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The Association of High-Magnitude Cerebral Passivity and Intraventricular Hemorrhage in Premature Infants

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Despite advances in neonatal-perinatal medicine, the prevalence (10%–12%) of severe intraventricular hemorrhage (IVH) among very low birth weight (VLBW) (birth weight ≤ 1500 g) infants has remained constant over the last 15 years.^{1,2} Lifetime care costs for a yearly cohort of VLBW infants with severe IVH is estimated to exceed \$3 billion.³ Thus, understanding the pathophysiology and ultimately preventing IVH has been an important goal of neonatal researchers. Although the etiology of IVH is multifactorial, disturbances of cerebral blood flow (CBF) and cerebral autoregulation play an important role.^{4–6} Cerebral autoregulation is an essential physiologic mechanism that maintains constant blood flow to the brain despite wide variations in cerebral perfusion pressure. Cerebral pressure passivity results when cerebral autoregulation is impaired, and it indicates that CBF passively depends on blood pressure. Importantly, premature infants with impaired cerebral autoregulation more commonly develop IVH compared with those with intact autoregulation.^{5,6}

In this issue of *Pediatrics*, O’Leary et al⁷ describe their use of a novel physiologic monitoring technique, with sophisticated computational and statistical analyses (coherence analysis, power spectral analysis, and transfer function analysis), to quantify the magnitude of cerebral passivity in a cohort of VLBW infants, who have been studied previously.⁸ Mean arterial blood pressure and near-infrared spectroscopy hemoglobin difference (as a proxy for CBF) were determined for each 10-minute epoch and assessed for pressure passivity. Then the magnitude of pressure passivity was examined for a relationship to early cranial ultrasound findings of IVH. For the first time, in a large sample of sick VLBW infants, this group has demonstrated that a high magnitude of cerebral pressure passivity is associated with IVH. Although the findings were not surprising, given their own work showing a relationship between impaired cerebral autoregulation and severe brain injury,⁶ O’Leary et al used dynamic techniques with continuous high-frequency measurements during the first 5 days of life to confirm this important association.

The major strength of this study is that mean arterial blood pressure and near-infrared spectroscopy hemoglobin difference were recorded at the bedside continuously for up to 12 hours/day and up to 5 days in 88 VLBW infants. Moreover, although the concept of magnitude of cerebral pressure passivity using transfer function analysis is quite complex, the authors present a thorough description in their methods section. Lastly, the purpose of the authors to characterize cerebral passivity and elements of cerebral passivity associated with IVH was met.

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There are 2 important limitations of this study, however, that limit generalizability of the results to other neonatology populations. First, 90% of the study cohort received vasopressors for the treatment of presumed hypotension. Moreover, the general unit policy for beginning vasopressors was not presented. Although the infants in this study were clearly sick, given the high Score for Neonatal Acute Physiology II (mean: 23),⁹ high use of vasopressors, and high incidence of early IVH (37%) and parenchymal echodensities (12%), it is quite surprising that a majority of them survived beyond 30 days of age (given the inclusion criteria). The 90% use of vasopressors is an outlier¹⁰ and may have confounded the results.

Vasopressors may affect the capacity for cerebral autoregulation by virtue of their effect on blood pressure and/or CBF. A majority of studies that have examined the effects of vasopressors in hypotensive premature infants reported that cerebral hemodynamics were altered through changes in blood pressure.^{11–13} Although the primary purpose of this study was not to determine how high-magnitude cerebral pressure passivity develops, this is one of the fundamental problems that confronts neonatal cerebral autoregulation investigators. It is unknown whether the treatment of hypotension with vasopressors restores intact cerebral autoregulation (assuming that premature infants with hypotension have impaired cerebral autoregulation), attenuates or worsens impaired autoregulation, or does not affect the magnitude of impaired autoregulation at all. Thus, in the hypotensive VLBW infants in the O’Leary et al study, it is unclear how vasopressors affected their capacity for cerebral autoregulation. In addition, it is possible that abrupt increases in blood pressure by vasopressors in hypotensive VLBW infants with otherwise adequate cerebral perfusion, despite their cerebral pressure passivity magnitude, could be transmitted to the cerebral circulation, causing hyperperfusion and IVH.

The second limitation of this study is the lack of information about ventilation strategies (ie, permissive hypercapnia) used during the study period. PaCO_2 is a potent regulator of CBF, and the capacity for intact cerebral auto-regulation is highly influenced by PCO_2 level.¹⁴ Is the high magnitude of pressure passivity associated with IVH observed in these infants because of hypercapnia? In addition, this group reported previously that hypercapnia was associated with increased odds of autoregulatory failure, but in an older population of infants undergoing cardiac surgery.¹⁵ Unfortunately, continuous measurements of CO_2 (transcutaneous or end-tidal) were not performed during this study.

Given this important topic in neonatal neurology, a new study with continuous measures of CO_2 as well, in both hypotensive and normotensive (not receiving vasopressors) VLBW infants, may make the eventual results more generalizable. Because cerebral autoregulation is a dynamic process, autoregulatory studies in premature infants in the future must include continuous dynamic measures of at least blood pressure, CBF parameters (near-infrared spectroscopy and/or Doppler ultrasound), and CO_2 . If, in the future, high-magnitude cerebral pressure passivity can be shown to precede IVH, then interventions could be provided to these high-risk infants in the hopes of reducing this devastating complication of prematurity.

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ABBREVIATIONS

IVH	intraventricular hemorrhage
VLBW	very low birth weight

CBF cerebral blood flow

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