was not associated with thalamic injury (p>0.05 for all comparisons; data not shown).

rSO_2 and Blood Pressure Threshold 5 mmHg Above Gestational Age

In the adjusted analysis of all neonates with an identified MAP_{OPT}, rSO_2 was unrelated to brain injury in any anatomic region (p>0.05; data not shown). Moreover, the duration of blood pressure below the gestational age+5 in any period was not associated with injury in any brain region in the adjusted analysis of neonates with an identified MAP_{OPT} (p>0.05; data not shown).

Blood pressure in relation to MAP_{OPT} during progression from hypothermia to normothermia

Neonates with greater duration of blood pressure below MAP_{OPT} during hypothermia also spent more time with blood pressure below MAP_{OPT} during rewarming (r=0.49; p<0.001). The durations of blood pressure below MAP_{OPT} were not correlated between hypothermia and normothermia (r-0.20; p=0.17) or between rewarming and normothermia (r=0.20; p=0.16). Neonates who spent more time during hypothermia with blood pressure above MAP_{OPT} also spent more time with blood pressure above MAP_{OPT} during rewarming (r=0.50, p<0.001). Time with blood pressure above MAP_{OPT} was not correlated between hypothermia vs. normothermia (r=0.21; p=0.15) or rewarming vs. normothermia (r=0.22; p=0.12). Finally, neonates with greater duration of blood pressure within MAP_{OPT} during hypothermia also spent more time with blood pressure within MAP_{OPT} during rewarming

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(r=0.40; p=0.007) and normothermia (r=0.32; p=0.025). Time with blood pressure within MAP_{OPT} during rewarming and normothermia were not correlated (r=0.16; p=0.273).

DISCUSSION

We provide evidence that blood pressure deviations from the range of optimal autoregulation during and after therapeutic hypothermia are associated with brain injury on MRI in neonates with HIE, but this relationship is complex and varies by anatomic region. Brain injury was not affected by perinatal insult severity in most regions; thus blood pressures that do not optimize autoregulation during and after therapeutic hypothermia independently affect subsequent brain injury measurements on MRI. Greater duration and deviation of blood pressure below MAP_{OPT} were associated with greater injury in the white matter and paracentral gyri. Blood pressure within MAP_{OPT} related to lesser injury in the white matter, putamen, globus pallidus, and brainstem. Hence, hemodynamic management to optimize autoregulation using HVx could serve as a therapeutic adjunct to hypothermia in HIE.

Brain MRI is a biomarker of neurodevelopmental outcome in HIE. [26, 27] We used T1/T2-weighted images, trace of diffusion images, and ADC maps given the high specificity and sensitivity of these sequences in predicting neurodevelopmental outcomes. [28] In addition, qualitatively scoring brain injury on MRI during the first two weeks of life and after therapeutic hypothermia has consistent and high predictive accuracy for neurodevelopmental outcome. [29] Signal abnormalities in conventional MRI, trace of diffusion images, and ADC maps in the cortex, PLIC, white matter, putamen and globus pallidus, thalamus, and brainstem predict disability or death after HIE. [9, 18–21] Thus, identifying methods to reduce brain injury on MRI may improve neurodevelopmental outcomes.

The potential of targeting the autoregulatory blood pressure range as a therapeutic adjunct to hypothermia is unclear. Hypothermia after hypoxic-ischemic brain injury is known to decrease cerebral blood flow,[30, 31] although the blood pressure limits of autoregulation and MAP_{OPT} can still be determined during hypothermia.[3, 14, 31] Severe birth asphyxia may cause brain damage with dysfunctional autoregulation and/or hemodynamic instability. Alternatively, some neonates' outcomes might improve if their blood pressure is maintained to support autoregulation. We developed a perinatal insult severity score to account for the effects of birth asphyxia on autoregulation and subsequent brain injury. Reliable and accurate risk stratification methods to differentiate neonates with favorable or unfavorable neurologic outcomes are not available in HIE, although the 10-min Apgar score may be associated with neurocognitive outcomes at 5–6 years of age.[32] The perinatal insult score, which is derived from common clinical perinatal parameters, did not relate to brain injury in any region except for paracentral gyri. New and non-invasive methods that can identify neonates soon after birth who are at high risk of permanent neurologic injury are urgently needed. These high-risk babies may benefit from adjuvant treatments, such as methods that support autoregulatory function. Alternatively, identifying neonates with poor autoregulation using HVx may indicate those at highest risk of neurologic injury on MRI. Nonetheless, the fact that the perinatal insult score was not associated with brain injury in most regions suggests blood pressures that do not support autoregulation during the first 4 days of life may independently relate to injury evolution in the white matter, putamen and globus

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pallidus, and brainstem. Such an independent relationship does not strictly distinguish whether blood pressure deviation from MAP_{OPT} causes additional injury or if the greater injury, particularly in brainstem, produces greater blood pressure lability.

Blood pressure deviation from MAP_{OPT} measured by frontal NIRS, which predominantly measures frontal cortex, related to injury in regions not captured by NIRS, including other cortical (i.e. paracentral gyri) and non-cortical regions. Autoregulation involves large cerebral arteries and pial arterioles and thus has a prominent macrocirculatory component upstream of local parenchymal tissue. Much of the autoregulatory vasoactivity is attributed to the intrinsic myogenic response to transmural pressure. Thus, large regional differences in MAP_{OPT} are not expected after global cerebral ischemia, and large and prolonged deviations of blood pressure from MAP_{OPT} measured in frontal lobe will likely affect perfusion throughout much of the brain. While more precise methods for determining regional autoregulatory properties would be ideal, using MAP_{OPT} from the frontal lobe is a reasonable first approximation for targeting hemodynamic management.

We identified associations between the autoregulation parameters and brain injury during hypothermia (paracentral gyri injury), rewarming (white matter injury), and normothermia (putamen, globus pallidus, and brainstem injuries). Larger studies are needed to define the interactions between temperature and autoregulation in specific regions. Hypothermia and rewarming do not fully protect cortical grey matter and white matter from apoptotic cell death, [33–35] and blood pressure below the optimal autoregulatory level may render these regions more vulnerable to cell death. By contrast, the neuroprotection afforded by hypothermia in the putamen [36] may delay vulnerability to sub-optimal autoregulatory function until normothermia.

Blood pressure within MAP_{OPT} was associated with lesser injury in the white matter, putamen and globus pallidus, and brainstem. Blood pressure above MAP_{OPT} was related to lesser injury in paracentral gyri. Although it is tempting to speculate that targeting or exceeding MAP_{OPT} would confer neuroprotection, caution must be exercised when raising blood pressure to not induce cardiopulmonary injury with increases in afterload, intravascular volume, and cardiogenic strain. Nonetheless, identifying MAP_{OPT} related better to brain injury than did rSO_2 or blood pressure based on gestational age+5. Larger studies across multiple institutions are needed to further explore whether hemodynamic management that targets MAP_{OPT} reduces neurologic injury compared to conventional neonatal clinical guidelines, including those based on the gestational age. [16]

Neonates who spent a greater duration of time with blood pressure below MAP_{OPT} during hypothermia also spent more of rewarming with blood pressure below MAP_{OPT}. Conversely, neonates with greater duration of blood pressure above MAP_{OPT} during hypothermia also had more time with blood pressure above MAP_{OPT} during rewarming. The neonates' time with blood pressure within the 5-mmHg bin of MAP_{OPT} were also correlated across hypothermia, rewarming, and normothermia. This consistent relationship between blood pressure and MAP_{OPT} across time and temperature phases emphasizes the importance of using continuous HVx monitoring to identify neonates with sub-optimal autoregulation early

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in hypothermia because these neonates are at high risk of continued sub-optimal autoregulation during rewarming and normothermia.

Causal relationships were not addressed by this observational study. Because of the small sample size, the results may under-identify associations between injury and autoregulation in this single-center study. The exclusion of neonates who received ECMO or had withdrawal of care and did not receive HVx monitoring or brain MRIs creates selection bias. Neonates excluded from the study because they lacked MRI data were similar in perinatal insult score and autoregulation data to those included in the study with the exception of MAP_{OPT} during normothermia; 5 neonates without MRI had lower MAP_{OPT} values and greater blood pressure deviation above MAP_{OPT} during normothermia than the 55 neonates who received MRI. HVx monitoring could only begin after an arterial blood pressure cannula was established; therefore early autoregulatory instability may not have been captured. We analyzed the data as a percentage of the autoregulation monitoring period and normalized the AUC for the monitoring duration to account for different monitoring durations in hypothermia. We monitored HVx more consistently during rewarming and normothermia. Steroid use and delays in initiating hypothermia may affect blood pressure and neurologic injury, and we did not adjust for these potential confounders.

CONCLUSIONS

NIRS-derived HVx autoregulation monitoring can identify the blood pressure range with most robust autoregulatory vasoreactivity in neonates who receive therapeutic hypothermia for HIE. The relationship between cerebrovascular autoregulation and MRI-documented neurologic injury in HIE patients is complex, may vary by anatomic region, and is largely independent of the perinatal injury insult severity. Determination of MAP_{OPT} that supports maximal cerebrovascular reactivity to perturbations in MAP may identify hemodynamic ranges that limit the progression of neural injury in several regions. The influence of hypothermia and rewarming on the effects of autoregulatory hemodynamics and brain injury requires further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AUC	area under the curve

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ECMO	extracorporeal membrane support
HIE	hypoxic-ischemic encephalopathy
HVx	hemoglobin volume index
MAP	mean arterial blood pressure
NIRS	near-infrared spectroscopy
PLIC	posterior limb of the internal capsule
rSO_2	regional cerebral oximetry
SD	standard deviation

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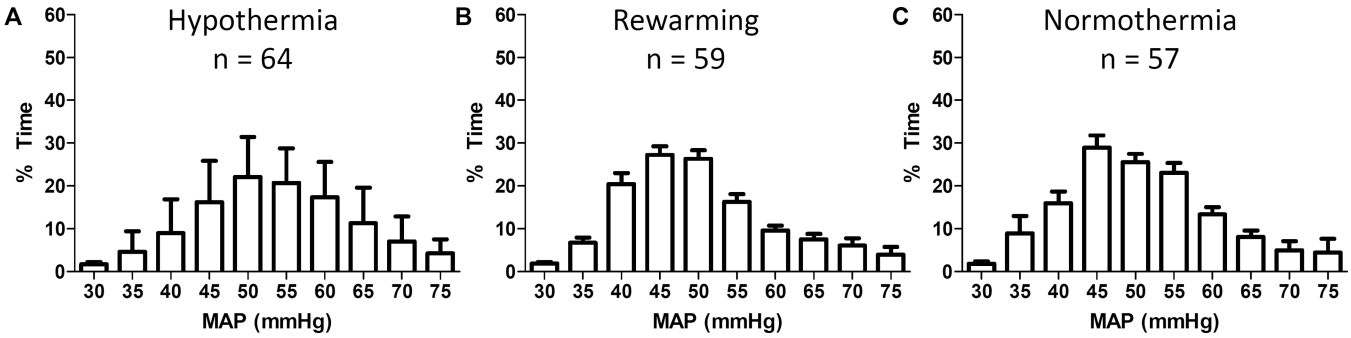

Figure 1.

The distribution of neonates' mean arterial blood pressure (MAP) during hypothermia (A), rewarming (B), and normothermia (C). Means with SD are shown.

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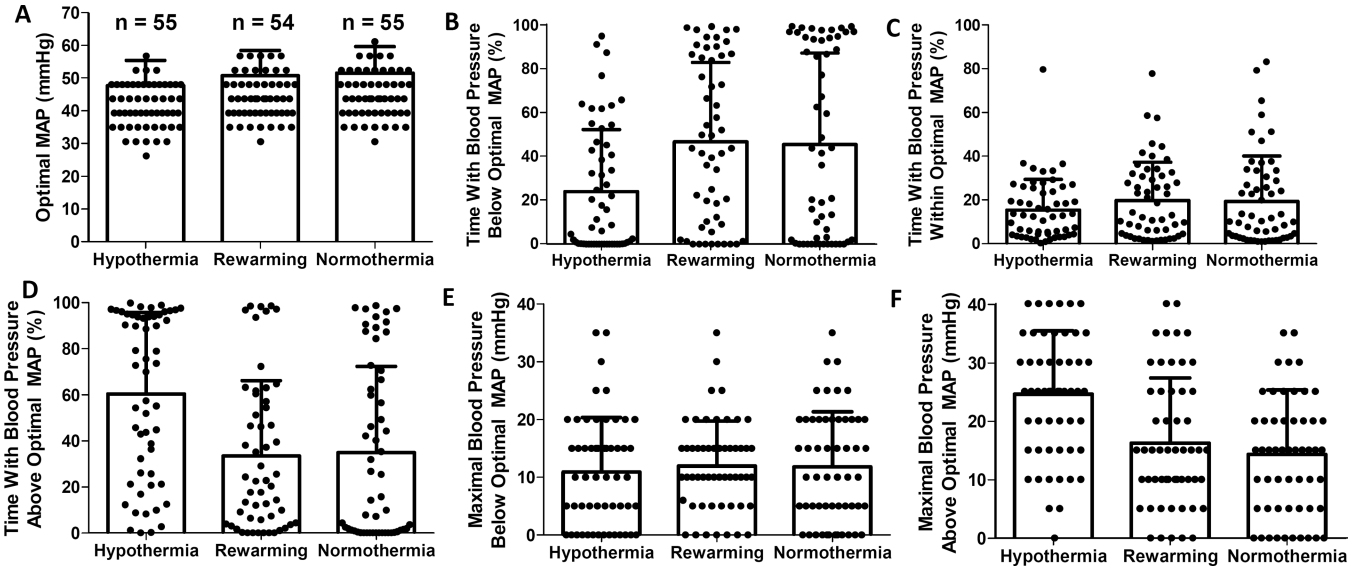

Figure 2.

The neonates' optimal mean arterial blood pressure (MAP) values (A), the percentage of each period spent with blood pressure below (B), within (C), or above (D) optimal MAP, and the maximal blood pressure deviation below (E) or above (F) optimal MAP. Means with SD are shown. Each circle represents one neonate.

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TABLE 1

Perinatal Insult Score for Grading Birth Asphyxia Severity [a]

Parameter	2 points	1 point	0 points
pH from the umbilical cord or arterial blood gas from first hour of life	≤7.00	7.01 to ≤7.15	>7.15
Base deficit from the umbilical cord or arterial blood gas from the first hour of life	≤ −16	−15 to ≤ −10	> −10
Sarnat stage	3	2	1
Apgar score at 10 min[b]		≤ 5	>5
Mechanical ventilation[b]		Yes	No
Emergency delivery		Yes	No

[a] The perinatal insult score ranges from 1 (mild perinatal event) to 8 (severe perinatal event) and measures the severity of birth asphyxia

[b] If the Apgar score was not available, the baby received 1 point if mechanical ventilation was provided.

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TABLE 2

Neonate Parameters That May Influence Blood Pressure Autoregulation[a]

	N	N (%) or median (IQR)
Vasopressor (any), n (%)	64	41 (64%)
Seizures (any), n (%)	64	24 (38%)
$PaCO_2$ (mmHg), n (%)	64	
All (35 – 45)		6 (10%)
Some < 35, all < 45		11 (17%)
None < 35, some > 45		29 (45%)
Some < 35, some > 45		18 (28%)
Birth injury score, median (IQR)	64	6 (5, 7)

IQR, interquartile range. $PaCO_2$, arterial partial pressure of carbon dioxide.

[a]These covariates were adjusted for in the analysis.

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TABLE 3

Distribution of Categorical Brain Injuries Among the Neonates

Region	N	Injury N (%)			
		None	Mild	Moderate	Severe
Central gyrus	64	37 (58%)	14 (22%)	6 (9%)	7 (11%)
White matter	64	13 (20%)	28 (44%)	10 (16%)	13 (20%)
Basal ganglia	64	28 (44%)	19 (30%)	10 (15%)	7 (11%)
Thalamus	64	27 (42%)	17 (27%)	11 (17%)	9 (14%)
Posterior limb of internal capsule	64	42 (66%)	11 (17%)	6 (9%)	5 (8%)
Brainstem	64	28 (43%)	19 (30%)	10 (16%)	7 (11%)