Detection of Neurologic Injury Using Vascular Reactivity Monitoring and Glial Fibrillary Acidic Protein

abstract

New noninvasive methods for monitoring cerebrovascular pressure reactivity coupled with a blood-based assay for brain-specific injury in preterm infants could allow early diagnosis of brain injury and set the stage for improved timing and effectiveness of interventions. Using an adaptation of near-infrared spectroscopy, we report a case of a very low birth weight infant undergoing hemoglobin volume index monitoring as a measure of cerebrovascular pressure reactivity. During the monitoring period, this infant demonstrated significant disturbances in cerebrovascular pressure reactivity that coincided with elevation of serum glial fibrillary acidic protein and new findings of brain injury on head ultrasound. This case report demonstrates the potential of emerging noninvasive monitoring methods to assist in both detection and therapeutic management to improve neurologic outcomes of the very low birth weight neonate. Pediatrics 2013;131: e950–e954

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KEY WORDS
cerebrovascular pressure reactivity, glial fibrillary acidic protein, head ultrasound, intraventricular hemorrhage, prematurity, very low birth weight

ABBREVIATIONS
ABP—arterial blood pressure
CBV—cerebrovascular blood volume
FIO2—fraction of inspired oxygen
GFAP—glial fibrillary acidic protein
HUS—head ultrasound
HVx—hemoglobin volume index
IVH—intraventricular hemorrhage
MAP—mean arterial blood pressure
NIRS—near-infrared spectroscopy
PWMI—periventricular white matter injuries
rTHb—relative total tissue hemoglobin
VLBW—very low birth weight

Dr Rhee conceptualized and designed the study, collected the primary data, drafted the initial manuscript, and reviewed and revised the manuscript; Ms Kibler conducted the initial analyses and reviewed and revised the manuscript; Dr Brady conceptualized and designed the study, conducted the initial analyses, and reviewed and revised the manuscript; Dr Everett performed the biomarker analysis and critically reviewed and revised the manuscript; Drs Graham and Andropoulos reviewed and revised the manuscript; and Dr Easley conceptualized and designed the study, conducted the initial analyses, supervised the data collection, drafted the initial manuscript, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

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Over the past 10 years, neonatal critical care has decreased the incidence of the most severe form of neonatal brain injuries; however, the overall incidence of periventricular white matter injuries (PWMI) on head ultrasound (HUS) in very low birth weight (VLBW) infants (birth weight <1500 g) has not decreased. The survival rate among VLBW infants is 85% to 90%; however, 5% to 10% of survivors exhibit overt motor deficits (ie, cerebral palsy) with an additional 25% to 50% exhibiting cognitive, behavior, and/or attention deficits that affect school performance.1 Unfortunately, both the diagnostic and therapeutic means to develop strategies to further reduce brain injury in VLBW infants are lacking. To address these knowledge deficits, we developed a novel serum assay for glial fibrillary acidic protein (GFAP), which is a significant diagnostic biomarker of acute brain injury and predictor of outcome in term neonates with hypoxic-ischemic encephalopathy and extracorporeal membrane oxygenation support.2,3

In addition, we have developed a new noninvasive, real-time monitor of cerebrovascular pressure reactivity derived from near-infrared spectroscopy (NIRS) called the hemoglobin volume index (HVx). Previously, we successfully monitored NIRS-based autoregulation metrics in critically ill neonates and found that they experience periods of intact and impaired autoregulation most closely associated with blood pressure, thus providing a potential therapeutic metric that could assist in identifying blood pressure goals that support autoregulation and maintain brain perfusion.4-6 Autoregulation is mediated by vascular reactivity and occurs most robustly in the brain. The HVx explores the role of continuous vascular reactivity monitoring to indicate changes in cerebral blood volume due to low-frequency diameter changes in the resistance vessels of the brain.

In the current study, we report the HVx monitoring period of a VLBW infant who experienced a significant period of impaired cerebrovascular pressure reactivity that coincided with elevation of serum GFAP and new HUS findings. This case illustrates the potential diagnostic and therapeutic synergy of the GFAP and HVx monitoring methods.

### CASE REPORT

A 25-week gestation, 840-g male was born to a 22-year-old G3P1011 by cesarean delivery because of non-reassuring fetal heart rate and breech presentation. Apgar scores were 3, 6, and 7 at 1, 5, and 10 minutes, respectively. Maternal history was unremarkable. Upon delivery, tracheal intubation and surfactant administration were performed. Arterial and venous umbilical catheters were placed, and a septic evaluation was initiated. An intravenous saline bolus (10 mL/kg) and dopamine infusion (10 μg/kg per minute) were administered for persistent hypotension before

### Table 1 Physiologic Parameters in a Preterm Infant on Day 1 to Day 5 During Monitoring Period

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 1</th>
<th>Day 2*</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats per min</td>
<td>117 ± 20</td>
<td>114 ± 21</td>
<td>108 ± 23</td>
<td>118 ± 16</td>
<td>115 ± 21</td>
<td>.30</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>37 ± 4.3</td>
<td>42 ± 7.5</td>
<td>41 ± 4.5b</td>
<td>36 ± 5.1</td>
<td>38 ± 3.4b</td>
<td>.008b</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>89 ± 15</td>
<td>85 ± 17</td>
<td>81 ± 17</td>
<td>88 ± 12</td>
<td>85 ± 15</td>
<td>.69</td>
</tr>
<tr>
<td>Po2, mm Hg</td>
<td>0.65 ± 0.2b</td>
<td>0.67 ± 0.2c</td>
<td>0.47 ± 0.2</td>
<td>0.33 ± 0.05b</td>
<td>0.29 ± 0.01b</td>
<td>.008b</td>
</tr>
<tr>
<td>RR, breaths per min</td>
<td>59 ± 17</td>
<td>51.4 ± 15</td>
<td>57 ± 5.7</td>
<td>45 ± 7.5</td>
<td>46 ± 6.9</td>
<td>.43</td>
</tr>
<tr>
<td>TcSO2C, %</td>
<td>57 ± 12</td>
<td>50 ± 11</td>
<td>61 ± 6</td>
<td>52 ± 13</td>
<td>52 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>36.7 ± 0.1</td>
<td>36.5 ± 0.2</td>
<td>36.3 ± 0.2</td>
<td>36.5 ± 0.4</td>
<td>36.3 ± 0.1</td>
<td>.08</td>
</tr>
<tr>
<td>pH</td>
<td>7.15 ± 0.11b</td>
<td>7.18 ± 0.10b</td>
<td>7.30 ± 0.06</td>
<td>7.38 ± 0.05</td>
<td>7.31 ± 0.04</td>
<td>.01b</td>
</tr>
<tr>
<td>PO2, mm Hg</td>
<td>50 ± 12</td>
<td>50 ± 16</td>
<td>45 ± 4</td>
<td>42 ± 6.4</td>
<td>48 ± 4.6</td>
<td>.80</td>
</tr>
<tr>
<td>PC02, mm Hg</td>
<td>43 ± 7.7b</td>
<td>65 ± 17b</td>
<td>57 ± 10</td>
<td>49 ± 10</td>
<td>48 ± 6.6b</td>
<td>.02b</td>
</tr>
<tr>
<td>HCO3, mmol/L</td>
<td>17 ± 1.2b</td>
<td>18 ± 3.6b</td>
<td>22 ± 1.5</td>
<td>25 ± 1.3c</td>
<td>24 ± 2.2b</td>
<td>.001b,c</td>
</tr>
<tr>
<td>BD, mmol/L</td>
<td>−12 ± 2.3b</td>
<td>−10 ± 2.7c</td>
<td>−4 ± 2.2c</td>
<td>−0.8 ± 1.2c</td>
<td>−2.3 ± 2.6c</td>
<td>.001b,c</td>
</tr>
<tr>
<td>Hgb, g/dL</td>
<td>9.7 ± 0.3</td>
<td>7.2 ± 2.4</td>
<td>9.0 ± 0.8</td>
<td>10.7 ± 0.7</td>
<td>9.7±d</td>
<td>NS</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>4.1±a</td>
<td>5.9 ± 3.7</td>
<td>3.2±a</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>SUN, mg/dl</td>
<td>34±a</td>
<td>58±a</td>
<td>37±a</td>
<td>42±a</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>155 ± 13</td>
<td>95 ± 43</td>
<td>65±b</td>
<td>63 ± 7.1</td>
<td>86±d</td>
<td>—</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. Statistical analysis was performed by using 1-way analysis of variance, with P values < .05 considered statistically significant. BD, base deficit; FiO2, serum bicarbonate; Hgb, serum hemoglobin; HR, heart rate; NS, not significant; RR, respiratory rate; rSO2C, cerebral oxygenation saturation; SaO2, arterial oxygen saturation; SUN, serum urea nitrogen; —, not applicable.

a Suspected day of injury.

b Significant difference for parameter value between specific days.

c Another significant difference between days.

d Single daily values of laboratory tests.
the monitoring period for low blood pressure. Daily parameters are summarized in Table 1. On day 1, the infant remained on mechanical ventilation and received 2 further doses of surfactant. Written informed consent was obtained, and dynamic cerebrovascular pressure reactivity monitoring was initiated per protocol (see Methods). HUS was interpreted as appropriately normal for age. The patient’s chest radiograph demonstrated pulmonary interstitial emphysema, and he required fraction of inspired oxygen (FiO2) of 1.0 to maintain pulse oximetry saturations between 80% and 90%. After a blood transfusion for anemia, the FiO2 decreased to 0.6. On day 2, the infant had an acute deterioration with desaturation to a pulse oximetry saturation of 50%, requiring an increase of FiO2 to 1.0 secondary to pulmonary hemorrhage. HUS was significant for bilateral intraventricular hemorrhages (IVHs) (Figs 1 and 2).

Subsequent days were without life-threatening instability. On day 5, umbilical lines were removed, and the study protocol stopped. At 7 weeks of age, the infant was extubated. At the time of discharge, his hospital course was also remarkable for osteomyelitis, obstructive hydrocephalus requiring placement of a ventriculoperitoneal shunt at 35 weeks’ postmenstrual age, PWMI, developmental delay, and retinopathy of prematurity.

METHODS

Institutional review board approval was provided for this study, and parental consent was obtained before any monitoring or blood collection. This neonate was enrolled in an ongoing observational study collecting GFAP and NIRS-based measurements during routine clinical care. All vascular access, ventilator parameters, medications, and laboratory tests were at the discretion of bedside clinicians who were blinded to the study metrics.

GFAP testing was performed on waste blood from routine blood gas testing. After salvage, the serum was recovered by centrifugation for 8 minutes at 3000 rpm, pooled for each day into 1.5-mL cryotubes, and stored at –70°C until assayed (Meso Scale Discovery, Gaithersburg, MD), as previously described. Normally, GFAP is undetectable in the serum.

HVx monitoring was derived from routine bedside monitoring of NIRS and arterial blood pressure (ABP). Although NIRS monitoring is approved for use in preterm infants, cerebral oximetry is not a part of routine care at our institution. NIRS-based monitoring was obtained from a single pad on the forehead per manufacturer specifications (INVOS, Covidien, Mansfield, MA). NIRS signal of total hemoglobin

![FIGURE 2](image1)

**FIGURE 2**


![FIGURE 3](image2)

**FIGURE 3**

An example of HVx monitoring during periods of functional and impaired cerebrovascular pressure reactivity in this preterm infant. A and B, When cerebrovascular pressure reactivity is intact, mean ABP waves negatively correlate to changes in NIRS-measured rTHb. C and D, When cerebrovascular pressure reactivity is impaired, ABP and rTHb become positively correlated, yielding a positive HVx. Thus, a more negative HVx indicates functional pressure reactivity, and a more positive HVx indicates impaired pressure reactivity.
transients that occur at $<0.05$ Hz. A continuous, moving Pearson correlation coefficient was repeatedly calculated between ABP and rTHb to generate the HVx index (Fig 3).

DISCUSSION

This case report illustrates the potential utility of both serum biomarkers and dynamic cerebrovascular monitoring to detect a risk in cerebrovascular blood volume (CBV) instability before a neurologic event in a critically ill neonate. Although this infant was critically ill and acidicotic (with significant changes in arterial oxygen, pH, and serum bicarbonate), ABP varied significantly across days and was highest on the day of the event (Table 1).

Our group has previously reported autoregulation monitoring by using NIRS-based indices in a multicenter study of premature neonatal patients. However, in the current patient, the previously reported method (cerebral oxygen saturation index) would not work and was confounded by pulmonary and cardiac sources of arterial desaturation. To this end, we developed the HVx to be a saturation-independent, NIRS-derived metric that would be applicable in all patient populations regardless of saturation state. First described and validated in a neonatal piglet model of hypotension, the HVx was demonstrated to be highly sensitive and specific for detecting the lower limit of pressure reactivity. Assessments of cerebrovascular pressure reactivity in infants and children by using the HVx have accurately identified the optimal blood pressure range to support autoregulation. In an adult study of patients with traumatic brain injury, the HVx compared favorably with an index derived from invasive autoregulation monitoring based on the intracranial pressure waveform.

The HVx is a moving, linear correlation coefficient between rTHb and ABP. Cerebrovascular pressure reactivity monitoring by using HVx is based on the assumption that vascular reactivity produces changes in CBV that are proportional to changes in rTHb that can be trended by using the NIRS. The HVx is a continuous measure of vascular pressure reactivity that ranges from $-1$ to $1$. When vascular pressure reactivity is functional, the indices are negative or near-zero because ABP and CBV (for HVx) are either not correlated or are negatively correlated (eg, vascular reactivity is functional and CBF is pressure reactive). When ABP is outside the limits of vascular pressure reactivity, the index becomes increasingly more positive and approaches 1 because ABP and CBV are positively correlated (eg, vascular reactivity is impaired and CBF becomes pressure passive) (Fig 3). Because of the continuous nature of the index, the limits within which vascular pressure reactivity is most robust can be identified as the ABP range with the most negative or near-zero values for HVx.

When comparing the serum biomarkers and vascular pressure reactivity data, the GFAP levels in our patient increased daily over the 5 days of monitoring (Fig 4), suggesting ongoing brain injury. Although the GFAP value on day 4 was low, GFAP levels peaked on day 5 (the last day measured). The decreased value on day 4 was thought to be a dilution artifact of the small waste blood sample. Unfortunately, the volume was insufficient for remeasure. Previously, it was shown that in 36- to 40-week neonates, the majority have an unmeasurable level of GFAP during the first 4 days of life or, if measurable at birth, became unmeasurable after the first 24 hours of life. In neonates with hypoxic-ischemic encephalopathy who underwent whole-body cooling, Ennen et al demonstrated that persistent measurement of GFAP was significantly associated with an abnormal MRI at 7 days of age.
Therefore, elevations of GFAP from baseline in this VLBW infant are consistent with the development and extent of brain injury seen in Fig 2.

Concurrently, the patient's monitored values of HVx became higher, suggesting more impaired vascular pressure reactivity on days 1 and 2, with the highest mean HVx occurring the day of new HUS findings. Subsequent HVx measurements decreased on days 3 to 5, suggesting less impaired vascular pressure reactivity. Because an absolute vascular pressure reactivity threshold in humans is unclear, relative thresholds can be used to demonstrate the proportion of time spent with impairment. For instance, we have categorized this time as impaired (HVx $> 0.3$), moderately impaired (HVx $> 0.4$), and significantly impaired (HVx $> 0.5$) vascular pressure reactivity. Importantly, on the day of injury (day 2), $> 40\%$ (9.6 hours) of the day was spent with impaired vascular pressure reactivity and 21\% (5 hours) was spent with severely impaired vascular pressure reactivity. In adult patients with traumatic brain injury and autoregulation monitoring, Aries et al$^9$ found that deviation of cerebral perfusion pressure management (both higher or lower) away from optimal blood pressure was associated with decreased survival and poor neurologic outcomes. These findings suggest that the decisions we make regarding blood pressure management could be better guided by autoregulation monitoring.

In our VLBW infant, during the 6 hours before the acute decompensation on day 2, the infant had a maximum mean arterial blood pressure (MAP) of 45 mm Hg, and during the 6 hours after the acute event, the infant had a maximum MAP of 50 mm Hg. The combination of the highest absolute MAP and also the longest duration of time spent with impaired pressure reactivity likely made this the most vulnerable for the brain to IVH. Although speculative, this infant's period of vascular pressure reactivity impairment on day 2 may have been related to this excessive blood pressure, possibly related to transfusions and use of inotropic medications, and it contributed to the brain injury detected on HUS.

Continuous cerebrovascular pressure reactivity monitoring may offer the clinician the ability to better balance these different therapies to optimize care.

Utilization of both diagnostic and therapeutic tools in goal-directed management of critically ill VLBW neonates does not exist at this time. A combination of serum biomarkers and noninvasive measures of cerebrovascular pressure reactivity may identify those neonates most at risk for brain injury from blood pressure that cannot maintain safe brain perfusion. As in adult brain injury, HVx monitoring provides a potential therapeutic guide. Because blood pressure management of the VLBW neonate is empirical, HVx monitoring offers the opportunity to individualize blood pressure to optimize brain blood flow. Neonatologists and others caring for critically ill neonates should be aware of these evolving methods that are under investigation for both the detection and therapeutic management of this vulnerable patient population.

REFERENCES

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