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Elevated Cerebral Pressure Passivity Is Associated With Prematurity-Related Intracranial Hemorrhage

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Abstract

OBJECTIVES—Cerebral pressure passivity is common in sick premature infants and may predispose to germinal matrix/intraventricular hemorrhage (GM/IVH), a lesion with potentially serious consequences. We studied the association between the magnitude of cerebral pressure passivity and GM/IVH.

PATIENTS AND METHODS—We enrolled infants <32 weeks' gestational age with indwelling mean arterial pressure (MAP) monitoring and excluded infants with known congenital syndromes or antenatal brain injury. We recorded continuous MAP and cerebral near-infrared spectroscopy hemoglobin difference (HbD) signals at 2 Hz for up to 12 hours/day and up to 5 days. Coherence and transfer function analysis between MAP and HbD signals was performed in 3 frequency bands (0.05–0.25, 0.25–0.5, and 0.5–1.0 Hz). Using MAP-HbD gain and clinical variables (including chorioamnionitis, Apgar scores, gestational age, birth weight, neonatal sepsis, and Score for Neonatal Acute Physiology II), we built a logistic regression model that best predicts cranial ultrasound abnormalities.

RESULTS—In 88 infants (median gestational age: 26 weeks [range 23–30 weeks]), early cranial ultrasound showed GM/IVH in 31 (37%) and parenchymal echodensities in 10 (12%) infants; late cranial ultrasound showed parenchymal abnormalities in 19 (30%) infants. Low-frequency MAP-HbD gain (highest quartile mean) was significantly associated with early GM/IVH but not other ultrasound findings. The most parsimonious model associated with early GM/IVH included only gestational age and MAP-HbD gain.

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CONCLUSIONS—This novel cerebrovascular monitoring technique allows quantification of cerebral pressure passivity as MAP-HbD gain in premature infants. We show that high MAP-HbD gain is significantly associated with GM/IVH. The precise temporal and causal relationship between MAP-HbD gain and GM/IVH awaits further study.

Keywords

prematurity; intraventricular hemorrhage; cerebral pressure passivity; transfer function analysis; cerebral autoregulation

WHAT'S KNOWN ON THIS SUBJECT

Blood pressure monitoring alone does not reliably predict brain injury in premature infants. Cerebral pressure passivity is common and fluctuates in the sick premature infant; its role in prematurity-related brain injury remains controversial, largely because cerebrovascular monitoring techniques remain lacking.

WHAT THIS STUDY ADDS

We describe a continuous technique for measuring the magnitude of cerebral pressure passivity at the bedside of sick premature infants that uses transfer functional analysis. Using this approach we confirm a significant association between high-magnitude pressure passivity and GM/IVH.

Germinal matrix/intraventricular hemorrhage (GM/IVH), the most commonly diagnosed brain lesion in premature newborns,^{1–4} has potentially serious neonatal complications and lifelong sequelae.^{5–11} Its prevention is impeded by incomplete understanding of its underlying mechanisms and by lack of reliable bedside monitoring techniques for identifying its hemodynamic antecedents.

Both incidence and severity of GM/IVH are greatest among the smallest, most premature infants,^{1,12} suggesting a central role for vascular and hemodynamic immaturity in its development. In this paradigm, systemic hemodynamic instability and inefficient cerebral pressure autoregulation result in cerebral pressure passivity, with rupture of fragile cerebral vessels causing GM/IVH. We focus on GM/IVH because of its enormous clinical importance and rapid and reliable identification by cranial ultrasound, which unlike MRI allows early and repeated imaging at the bedside of sick infants, enabling better temporal resolution between potential insults and brain injury.

The overall purpose of this work was to characterize cerebral pressure passivity in premature infants and identify features of cerebral pressure passivity associated with brain injury. Cerebral pressure passivity cannot currently be detected at the bedside of critically ill infants; development of techniques to do so remains frustrated by challenges in acquisition, analysis, and interpretation of continuous cerebral and systemic hemodynamic signals. To detect cerebral pressure passivity in sick preterm infants, we described identification of a critical level of coherence between continuous measurements of blood pressure and cerebral perfusion measured as the hemoglobin difference (HbD) signal by near-infrared spectroscopy (NIRS).^{13–15} Using this approach we described a high prevalence of cerebral

pressure passivity in premature infants, a population at significant risk for GM/IVH.¹⁵ Our studies have shown that cerebral pressure passivity is not “all-or-nothing” but fluctuates over time in a manner that cannot be predicted by “hypotension” as currently defined.¹⁵ To date, the relationship between prevalence of cerebral pressure passivity and GM/IVH has been inconsistent.^{13, 15} In this study, we extend our investigations by examining the association between the magnitude of cerebral pressure passivity and development of GM/IVH.

METHODS

Subjects

Eligible infants were <32 weeks' gestational age at birth, <12 hours' post-natal age at onset of recording, and required continuous mean arterial pressure (MAP) monitoring through an umbilical arterial catheter. Infants with known congenital syndromes or evidence by cranial ultrasound of antenatal brain injury were ineligible. In addition, we included only infants who had cranial ultrasound studies between 5 to 10 and/or 30 days of life or later. The study cohort was recruited between 2000 and 2005 and described in a previous report.¹⁵ The Brigham and Women's Hospital Institutional Review Board approved the study; informed written consent was obtained in all cases.

Data Recording

Time-locked continuous MAP and NIRS (NIRO-500 [Hamamatsu Photonics, Hamamatsu City, Japan]) recordings were made at 2 Hz for 12 hours on each of the first 5 days of life or until the umbilical arterial catheter was discontinued. MAP data from the bedside monitor (Marquette, Milwaukee, WI) and NIRS data were time-locked and stored on a laptop. Cranial ultrasound (Acuson Sequoia [Siemens, Malvern, PA]) studies were obtained as clinically indicated by the treating neonatologists.

Data Processing

Artifact detection and exclusion were described elsewhere.¹⁵ Continuous data were divided into 10-minute epochs. Changes in cerebral HbD concentration signal were calculated as the difference between changes in oxygenated hemoglobin (HbO₂) and hemoglobin. A strong association between changes in HbD and those in quantitative cerebral blood flow has been validated in previous animal studies.^{16, 17}

We used a systems-analysis approach based on the concept that function of a biological regulating system may be studied by examining the relationship between input and output signals. Application of coherence and transfer function analysis to this approach has become a powerful tool for the study of biological systems,^{18, 19} including cerebral autoregulation.^{20, 21} Coherence at a specific frequency describes the extent to which variability in the output signal is attributable to variability in the input signal. When coherence between signals reaches significance at a specific frequency, transfer gain is the magnitude of input signal power passing through the system unmodified into the output signal. In this study, we used a stringent threshold criterion of 0.69 for statistically significant coherence that was based on a published algorithm.²² Intact cerebral pressure autoregulation, which buffers changes in

the input blood pressure to maintain constant output of cerebral blood flow, presents as poor coherence and low transfer gain between the signals, whereas cerebral autoregulatory failure with cerebral pressure passivity presents as the reverse.

We calculated the power spectrum for each signal by using the Welch algorithm²³ with the direct current term (estimated from the epoch mean) removed. Minimum frequency cutoff was set conservatively at 0.05 Hz to ensure that all power values were derived from a statistically significant number of samples. Power estimates above 0.05 Hz were considered significant because their confidence intervals, based on 95% confidence, were <5% of the interval observed at 0.004 Hz, the lowest frequency at which the power estimate was considered to be the least statistically significant. Given our sampling frequency of 2Hz, the Nyquist theorem²⁴ allowed frequency-domain analyses up to 1 Hz.

Next we calculated power spectral density (PSD) for MAP and HbD and the gain spectrum of the transfer function between MAP and HbD. We then measured coherence function between MAP and HbD and excluded from further analysis all components of the gain spectrum below the coherence threshold for significance. We then divided the spectrum into 3 major frequency bands: low(0.05–0.25 Hz), medium (0.25–0.5 Hz), and high (0.5–1.0 Hz). The lower bound of the low-frequency band was selected to exclude those very low frequencies at which the power estimate was not statistically significant²⁵ while still capturing frequencies within which intact cerebral pressure autoregulation would be expected to operate, given its impulse response times of 5 to 20 seconds.^{20,26,27}

Continuous blood pressure recordings were divided into 10-minute epochs. For each epoch we calculated a value of MAP-HbD gain in each of the 3 frequency bands and for each subject the mean gain across each frequency band for all that subject's epochs. Because impaired hemodynamics in a single or relatively few "high-gain" epochs may be associated with GM/IVH, we also calculated for each subject the single highest gain in an epoch (maximum gain) as well as the highest quartile mean (HQM) gain. We calculated HQM gain by ranking the MAP-HbD gain values, selecting the highest 25%, and calculating the mean gain for this highest quartile. This HQM-gain value was the primary independent variable of interest in our study.

Cranial Ultrasound Outcomes

Cranial ultrasound studies were interpreted by 2 experienced investigators (Drs Di Salvo and du Plessis), blinded to the clinical and study data, using standard diagnostic criteria.^{28,29} The primary outcome was GM/IVH on a cranial ultrasound between 5 and 10 days after birth, using the single ultrasound study on or closest to day 5. We used 3 secondary outcomes: (1) grade of GM/IVH (I–III)^{28,29}; (2) presence of parenchymal echodensities on this early cranial ultrasound study; and (3) abnormalities on a late cranial ultrasound (ie, on day 30 of life or soonest thereafter). Parenchymal echodensities were not categorized further into suspected periventricular leukomalacia or periventricular hemorrhagic infarction (previously grade IV GM/IVH). Echolucencies on early scans were interpreted as evidence of antenatal injury, and infants showing such were excluded from the study.³⁰ Late ultra-sound study results were considered abnormal if ventriculomegaly or parenchymal echolucency was present.

Clinical Factors Associated With Cranial Ultrasound Outcomes or Frequency-Domain Indices

We documented specific clinical features for each infant, including use of maternal steroids, diagnosis of chorioamnionitis (clinical and/or placental pathology), birth weight, gender, gestational age, 5-minute Apgar scores, neonatal pressor/inotrope use, neonatal sepsis, carbon dioxide (CO₂) measurements, and Score for Neonatal Acute Physiology II. CO₂ levels were obtained from intermittent clinically indicated blood gas measures; continuous CO₂ measurements were not in routine use in our ICU. Pressor/inotrope management in our ICU is individualized by the attending neonatologist and not based solely on MAP thresholds. Gestational age was used as a continuous and categorical (23–25, 26–28, and 29–30 weeks) variable. Finally, we calculated mean MAP for each epoch of data and examined relationships between mean MAP, PSD-MAP, PSD-HbD, and MAP-HbD gain in each epoch for the 3 frequency bands.

Data-Analysis Methods

Our primary hypothesis was that high MAP-HbD gain would predict GM/IVH on early cranial ultrasound. For each infant, we examined the association between cranial ultrasound findings and each of the mean, maximum, and HQM MAP-HbD gain values. The statistical method used to test this hypothesis was model building through logistic regression.

Because the relationship between the MAP-HbD gain measures and cranial ultrasound events is not known, several models were considered before settling on a model that best fit the data. The models fit included transformations of the MAP-HbD gain variable in each of the 3 frequency bands and inclusion into the model of the clinical variables (described above). Model comparison was made through AIC (Akaike information criteria) and likelihood ratio tests when appropriate. Separate analyses were performed for each dependent variable.

RESULTS

We studied 88 infants with gestational ages of 23 to 30 weeks (median: 26 weeks) at birth. Mean birth weight was 896 g (range: 460–1490 g). Relevant clinical and demographic features are described in Table 1. Three infants died in the newborn period; this small number precluded further analysis with death as outcome.

Median onset of recordings was 11 hours (range: 4–52 hours) after birth, and their median duration was 75.2 hours (range: 9.9–104.3 hours). We analyzed 9120 ten-minute epochs, a mean of 101 per patient (range: 18–202 per patient). Median postnatal age at cranial ultrasound was 8 days (range: 5–10 days) for early studies and 32 days (range: 30–78 days) for late studies. The frequency and distribution of cranial ultrasound abnormalities according to gestational-age category are shown in Table 1.

Unadjusted Analysis

To analyze the association between GM/IVH and the clinical variables, we first fit each variable individually. Association between GM/IVH and these clinical variables was

nonsignificant ($P = .05$) for all variables. A majority of the infants were exposed to maternal steroids ($n = 77$) and neonatal pressor support ($n = 78$) during the first 5 days of life, precluding a meaningful analysis of their role.

Predictors of GM/IVH on Early Cranial Ultrasound

We fit models for each of the 3 major frequency bands. Results were significant only in the low-frequency band, and subsequent discussion relates only to these low-frequency measures of MAP-HbD gain. Higher HQM gain was significantly associated with increased likelihood of GM/IVH on early cranial ultrasound scans (Table 2) but only weakly correlated with GM/IVH grade. The other significant factor included with HQM gain in the same model was continuous gestational age. Association between gestational age and GM/IVH was negative; the smaller the gestational age, the greater likelihood of GM/IVH. Chorioamnionitis, 5-minute Apgar scores, neonatal sepsis, mean MAP, birth weight, and Score for Neonatal Acute Physiology II were strongly collinear with gestational age and not important predictors of GM/IVH once gestational age and HQM gain were included in the model. This model is the most parsimonious model that explains the response, GM/IVH.

Predictors of Other Cranial Ultrasound Abnormalities

Measures of MAP-HbD gain were poorly correlated with parenchymal echodensities on early cranial ultrasound as well as with any abnormal findings on late cranial ultrasound. Gestational age was significantly and inversely correlated with abnormal late cranial ultrasound studies ($P < .05$), but other clinical variables were not significant predictors once gestational age was included in the model.

Other independent variables were considered in the model in place of HQM gain, including mean gain, maximum gain, and mean, maximum, and HQM of PSD MAP and PSD HbD. Mean and maximum MAP-HbD gain values were significant predictors of GM/IVH (Table 2), although mean gain was marginally so. Neither PSD MAP nor PSD HbD was a significant predictor of GM/IVH. None of the hemodynamic indices described predicted other cranial ultrasound abnormalities. Low-frequency PSD MAP correlated positively ($r = 0.20$; $P = .001$) with gestational age but not with GM/IVH.

DISCUSSION

In this study we show a significant association between high-magnitude cerebral pressure passivity and development of GM/IVH in premature infants. Using the gain between changes in MAP and those in cerebral HbD (measured by NIRS), we describe transfer of blood pressure power into the cerebral circulation, thereby quantifying the magnitude of cerebral pressure passivity. The only 2 predictors showing a significant independent association with GM/IVH are lower gestational age and high MAP-HbD gain. Association between MAP-HbD gain and GM/IVH is significant only in the low-frequency range, where intact cerebral pressure autoregulation would be expected to prevent cerebral pressure passivity.^{20,26,31}

“Power” of signals in the frequency domain measures their variance at specific frequencies. Notably, although high MAP-HbD gain in the low-frequency band predicted GM/IVH,

spectral power (variance) of neither MAP nor HbD in isolation was associated with GM/IVH.

We previously used coherence function analysis^{13–15} in sick premature infants to describe high prevalence of cerebral pressure passivity that waxed and waned over relatively short periods, being present on average ~20% of the time and increasing with lower gestational age.¹⁵ However, although this coherence-based approach is valuable for identifying the presence of cerebral pressure passivity, it does not reflect the magnitude of blood pressure power passing from systemic to cerebral circulation; perhaps not surprising, then, we found no significant association between prevalence of cerebral pressure passivity and GM/IVH in these premature infants.¹⁵ To further examine the impact of cerebral pressure passivity, we measured transfer gain between blood pressure and cerebral HbD signals during periods of significant coherence.

In the absence of bedside techniques for continuous monitoring of cerebral perfusion, clinicians have had to base their management of cerebral perfusion in critically ill infants on the assumption that maintaining blood pressure between certain population-based normal limits^{32–34} would optimize cerebral pressure-flow regulation and cerebral blood flow and minimize the risk of cerebrovascular injury. However, data from our studies^{15,35} and others^{36–38} have seriously challenged this approach. In our recent studies of premature infants, neither mean blood pressure¹⁵ nor duration of hypotension (as defined by different commonly used criteria)³⁵ was associated with GM/IVH. Consequently, the benefit of medications used to achieve blood pressure goals, and even the potentially injurious role of these agents, has come under scrutiny.^{36–42}

Variability of systemic blood pressure has also been implicated in the pathogenesis of GM/IVH,^{34,43–47} with this blood pressure fluctuation ascribed to factors such as autonomic^{48,49} and myocardial immaturity and positive pressure ventilation.^{46,50,51} However, others have described a decrease in blood pressure variability among infants at greatest risk for GM/IVH (ie, those with lowest gestational age). Menke et al⁵² showed that in premature infants the spectral power (variability) in both MAP and cerebral perfusion are low soon after birth (when risk of GM/IVH is highest), increasing thereafter over the first 4 days of life. In our studies, blood pressure variability has not been a significant independent predictor of GM/IVH, whether measured as frequency-domain spectral power in the current study or in our earlier time-domain studies.^{15,35} Of interest, variability in cerebral HbD in the current study was not associated with GM/IVH. In fact, spectral power in both the MAP and cerebral HbD signals was directly related to gestational age, whereas the incidence of GM/IVH was inversely related to gestational age. Taken together, these data suggest that variabilities in MAP and HbD are poor predictors of GM/IVH in isolation, but when the relationship between these 2 signals is quantified by using gain, the association with GM/IVH may be significant. Therefore, monitoring systemic blood pressure or cerebral HbD separately will not identify infants at risk for GM/IVH.

This study has a number of strengths. A large number of infants were studied for prolonged periods by using high-frequency sampling rates for both systemic and cerebral hemodynamic signals. Rigorous criteria were used to exclude potential artifact, and

coherence constraints on transfer function analysis were stringent. We excluded subjects with evidence of antenatal injury and based our early cranial ultra-sound out comes on studies performed soon after the expected time by which the vast majority of GM/IVHs would have occurred.²⁸

Because cranial ultrasound is particularly sensitive to hemorrhage, it is unlikely that any significant GM/IVH went undetected. However, several important limitations of our study need to be considered. First, cranial ultrasound studies were clinically indicated, with their timing inconsistent among subjects. Therefore, precise timing of the GM/IVH lesions is not possible, which limited our ability to define the temporal association between hemodynamic measures and GM/IVH. Furthermore, although we attempted to start our recordings as early as possible after birth, there were inevitable delays caused by enrollment, arterial line placement, and a complex recording set-up. Our studies lasted a maximum of 12 hours on each study day and may have missed important hemodynamic changes outside these recording periods. Although cranial ultrasound is sufficiently sensitive to detect hemorrhagic lesions and larger ischemic lesions, its ability to detect more modest and diffuse forms of parenchymal injury is significantly limited. Our goal was to investigate the relationship between cerebral pressure passivity and cranial ultrasound evidence of brain injury. The study population, infants in whom clinical hemodynamic concerns warranted in dwelling arterial catheter placement and a high rate of pressor/inotrope use, represents a population at high risk for pressure passivity and for cranial ultrasound lesions. However, these features of our population may limit the generalizability of our findings. Finally, because we did not measure continuous CO₂ levels and our blood gas measurements were often hours apart, the role of CO₂ levels in cerebral pressure passivity and GM/IVH could not be tested reliably.

CONCLUSIONS

This study extends our characterization of cerebral pressure passivity in sick premature infants, showing that magnitude of cerebral pressure passivity is significantly associated with GM/IVH. Independent measures of changes in systemic blood pressure and cerebral perfusion were not associated with GM/IVH, emphasizing the importance of monitoring interactions between systems in critically ill patients. Future studies will focus on more precise timing of GM/IVH injuries to determine if the relationship between high-magnitude cerebral pressure passivity and these lesions is causative. Finally, nonhemorrhagic injuries may be missed on cranial ultrasound and will require the availability of brain-imaging techniques that are not only sensitive to hypoxia-ischemia/reperfusion injury but also capable of early and repeated scanning in sick premature infants.

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ABBREVIATIONS

GM/IVH	germinal matrix/intraventricular hemorrhage
HbD	hemoglobin difference
NIRS	near-infrared spectroscopy
MAP	mean arterial pressure
PSD	power spectral density
HQM	highest quartile mean

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TABLE 1

Clinical and Cranial Ultrasound Characteristics of the Population as an Overall Group and Within the 3 Gestational-Age Groups

	Overall Group	23–25 wk	26–28 wk	29–30 wk
Clinical feature				
Chorioamnionitis, <i>n/N</i> (%)	16/86 (19)	5/24 (21)	9/51 (18)	2/11 (18)
Maternal steroids, <i>n/N</i> (%)	77/88 (87.5)	22/24 (91.7)	46/52 (88.5)	9/11 (81.8)
Gender male, <i>n/N</i> (%)	51/88 (58.0)	16/24 (67.7)	29/52 (55.8)	6/11 (54.5)
Neonatal sepsis, <i>n/N</i> (%)	25/87 (29)	11/24 (45)	13/52 (25)	1/11 (9)
SNAP-II score, mean (range)	23 (0–56)	32 (5–56)	21 (0–40)	14 (0–26)
Pressor support, <i>n/N</i> (%)	78/87 (90)	24/24 (100)	46/52 (88)	8/11 (72)
Cranial ultrasound findings				
Early cranial ultrasound, <i>n</i>	84	23	52	9
GM/IVH, <i>n</i> (%)	31 (37)	13 (57)	15 (29)	3 (33)
Grade I	6/84 (7)	1/23 (4)	4/52 (8)	1/9 (11)
Grade II	14/84 (14)	9/23 (39)	3/52 (6)	2/9 (22)
Grade III	11/84 (11)	3/23 (13)	8/52 (16)	0/9 (0)
Parenchymal EDs, <i>n</i> (%)	10 (12)	5 (22)	5 (10)	0 (0)
GM/IVH or ED, <i>n</i> (%)	31 (37)	13 (57)	15 (29)	3 (33)
Late cranial ultrasound, <i>n</i>	63	20	37	6
Parenchymal abnormality, <i>n</i> (%)	19 (30)	10 (50)	9 (25)	0 (0)

SNAP-II indicates Score of Neonatal Acute Physiology II; ED, echodensity.

TABLE 2

Significance (*P*) of Relationship Between Predictive Model (Includes Gestational Age) and GM/IVH for the Different Frequency Bands

	LF (0.05–0.25 Hz)	MF (0.25–0.5 Hz)	HF (0.5–1.0 Hz)
Hemodynamic function			
MAP PSD	.15	.11	.49
HbD PSD	.75	.85	.96
MAP-HbD gain			
Mean gain	.05	.44	.85
Maximum gain	.03	.77	.79
HQM gain	.03	.53	.98

LF, MF, and HF indicate low-, medium-, and high-frequency bands, respectively.