Cerebral Hemodynamics in Premature Infants

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ABSTRACT

Extremely low birth weight infants remain at increased risk of intraventricular hemorrhage from the fragile vascular bed of the germinal matrix; the roles of hypotension (ischemia) and reperfusion (hyperemia) in the development of intraventricular hemorrhage are still debated. Cerebrovascular pressure autoregulation protects the brain by maintaining constant cerebral blood flow despite changes in blood pressure. The ontogeny of cerebrovascular pressure autoregulation has not been well established and uncertainty remains about the optimal arterial blood pressure required to support brain perfusion. Another important aspect of premature cerebral hemodynamics is the critical closing pressure--the arterial blood pressure at which cerebral blood flow ceases. Interestingly, in premature infants, the critical closing pressure approximates the mean arterial blood pressure. Often in this unique population, cerebral blood flow occurs only during systole when the diastolic arterial blood pressure is equal to the critical closing pressure. Moreover, the diastolic closing margin, a metric of cerebral perfusion that normalizes diastolic arterial blood pressure to the critical closing pressure, may be a better measure than arterial blood pressure for defining cerebral perfusion in premature infants. Elevated diastolic closing margin has been associated with intraventricular hemorrhage. This review summarizes the current state of understanding of cerebral hemodynamics in premature infants.

Key Words: Premature, Intraventricular hemorrhage, Cerebral autoregulation, Critical closing pressure, Diastolic closing margin

INTRODUCTION

Extremely low birth weight (ELBW, birth weight $\leq 1,000$ g) infants are at high risk for developing brain injury early in life. Intraventricular hemorrhage (IVH) is the most common form of brain injury, and its incidence is inversely proportional to gestational age (GA) and birth weight (BW). IVH is associated with long-term neurodevelopmental delay, poor cognitive performance, visual and hearing impairment, epilepsy and cerebral palsy¹⁾. Despite impro-

Received: 16 December 2017

Revised: 21 January 2018

Accepted: 24 January 2018

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vements in overall ELBW infant survival, they remain at high risk for poor neurodevelopmental outcomes.

The thin-walled, immature vessels of the germinal matrix contribute to the increased risk for IVH in ELBW infants^{2,3}. In addition, hypotension (ischemia) followed by reperfusion (hyperemia) have been implicated in the pathogenesis of IVH in human premature infants⁴⁻⁷ and in experimental animal models^{8,9}. A delicate balance is required to maintain adequate cerebral perfusion while avoiding ischemia or hyperemia, both of which may result in brain injury.

Arterial blood pressure (ABP) is the most frequently monitored parameter for assessment of hemodynamics in ELBW infants; however, there is little-to-no correlation between systemic blood flow and ABP, as shock occurs even with normal ABP^{10,11}. The goal of ABP management in premature infants is to maintain adequate perfusion to the brain and other vital organs. Despite this objective, neonatologists have been unable to determine evidence-based ABP values or thresholds to define hypotension, the most appropriate treatments and whether treatment is even required for some infants. This highlights the importance of defining optimal ABP management that is supportive of cerebral and other organ perfusion^{12,13}.

In order to define optimal brain perfusion, several key aspects of cerebral hemodynamics must be included to understand this complex physiology: cerebrovascular pressure autoregulation, critical closing pressure (CrCP) and the diastolic closing margin (DCM). Cerebrovascular pressure autoregulation protects the brain by maintaining constant cerebral blood flow (CBF) across a wide range of ABPs and has been shown to be impaired in sick premature infants¹⁴. Determining the effective cerebral perfusion pressure requires knowledge of the CrCP, the ABP at which the CBF ceases. When diastolic ABP is equal to the CrCP, CBF occurs only during systole. Therefore, a metric is needed that accounts for CrCP and the observations of passive or absent CBF during diastole. The DCM, diastolic ABP minus CrCP, provides a metric of effective cerebral perfusion pressure, and when elevated, has been associated with IVH in premature infants¹⁵.

This review summarizes the current state of understanding of cerebral hemodynamics in premature infants.

CEREBROVASCULAR PRESSURE AUTOREGULATION

Mammalian cerebral vasculature muscularity develops at approximately 0.65 gestation (at approximately 26 weeks' gestation in humans)^{16,17}. Cerebrovascular pressure autoregulation protects the brain during transient fluctuations in ABP from diminished or excessive CBF over a wide range of ABPs. An autoregulatory plateau exists whereby CBF is held constant across changing ABP (Figure 1). In addition, both an upper and a lower limit exist on the autoregulation curve. Above the upper limit, if the ABP increases, the CBF increases and below the lower limit, if the ABP decreases, the CBF decreases.

Importantly, autoregulation is mediated by vascular reactivity, which is defined as low-frequency (0–0.04 Hz) diameter changes in resistance vessels in response to changes in ABP¹⁸. Premature infants maintain adequate cerebral perfusion across a wide ABP range from approximately 24 to 39 mm Hg, and evidence exists that many premature infants have periods of intact autoregulation¹⁹⁻²². At ABPs below and above the autoregulatory plateau, CBF becomes pressure passive. However, cerebral autoregulation is likely increasingly impaired with decreasing GA and BW, and infants with impaired autoregulation more commonly develop IVH^{20,23,24}. In addition, cerebral autoregulation in premature infants is influenced by hypercapnia, surfactant administration and other neonatal intensive care procedures^{19,25-27}. Finally, impaired autore-

Figure 1. Autoregulation curve. Autoregulatory plateau is shown as the flat part of the curve where cerebral blood flow is constant across varying blood pressure. The upper and lower limit of autoregulation are depicted, above and below which the brain is more susceptible to injury. The critical closing pressure (CrCP) is the arterial blood pressure at which the cerebral blood flow is zero.

gulation was associated with increased mortality in this at-risk population^{28,29}.

While the capacity for intact autoregulation has been demonstrated in premature infants using both transcranial Doppler ultrasound and near-infrared spectroscopy techniques, there is limited information about its ontogeny²¹. In a re-analysis of previously published data, regulation of CBF velocity (CBFV) was examined in 179 premature infants with GA from 23–33 weeks' gestation comparing systolic, diastolic and mean CBFV patterns separately³⁰. Vascular resistance changes mediating autoregulation were effective at regulating systolic CBFV while diastolic CBFV was both low and passive to ABP changes. In addition, there was an association between increasing GA and intact cerebral autoregulation during systole.

The results of this study imply three practicalities related to premature cerebrovascular pressure autoregulation: 1) When Doppler ultrasound is used to study autoregulation in premature infants, those <26 weeks are likely to demonstrate pressure-passivity regardless of care strategy. Therefore, autoregulation monitoring with Doppler is not likely to elucidate optimal care strategies for most ELBW infants. 2) If Doppler is used to study autoregulation in premature infants, evaluation of the systolic phase of the cardiac cycle is more likely to demarcate optimal care strategies than evaluation of mean values across the cardiac cycle. Premature infants demonstrate an ability to autoregulate the surge of CBFV during systole before any apparent autoregulation of diastolic CBFV. 3) ABP is a poor surrogate of cerebral perfusion pressure in premature infants.

CRITICAL CLOSING PRESSURE

CrCP is the ABP where CBF ceases due to vascular collapse, and it is posited to be the sum of vascular wall tension and intracranial pressure³¹. In concept, CrCP is a factor for the normalization of ABP to an "effective cerebral perfusion pressure" or "closing margin," whereby "effective cerebral perfusion pressure" is equal to ABP minus CrCP^{32,33}. CrCP in infants ranges from 24–33 mm Hg, similar to reported CrCP values in mature subjects^{34,35}. Low ABP in ELBW infants results in a strikingly low effective cerebral perfusion pressure. Small variances of CrCP and ABP, therefore, may result in more dramatic changes in the premature infant's effective cerebral perfusion pressure. This important factor confounds the clinical usefulness of ABP alone as a marker of adequate cerebral

perfusion. Moreover, when compared to term infants and adults, the closing margin has greater relevance accounting for the low ABP of premature infants (Figure 2).

CrCP has been calculated using two methods. The first method used a model of linear regression plotting multiple measures of mean CBFV and mean ABP. The CrCP was then determined as the mean ABP where the linear regression line crossed the x-axis³⁵. More recently, a new method to calculate CrCP using ABP and CBFV tracings was proposed³³. In this method, CBFV is described by alternating flow velocity at the frequency of the cardiac cycle, and CrCP is derived from an equation of impedance to flow velocity.

In premature infants, CrCP increased significantly from 23–31 weeks' gestation at a rate of 1.4 mm Hg per week of gestation³⁶. An individual infant's ability to tolerate low ABP without global cerebral infarct or hemorrhage may be related to the low CrCP observed in this population. While there may be limitations to measuring CrCP, it will likely have relevance to identifying those premature infants most at risk for brain injury.

DIASTOLIC CLOSING MARGIN

The "effective cerebral perfusion" or "closing margin" can be determined for any phase of the cardiac cycle by subtracting the

Figure 2. Comparison of CrCP and mean ABP in adults, term and preterm infants. CrCP is near mean ABP in preterm infants demonstrating a low "effective cerebral perfusion pressure" relative to the range of CrCP. The effective cerebral perfusion pressure is defined as ABP minus CrCP. This may be the reason premature infants tolerate low ABP without compromised CBF. Abbreviations: CrCP, critical closing pressure; ABP, arterial blood pressure; CBF, cerebral blood flow.

Figure 3. DCM is associated with severe IVH ($P < 0.0001$). For an increase in DCM by 1 mmHg, the risk for severe IVH increases by 15%. Abbreviations: DCM, diastolic closing margin; IVH, intraventricular hemorrhage.

CrCP from systolic, mean or diastolic ABP. In premature infants, CBF is often passive to ABP or absent during diastole, and this unique physiology has only been described in the presence of severe neuropathology in mature subjects³⁷. The DCM, diastolic ABP minus CrCP, provides a metric of “effective cerebral perfusion” that can be related to premature brain injury.

In premature infants, increased DCM was associated with developing severe IVH (Grade 3–4) ($P < 0.0001$, Figure 3)¹⁵. Interestingly, when comparing infants with severe IVH to those with non-severe IVH, both mean CBFV and mean ABP were not different; the DCM, however, was statistically higher in those infants with severe IVH ($P = 0.0063$). This result may be evidence for a reperfusion injury associated with the pathogenesis of IVH. By simply having a 1-mm Hg increase in DCM, there was a 15% increased odds of developing severe IVH. Further, a 5-mm Hg increase in DCM was associated with an 89% increased odds of developing severe IVH. Thus, DCM may be a better measure than ABP for defining premature infant cerebral perfusion.

Further studies are needed to corroborate our findings that elevated DCM can be predictive of developing severe IVH in at-risk premature infants. More comprehensive physiologic monitoring data is necessary and may include targeted neonatal echocardiography, near-infrared spectroscopy, transcranial Doppler ultrasound and amplitude-integrated electroencephalography.

SUMMARY

Premature infants remain at high-risk for the development of IVH early in life. This unique population has low and almost always pressure-passive diastolic CBF. By contrast, the regulation of systolic CBFV by pressure autoregulation develops between 23 and 33 weeks’ gestation. Another important related aspect of cerebral hemodynamics is the CrCP. CrCP can serve as a zero-point reference for determining cerebral perfusion pressure, and it increases gradually with advancing gestational age making it a very useful metric in understanding cerebral perfusion in premature infants. The low CrCP observed in very premature infants may explain their ability to tolerate low ABP without global cerebral infarct or hemorrhage. By using the CrCP to normalize diastolic ABP to an “effective cerebral perfusion pressure,” DCM was shown when elevated to be strongly associated with severe IVH when ABP alone was not predictive of neurologic injury. Measurement of CrCP and DCM may be more useful than ABP to define individualized hemodynamic management and mitigate the risk for brain injury in this vulnerable population.

CONFLICTS OF INTEREST AND SOURCE OF FUNDING

The authors declare no conflict of interest. Christopher Rhee is supported by the NIH NINDS (1K23NS091382-01A1) and the NIH Loan Repayment Program (K23NS091382). He was also previously supported by the Chao Physician Scientist Award (Baylor College of Medicine). Danielle Rios is supported by the NIH NHLBI (1K23HL130522-01) and the NIH Loan Repayment Program (K23HL120522). The authors declare no other financial support.

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