



Published in final edited form as:

*J Perinatol.* 2017 August ; 37(8): 938–942. doi:10.1038/jp.2017.64.

## Relationships between cerebral autoregulation and markers of kidney and liver injury in neonatal encephalopathy and therapeutic hypothermia

Jennifer K. Lee, MD<sup>1,2</sup>, Jamie Perin, PhD<sup>3</sup>, Charlamaine Parkinson, MS, RNC<sup>2,4</sup>, Matthew O'Connor, MD<sup>4</sup>, Maureen M. Gilmore, MD<sup>2,4</sup>, Michael Reyes, BA<sup>1</sup>, Jillian Armstrong, BS<sup>1</sup>, Jacky Jennings, PhD<sup>3</sup>, Frances J. Northington, MD<sup>2,4</sup>, and Raul Chavez-Valdez, MD<sup>2,4</sup>

<sup>1</sup>Department of Anesthesiology and Critical Care Medicine, Johns Hopkins School of Medicine, Baltimore, MD

<sup>2</sup>Neurosciences Intensive Care Nursery, Johns Hopkins School of Medicine, Baltimore, MD

<sup>3</sup>Center for Child and Community Health Research (CCHR), Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, MD

<sup>4</sup>Division of Neonatology, Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, MD

### Abstract

**Objective**—We studied whether cerebral blood pressure autoregulation and kidney and liver injuries are associated in neonatal encephalopathy (NE).

**Study Design**—We monitored autoregulation of 75 newborns who received hypothermia for NE in the neonatal intensive care unit to identify the mean arterial blood pressure with optimized autoregulation (MAP<sub>OPT</sub>). Autoregulation parameters and creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were analyzed using adjusted regression models.

**Results**—Greater time with blood pressure within MAP<sub>OPT</sub> during hypothermia was associated with lower creatinine in girls. Blood pressure below MAP<sub>OPT</sub> related to higher ALT and AST during normothermia in all neonates and boys. The opposite occurred in rewarming when more time with blood pressure above MAP<sub>OPT</sub> related to higher AST.

---

Users may view, print, copy, and download text and data-mine the content in such documents, for the purposes of academic research, subject always to the full Conditions of use: [http://www.nature.com/authors/editorial\\_policies/license.html#terms](http://www.nature.com/authors/editorial_policies/license.html#terms)

Address correspondence to: Jennifer K. Lee, MD, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, 1800 Orleans Street, Room 6321, Baltimore, MD 21287 [jkleee@jhmi.edu](mailto:jkleee@jhmi.edu), office 410-955-6412, fax 410-502-5312.

**Dedication:** We dedicate this manuscript to the Poretti family in loving memory of Dr. Andrea Poretti.

Supplementary information is available at The Journal of Perinatology's website.

**Funding Disclosure:** Funding for the study described in this manuscript was provided in part by Medtronic. Dr. Lee was the principal investigator of this grant. The funding was used to support research effort by Dr. Raul Chavez-Valdez, Dr. Frances Northington, Dr. Jamie Perin, Ms. Charlamaine Parkinson, and Mr. Michael Reyes.

**Conflict of Interest:** Funding for the study described in this manuscript was provided in part by Medtronic. In addition, Dr. Lee was 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. In addition, Drs. Lee and Northington have been funded by the NIH.

**Conclusions**—Blood pressures that optimize cerebral autoregulation may support the kidneys. Blood pressures below  $MAP_{OPT}$  and liver injury during normothermia are associated. The relationship between  $MAP_{OPT}$  and AST during rewarming requires further study.

### Keywords

newborn; hypoxia; cerebrovascular circulation; kidney; liver

## INTRODUCTION

Therapeutic hypothermia (TH) for neonatal encephalopathy (NE) from birth asphyxia<sup>1</sup> primarily focuses on preserving neurologic function and reducing secondary brain injury. Strategies to protect non-neurologic organs are also critical. Because kidney<sup>2</sup> and liver<sup>3</sup> injuries may slow recovery from NE, clarifying the relationships between brain injury and these organ systems may improve outcomes. The increasing use of cerebral near-infrared spectroscopy (NIRS) in the management of NE, including NIRS-derived autoregulation monitoring,<sup>4-9</sup> provides an opportunity to explore these relationships.

The NIRS hemoglobin volume index (HVx) measures cerebral autoregulatory vasoreactivity in frontal cortex and can be used to identify the mean arterial blood pressure at which cerebral autoregulatory vasoreactivity is optimized ( $MAP_{OPT}$ ).<sup>4-6,10</sup> HVx is calculated by correlating mean arterial blood pressure (MAP) and NIRS total tissue hemoglobin, which can be used as a surrogate measure of cerebral blood volume.<sup>10</sup> The  $MAP_{OPT}$  is defined as the 5-mmHg range of MAP with the most negative HVx where cerebral vasoreactivity is most robust. Blood pressure deviation from  $MAP_{OPT}$  is associated with greater brain injury on MRI at approximately 1–2 weeks in patients with NE<sup>5,6,9</sup> and worse neurodevelopmental outcomes at approximately 2 years.<sup>4</sup> Here, we used HVx to determine the relationships between blood pressure deviation from  $MAP_{OPT}$  and laboratory markers of kidney and liver injury.

Studies in rodents provide evidence that sex also may affect injury after hypoxia ischemia, a common cause of NE in humans, and suggest that males may have worse outcomes than females.<sup>11,12</sup> However, most large clinical trials only control for sex rather than analyzing boys and girls separately,<sup>11</sup> leaving little information about the role of sex in NE outcomes. Our objective was to measure cerebral autoregulatory vasoreactivity with HVx and laboratory indicators of kidney and liver injuries in neonates receiving TH for NE. We stratified the data by sex to test the hypothesis that neonates whose blood pressures remain close to  $MAP_{OPT}$  will have less kidney and liver injuries than those with greater blood pressure deviation from  $MAP_{OPT}$ .

## MATERIALS AND METHODS

In an observational, prospective study approved by the Johns Hopkins University Institutional Review Board, we sequentially screened all neonates admitted to the neonatal intensive care unit (NICU) with NE between September 2010 and July 2015. We used eligibility criteria that we have previously reported<sup>4-6</sup> and NE diagnosis criteria from the NICHD Neonatal Research Network's trial of TH in NE.<sup>13</sup> These eligibility criteria include

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 an arterial blood pressure cannula or with coagulopathy and active bleeding or congenital anomalies that could make cooling unsafe were ineligible. We obtained written informed consent for the study until May 2013, when NIRS became standard of care for NE treatment in our hospital; after that time, we were granted a waiver of consent. Neonates reported in the current study include those from our pilot studies on brain injury<sup>4-6,9</sup> and are the same cohort used in a separate study that identified a relationship between cerebral autoregulation and cardiopulmonary injury in NE.<sup>14</sup>

### Clinical Care

Neonates received whole body TH for 72 hours as in our previously published protocol.<sup>4-6</sup> Clinicians decided the treatment course, including blood pressure goals and use of vasopressors and steroids. Clinicians could view the NIRS' regional cerebral oxygen saturation and arterial blood pressure, but they were blinded to HVx. When vasopressors were needed, dopamine was the first-line agent followed by dobutamine and epinephrine. Hydrocortisone was started for refractory hypotension and/or adrenal insufficiency; steroids were therefore considered a marker of severe illness. Seizures were diagnosed by electroencephalogram and treated with phenobarbital as first-line therapy. All neonates received intravenous morphine for sedation with the addition of benzodiazepines, clonidine, or other opiates when necessary.

### Cerebral Autoregulation Monitoring

Bilateral forehead NIRS monitoring with an INVOS 5100 (Medtronic, Minneapolis, MN) was used to calculate HVx during three periods: hypothermia, rewarming, and the first 6 hours of normothermia.<sup>4-6</sup> The HVx is based on deoxygenated and oxygenated hemoglobin optical densities,<sup>10</sup> making this index less sensitive to changes in systemic oxygenation than metrics based on oxyhemoglobin alone. ICM+ software (Cambridge Enterprises, Cambridge, UK) synchronously sampled NIRS and arterial blood pressure signals to calculate HVx as previously described.<sup>4-6,10,14,15</sup> After we determined that neonates did not have unilateral intracranial lesions on MRI, the right and left HVx values were averaged for sorting into 5-mmHg bins of MAP. The most negative HVx identified the MAP<sub>OPT</sub> with most robust autoregulatory vasoreactivity. When a nadir in HVx was not apparent, the neonate was coded as having an "unidentifiable MAP<sub>OPT</sub>."<sup>4-6</sup> An investigator blinded to the clinical history (JKL) identified MAP<sub>OPT</sub> with corroboration by additional investigators (FJN, MMG). Blood pressure relative to MAP<sub>OPT</sub> was analyzed in each of the three periods as 1) the duration spent with blood pressure below, within, or above MAP<sub>OPT</sub>; 2) maximal deviation in blood pressure below or above MAP<sub>OPT</sub>; and 3) the area under the curve (AUC) for time and deviation of blood pressure below MAP<sub>OPT</sub>.<sup>4,6</sup> The AUC (min•mmHg/h) is the amount of time (minutes) spent with blood pressure below MAP<sub>OPT</sub> and blood pressure deviation (mmHg) below MAP<sub>OPT</sub> normalized for the duration of monitoring (hours).<sup>4,6,9</sup> If the neonate was transferred to another unit for potential extracorporeal membrane oxygenation (ECMO), only pre-transfer and pre-ECMO autoregulation data were analyzed.

## Clinical Data Collection

Investigators blinded to blood pressure and HVx (RC-V, MOC) collected clinical data from the electronic medical record. Perinatal data included pH from the umbilical cord, blood gas from the first hour of life, and 10-minute Apgar score. Kidney injury was measured with maximum creatinine level between 24 and 96 hours of age. The creatinine from the first 24 hours was excluded because this value may reflect maternal clearance of creatinine rather than that of the infant.<sup>2</sup> Liver injury was measured with maximum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and prothrombin time (PT) during hypothermia, rewarming, and first 6 hours of normothermia. If the neonate received ECMO, only pre-ECMO liver and kidney injury data were analyzed.

Factors that may influence autoregulation were recorded, including vasopressor<sup>16</sup> or benzodiazepine use and arterial partial pressure of carbon dioxide (PaCO<sub>2</sub>)<sup>17</sup> during HVx monitoring, as well as steroid use during the first 7 days of life (a marker of critical illness). PaCO<sub>2</sub> was classified into four categories:<sup>18</sup> 1) all PaCO<sub>2</sub> 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. Clinicians determined the blood gas measurement timing.

## Statistical Analysis

Data are presented as means ± standard deviation (SD) or median with interquartile range, as appropriate. All analyses were adjusted for the use of any vasopressor, presence of seizures, use of a benzodiazepine, and PaCO<sub>2</sub> level during HVx monitoring as well as for the administration of steroids in the first 7 days of life. Indicators of the perinatal insult severity, including umbilical cord pH, first blood gas pH, and 10-minute Apgar score, were compared to the autoregulation parameters by using linear regression. We examined relationships between maximum creatinine from all observation times (days 2 and 3 of TH; rewarming; and normothermia) and the autoregulation parameters from hypothermia, rewarming, and the first 6 hours of normothermia with linear regression. We estimated the relationships between maximum ALT, AST, and PT with the autoregulation parameters in the same time period with linear regression. These analyses assume that measures of autoregulation are normally and similarly distributed across neonates. We further stratified the cohort by sex to estimate associations separately for boys and girls in an exploratory analysis, as little is known about sex differences in autoregulation or kidney or liver injury after birth asphyxia. Statistical significance was set at  $p < 0.05$ .

## RESULTS

We screened 122 newborns who were admitted to the NICU for NE. Forty-seven (39%) were ineligible for the study owing to unreliable arterial catheter blood pressure tracing (n=16), parents' refusal to consent for the study (n=9), death before initiation of HVx monitoring (n=5), transfer to the pediatric ICU for potential ECMO (n=6), technical difficulties (n=5), inadequate resources (n=3), coagulopathy (n=1), complex heart disease (n=1), and language barriers (n=1). The final sample size was 75 (62%) neonates, clinical descriptions of whom are provided in Table 1.

HVx was monitored in 75 neonates (44 boys, 31 girls) during hypothermia for a mean of  $45.8 \pm 20.6$  hours, 65 neonates (39 boys, 26 girls) during rewarming for  $6.4 \pm 2.3$  hours, and 63 neonates (38 boys, 25 girls) during normothermia for  $5.6 \pm 0.9$  hours. Blood pressures were similar between the boys and girls as previously reported.<sup>14</sup> We stopped HVx monitoring early during rewarming in neonates who were transferred to another unit for potential ECMO (n=5), withdrawal of care (n=3), or technical complications (n=2). HVx monitoring was stopped early in two additional neonates because NIRS (n=1) or arterial blood pressure (n=1) monitoring was discontinued after rewarming. MAP<sub>OPT</sub> was identified in 65 (87%) neonates during hypothermia at a mean of  $45 \pm 10$  mmHg, in 58 (89%) during rewarming at  $50 \pm 10$  mmHg, and in 60 (95%) during normothermia at  $50 \pm 10$  mmHg. As we previously reported,<sup>14</sup> MAP<sub>OPT</sub> values were similar among boys and girls ( $p > 0.20$ ). Blood pressure deviation from MAP<sub>OPT</sub> during hypothermia and rewarming was also similar between boys and girls ( $p = 0.15$ ). Duration of blood pressure within MAP<sub>OPT</sub> ( $p = 0.02$ ) during normothermia was shorter in girls than in boys.

We first assessed the associations between markers of perinatal insult severity and blood pressure in relation to MAP<sub>OPT</sub>. Umbilical cord pH and 10-minute Apgar score were not associated with any MAP<sub>OPT</sub>-derived autoregulation parameter. (Data not shown.) However, higher pH from the blood gas within the first hour of life was associated with greater time spent with blood pressure within MAP<sub>OPT</sub> during normothermia in all neonates ( $\beta = 0.002$ ,  $p = 0.025$ , n=58) and boys ( $\beta = 0.002$ ,  $p = 0.032$ , n=36), but not girls (Supplemental Table 1).

### Optimized Cerebral Autoregulation Related to Lower Creatinine in Girls

Seventy-two neonates had an identified MAP<sub>OPT</sub> in at least one period, and the maximum creatinine among these neonates was a mean of  $0.9 \pm 0.6$  mg/dL (Table 2). Creatinine levels were similar between neonates with and without identified MAP<sub>OPT</sub> ( $p > 0.05$ ; data not shown). After adjusting for PaCO<sub>2</sub>, seizures, vasopressors, benzodiazepines, and steroids, we found that higher MAP<sub>OPT</sub> values during hypothermia related to lower creatinine ( $\beta = -0.020$ ,  $p = 0.04$ , n=63). Blood pressure deviation from MAP<sub>OPT</sub> was not related to creatinine when all neonates were analyzed. However, relationships were identified when the data were stratified by sex. Among girls, higher MAP<sub>OPT</sub> ( $\beta = -0.035$ ,  $p = 0.019$ ) and longer blood pressure duration within MAP<sub>OPT</sub> ( $\beta = -0.029$ ,  $p = 0.030$ ) during hypothermia were associated with lower creatinine. No associations between blood pressure deviation from MAP<sub>OPT</sub> and creatinine were identified in boys (Supplemental Table 2).

### Hepatic Injury and Cerebral Autoregulation

The maximum ALT and AST levels were lower in neonates without an identified MAP<sub>OPT</sub> during hypothermia ( $63 \pm 10$  U/L for ALT;  $145 \pm 94$  U/L for AST; n=10) than in those with identified MAP<sub>OPT</sub> ( $201 \pm 400$  for ALT,  $p = 0.008$ ;  $460 \pm 898$  U/L,  $p = 0.017$ ; n=65; Table 2). There were no differences in ALT or AST during rewarming and normothermia and no differences in PT in any period between neonates with and without MAP<sub>OPT</sub> ( $p > 0.05$ ; data not shown).

We examined transaminase levels and blood pressure in relation to MAP<sub>OPT</sub> during the same periods. No significant relationships were observed during hypothermia. During rewarming,

higher maximum AST levels were associated with longer percentage of time with blood pressure above  $MAP_{OPT}$  ( $\beta=0.081$ ,  $p=0.02$ ) and smaller deviation below  $MAP_{OPT}$  ( $\beta=-0.019$ ,  $p=0.04$ ). In contrast, higher maximum ALT and AST during normothermia were associated with higher  $MAP_{OPT}$  ( $\beta=0.014$ ,  $p=0.02$  for ALT;  $\beta=0.034$ ,  $p<0.001$  for AST), longer percent time below  $MAP_{OPT}$  ( $\beta=0.065$ ,  $p=0.04$  for ALT;  $\beta=0.140$ ,  $p=0.02$  for AST), greater deviation below  $MAP_{OPT}$  ( $\beta=0.020$ ,  $p=0.01$  for ALT;  $\beta=0.042$ ,  $p=0.005$  for AST), and greater AUC ( $\beta=0.395$ ,  $p=0.05$  for ALT;  $\beta=0.888$ ,  $p=0.03$  for AST). Accordingly, higher AST during normothermia was also associated with shorter duration of blood pressure above  $MAP_{OPT}$  ( $\beta=-0.123$ ,  $p=0.03$ ; Supplemental Tables 3 and 4).

When data were stratified by sex, higher AST during rewarming related to greater percentage of time with blood pressure above  $MAP_{OPT}$  only in girls ( $\beta=0.075$ ,  $p=0.043$ ). Among boys, higher AST was associated with greater duration ( $\beta=0.144$ ,  $p=0.04$ ) and deviation ( $\beta=0.044$ ,  $p<0.01$ ) in blood pressure below  $MAP_{OPT}$  and shorter duration of blood pressure above  $MAP_{OPT}$  ( $\beta=-0.131$ ,  $p=0.04$ ) during normothermia. Higher maximal ALT in normothermia also related to greater blood pressure deviation below  $MAP_{OPT}$  in boys ( $\beta=0.022$ ,  $p=0.014$ ). Finally, higher maximum AST was associated with higher  $MAP_{OPT}$  in boys ( $\beta=0.032$ ,  $p<0.01$ ) and girls ( $\beta=0.040$ ,  $p=0.03$ ; Supplemental Tables 3 and 4). No associations between PT and blood pressure relative to  $MAP_{OPT}$  were detected ( $p>0.05$ ; data not shown).

## DISCUSSION

We identified associations between blood pressures that optimize cerebral autoregulation and serum markers of kidney and liver injuries in newborns who received TH for NE. Some of these relationships were sex-specific in this pilot cohort. We previously reported that the majority of neonates in this study had no, mild, or moderate brain injuries on MRI.<sup>9</sup> Therefore, this cohort largely represents neonates with mild to moderate HIE. Our findings suggest that having blood pressure within the range that optimizes cerebral autoregulatory vasoreactivity during hypothermia was associated with lower creatinine in girls. Blood pressure deviation below  $MAP_{OPT}$  related to higher ALT and AST during normothermia. The findings that blood pressure above  $MAP_{OPT}$  was associated with higher AST during rewarming requires further study, and we speculate that this may be due to cardiac strain from greater afterload at higher blood pressures. Altogether, our findings suggest that blood pressures that optimize cerebral autoregulation may also support the kidney and liver during TH treatment of NE.

Traditional measures of birth insult severity and perinatal depression—the umbilical cord pH and 10-minute Apgar score—were overall unrelated to the autoregulation parameters derived from  $MAP_{OPT}$ . Higher pH on the first-hour blood gas was associated with greater duration of blood pressure within  $MAP_{OPT}$  during normothermia, but not during hypothermia or rewarming. Therefore, neonates with NE who have better initial hemodynamic stability and perhaps less severe perinatal insult remain at risk of blood pressure deviation from  $MAP_{OPT}$  measured by HVx during hypothermia and rewarming. Their hemodynamics may not improve to optimally support autoregulation until normothermia. Given the increased risk of brain injury<sup>5,6,9</sup> and neurodevelopmental disability<sup>4</sup> with blood pressures below  $MAP_{OPT}$ ,

identifying patient-specific hemodynamic ranges that optimize cerebral autoregulation may be more promising than therapies largely based on pH or Apgar score.

Greater duration of blood pressure within  $MAP_{OPT}$  during hypothermia was associated with lower creatinine in girls. This finding agrees with evidence that blood pressure deviation below the cerebral autoregulatory threshold during hypothermic cardiopulmonary bypass increases renal injury.<sup>19</sup> Neonates who have NE with kidney injury have worse outcomes than those without, including longer duration of mechanical ventilation and NICU admission.<sup>2</sup> Therefore, maintaining blood pressures that optimize cerebral autoregulation during TH may also support the recovering kidneys in NE after birth asphyxia and improve outcomes. Additional studies with more thorough evaluation of renal function are needed, including urine output and urinalysis, to further explore this finding. It is unclear why we observed this result only in girls. It may reflect the small sample size in our pilot study or represent a sex-related difference.

We also studied whether blood pressure deviation from  $MAP_{OPT}$  would be associated with markers of liver injury. Indeed, greater duration and deviation in blood pressure deviation below  $MAP_{OPT}$  was associated with higher AST and ALT levels during normothermia in all neonates and boys. Liver injury after birth asphyxia may predict NE severity and worse neurodevelopmental outcomes.<sup>20</sup> These data suggest that blood pressure that optimize cerebral autoregulation could also support the liver in NE. The observed sex differences in the stratified analysis require further study in larger sample sizes.

The rationale behind the relationship between elevated AST and greater duration of blood pressure above  $MAP_{OPT}$  during rewarming is unclear. This fact may reflect AST release from cardiac strain with increased cardiac afterload rather than strict liver injury. Additional studies are needed on the relationships between rewarming, liver injury, and  $MAP_{OPT}$  that include markers more specific to liver and cardiac injury, such as aldolase and troponin.

This observational, pilot, cohort study had several limitations. The findings do not establish causal or temporal relationships between blood pressure autoregulation and kidney and liver injury. Additionally, the study was subject to selection bias because the sickest neonates were excluded when they were transferred for ECMO, care was withdrawn, or parents failed to consent. The small sample size of this single-center study may have under-identified associations between blood pressure and injury, particularly when data were stratified by sex. HVx monitoring, which only captures regional frontal cortex, could begin only after an arterial blood pressure catheter was established; thus we did not detect very early autoregulatory instability. Although creatinine was used to estimate kidney injury, additional clinical factors such as hydration status also influence creatinine levels. We used the maximum creatinine level after the first 24 hours of life as a marker of kidney injury rather than the rate of creatinine change, which also gauges postnatal kidney injury<sup>2</sup>. Lastly, we did not compare the cerebral NIRS measurements to splanchnic or renal NIRS.

## CONCLUSIONS

We identified potential relationships between blood pressure deviation from the range that optimizes cerebral autoregulation and kidney and liver injuries in a pilot study of TH-treated newborns with NE. Maintaining blood pressures within the range that optimizes cerebral autoregulation may also support the kidney and liver. Whether we can reduce kidney and liver injuries in infants with NE by using NIRS to identify hemodynamic goals and optimize cerebral autoregulatory vasoreactivity deserves further study.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

**Funding Sources:** Support was provided by the NIH R01HD070996 (FJN), R01HD074593 (FJN), K08NS080984 (JKL), and R21HD072845 (JKL); Johns Hopkins University Clinician Scientist Award (JKL); American Heart Association Grant-in-Aid (JKL); and the Sutland-Pakula Endowment for Neonatal Research (R C-V).

## Abbreviations

<b>AUC</b>	area under the curve
<b>AST</b>	aspartate aminotransferase
<b>ALT</b>	alanine aminotransferase
<b>BP</b>	blood pressure
<b>ECMO</b>	extracorporeal membrane oxygenation support
<b>HV<sub>x</sub></b>	hemoglobin volume index
<b>MAP</b>	mean arterial blood pressure
<b>NE</b>	neonatal encephalopathy
<b>NIRS</b>	near-infrared spectroscopy
<b>PT</b>	prothrombin time
<b>SD</b>	standard deviation
<b>TH</b>	therapeutic hypothermia

## References

1. Dammann O, Ferriero D, Gressens P. Neonatal encephalopathy or hypoxic-ischemic encephalopathy? Appropriate terminology matters. *Pediatr Res*. 2011 Jul; 70(1):1–2. [PubMed: 21654279]
2. Gupta C, Massaro AN, Ray PE. A new approach to define acute kidney injury in term newborns with hypoxic ischemic encephalopathy. *Pediatr Nephrol*. 2016 Jul; 31(7):1167–1178. [PubMed: 26857710]



3. Choudhary M, Sharma D, Dabi D, Lamba M, Pandita A, Shastri S. Hepatic dysfunction in asphyxiated neonates: prospective case-controlled study. *Clin Med Insights Pediatr*. 2015 Jan 12;9:1–6. [PubMed: 25674030]
4. Burton VJ, Gerner G, Cristofalo E, Chung SE, Jennings JM, Parkinson C, et al. A pilot cohort study of cerebral autoregulation and 2-year neurodevelopmental outcomes in neonates with hypoxic-ischemic encephalopathy who received therapeutic hypothermia. *BMC Neurol*. 2015 Oct 20;15:209-015-0464-4.
5. Howlett JA, Northington FJ, Gilmore MM, Tekes A, Huisman TAGM, Parkinson C, et al. Cerebrovascular autoregulation and neurologic injury in neonatal hypoxic-ischemic encephalopathy. *Pediatr Res*. 2013; 74(5):525–535. [PubMed: 23942555]
6. Tekes A, Poretti A, Scheurkogel MM, Huisman TA, Howlett JA, Alqahtani E, et al. Apparent diffusion coefficient scalars correlate with near-infrared spectroscopy markers of cerebrovascular autoregulation in neonates cooled for perinatal hypoxic-ischemic injury. *AJNR Am J Neuroradiol*. 2015 Jan; 36(1):188–193. [PubMed: 25169927]
7. Massaro AN, Govindan RB, Vezina G, Chang T, Andescavage NN, Wang Y, et al. Impaired cerebral autoregulation and brain injury in newborns with hypoxic-ischemic encephalopathy treated with hypothermia. *J Neurophysiol*. 2015 Aug; 114(2):818–824. [PubMed: 26063779]
8. Chalak LF, Tian F, Tarumi T, Zhang R. Cerebral Hemodynamics in Asphyxiated Newborns Undergoing Hypothermia Therapy: Pilot Findings Using a Multiple-Time-Scale Analysis. *Pediatr Neurol*. 2016 Feb;55:30–36. [PubMed: 26858217]
9. Lee JK, Poretti A, Perin J, Huisman TA, Parkinson C, Chavez-Valdez R, et al. Optimizing Cerebral Autoregulation May Decrease Neonatal Regional Hypoxic-Ischemic Brain Injury. *Dev Neurosci*. 2016 Dec 16.
10. Lee JK, Kibler KK, Benni PB, Easley RB, Czosnyka M, Smielewski P, et al. Cerebrovascular reactivity measured by near-infrared spectroscopy. *Stroke*. 2009 May; 40(5):1820–1826. [PubMed: 19286593]
11. Cohen SS, Stonestreet BS. Sex differences in behavioral outcome following neonatal hypoxia ischemia: Insights from a clinical meta-analysis and a rodent model of induced hypoxic ischemic injury. *Exp Neurol*. 2014 Jun;256:70–73. [PubMed: 24726666]
12. Smith AL, Alexander M, Rosenkrantz TS, Sadek ML, Fitch RH. Sex differences in behavioral outcome following neonatal hypoxia ischemia: insights from a clinical meta-analysis and a rodent model of induced hypoxic ischemic brain injury. *Exp Neurol*. 2014 Apr;254:54–67. [PubMed: 24434477]
13. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med*. 2005 Oct 13; 353(15):1574–1584. [PubMed: 16221780]
14. Chavez-Valdez R, O'Connor M, Perin J, Reyes M, Armstrong J, Parkinson C, et al. Associations between cerebrovascular blood pressure autoregulation and cardiopulmonary injury may be sex-specific in neonates treated with therapeutic hypothermia for hypoxic-ischemic encephalopathy. *Pediatr Res*. 2017 In press.
15. Larson AC, Jamrogowicz JL, Kulikowicz E, Wang B, Yang ZJ, Shaffner DH, et al. Cerebrovascular autoregulation after rewarming from hypothermia in a neonatal swine model of asphyxic brain injury. *J Appl Physiol* (1985). 2013 Sep 5; 115(10):1433–1442. [PubMed: 24009008]
16. Armstead WM, Kiessling JW, Kofke WA, Vavilala MS. Impaired cerebral blood flow autoregulation during posttraumatic arterial hypotension after fluid percussion brain injury is prevented by phenylephrine in female but exacerbated in male piglets by extracellular signal-related kinase mitogen-activated protein kinase upregulation. *Crit Care Med*. 2010 Sep; 38(9): 1868–1874. [PubMed: 20562700]
17. Siriussawakul A, Sharma D, Sookplung P, Armstead W, Vavilala MS. Gender differences in cerebrovascular reactivity to carbon dioxide during sevoflurane anesthesia in children: preliminary findings. *Paediatr Anaesth*. 2011 Feb; 21(2):141–147. [PubMed: 21210883]
18. Pappas A, Shankaran S, Laptook AR, Langer JC, Bara R, Ehrenkranz RA, et al. Hypocarbica and adverse outcome in neonatal hypoxic-ischemic encephalopathy. *J Pediatr*. 2011 May; 158(5):752–758. e1. [PubMed: 21146184]

19. Ono M, Arnaoutakis GJ, Fine DM, Brady K, Easley RB, Zheng Y, et al. Blood pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with acute kidney injury. *Crit Care Med*. 2013 Feb; 41(2):464–471. [PubMed: 23263580]
20. Karlsson M, Wiberg-Itzel E, Chakkarapani E, Blennow M, Winbladh B, Thoresen M. Lactate dehydrogenase predicts hypoxic ischaemic encephalopathy in newborn infants: a preliminary study. *Acta Paediatr*. 2010 Aug; 99(8):1139–1144. [PubMed: 20236255]

Table 1

## Patient Characteristics

Characteristic	n	Value
Antenatal demographic data		
Gestational age, weeks, mean (SD)	75	38 6/7 (1 5/7)
Birth weight, g, mean (SD)	75	3161 (869)
White, n (%)	75	37 (49%)
African-American, n (%)	75	28 (37%)
Hispanic, n (%)	75	12 (16%)
Delivery mode, cesarean section, n (%)	75	58 (77%)
Emergency delivery, n (%)	75	55 (73%)
Perinatal data		
Apgar score, 1 min, median (IQR)	71	1 (1, 2)
Apgar score, 5 min, median (IQR)	72	4 (2, 5)
Apgar score, 10 min, median (IQR)	56	5 (3, 7)
Cord pH, mean (SD)	57	6.94 (0.17)
Cord base deficit, mean (SD)	48	-15.2 (6.5)
First hour pH, mean (SD)	70	7.07 (0.27)
First hour base deficit, mean (SD)	56	-16.8 (5.5)
Admission Sarnat score, median (IQR)	75	2 (2, 2)
Severe encephalopathy, n (%)	75	13 (17%)
Hemoglobin (g/dL) during autoregulation monitoring, mean (SD) <sup>a</sup>	72	15.1 (1.9)
Difference between maximum and minimum hemoglobin levels (g/dL) during autoregulation monitoring, mean (SD)	72	2.4 (1.6)
Factors adjusted for in the analysis		
Sex, male, n (%)	75	44 (59%)
Vasopressor, any, n (%)	75	52 (69%)
Seizures, any, n (%)	75	27 (36%)
Benzodiazepine, any, n (%)	75	16 (21%)
Any steroids first 7 days of life, n (%)	75	17 (23%)
PaCO <sub>2</sub>		
All 35 – 45, n (%)	75	6 (8%)
Some < 35, all < 45, n (%)	75	14 (19%)
None < 35, some > 45, n (%)	75	30 (40%)
Some < 35, some > 45, n (%)	75	25 (33%)

IQR = interquartile range; SD = standard deviation.

<sup>a</sup>Three neonates did not have hemoglobin levels drawn during autoregulation monitoring.

Kidney and liver injury measurements among neonates with an identified optimal mean arterial blood pressure value in any period (hypothermia, rewarming, or normothermia).

**Table 2**

Parameter	All neonates		Boys		Girls	
	n	Value <sup>a</sup>	n	Value <sup>a</sup>	n	Value <sup>a</sup>
Maximum creatinine (mg/dL)	72	0.9 (0.6)	44	0.8 (0.5)	28	0.9 (0.8)
Maximum AST (U/L)						
Hypothermia	65	460 (898)	38	473 (1070)	27	443 (595)
Rewarming	51	105 (145)	29	77 (64)	22	143 (205)
Normothermia	30	93 (139)	19	96 (154)	11	88 (116)
Maximum ALT (U/L)						
Hypothermia	65	201 (400)	38	192 (458)	27	215 (306)
Rewarming	56	87 (143)	32	60 (86)	24	122 (191)
Normothermia	36	106 (230)	22	94 (245)	14	126 (211)
Maximum PT (seconds)						
Hypothermia	64	24 (13)	37	25 (14)	27	24 (12)
Rewarming	54	14 (5)	31	15 (5)	23	14 (4)
Normothermia	24	12 (2)	14	12 (2)	10	12 (1)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; PT = prothrombin time.

<sup>a</sup>All values are given as mean (SD)