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EDITORIAL

Cerebrovascular autoregulation among very low birth weight infants

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Despite advances in neonatal care, intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) remain significant morbidities in very low birth weight infants. Disturbed cerebral hemodynamics may be a major contributor to the pathogenesis of these lesions.[1,2] A growing body of literature describes cerebral autoregulation among at-risk very low birth weight infants, including an eloquent study by Gilmore *et al*.,[3] which describes the autoregulatory ability of preterm infants over the first 3 days of life—at the time they are most vulnerable to perinatal brain injury.

Autoregulation is the ability to maintain a constant cerebral blood flow over a physiological range of blood pressures (BPs), related to the constriction and dilation of the main capacitance vessels of the cerebral circulation. At BPs below and above the 'autoregulatory plateau', cerebral blood flow decreases or increases linearly with BP (so-called 'pressure passive' cerebral blood flow). The importance of autoregulation for the preterm infant relates to the vulnerability to both ischemic and hemorrhagic brain injury. The literature is somewhat conflicting as to whether preterm babies are able to autoregulate adequately. Studies of global cerebral blood flow, measured by either the 133Xenon clearance technique[4,5] or near infrared spectroscopy (NIRS) using the oxygen transient method,[6] suggested that, as a whole, preterm babies can autoregulate cerebral blood flow when the mean arterial pressure is at least 25–30 mm Hg.

With the development of sophisticated NIRS technology and computer systems, which can integrate NIRS data with simultaneous arterial BP data, descriptions of cerebral autoregulation in preterm infants have moved from the description of static autoregulation to dynamic autoregulation. That is, from descriptions of total cerebral blood flow responses to changes in BP over a minute or so in time, to the descriptions of the nearly continuous fluctuations in cerebral blood flow in response to nearly continuous changes in BP. Reports by Tsuji *et al*.[7] and O'Leary *et al*.[8] use frequency domain analysis to demonstrate that preterm infants can autoregulate cerebral blood flow, but that periods of pressure passivity are common and predispose to IVH.

In this issue of *The Journal of Perinatology*, Gilmore *et al*. report time-domain analysis of NIRS data to characterize dynamic cerebral autoregulation in 23 very low birth weight newborns. The detailed methodology, validated in animal models,[9] provides information on the relationship between cerebral oxygenated hemoglobin (a surrogate for cerebral blood flow) and mean arterial BP measured continuously over the first 3 days of life. The authors contribute the following to our understanding of autoregulation among very low birth weight infants: (1) the ability to autoregulate cerebral blood flow differs from infant to infant, with some infants able to autoregulate well at all BPs experienced and others unable to autoregulate despite 'normal' BPs; (2) a given infant may demonstrate intact autoregulation at some BPs, but not others; (3) autoregulation is more likely to be impaired at lower systemic arterial BP and more likely to be intact at higher BPs; (4) average mean arterial BP over the entire 3-day study period is proportional to time spent with intact autoregulation; and (5) although estimated gestational age is proportional to BP, estimated gestational age bears no relationship to the time spent with intact autoregulation.

A notable strength of this paper is the duration of monitoring accomplished in these very preterm and often unstable babies. The authors did not intervene in the clinical decision making regarding the treatment of hypotension, but were able to capture periods of low BP prior to treatment in their cohort. Thus, for individual babies, they were able to provide information about the ability to autoregulate over a range of BPs. This is crucial, as the controlled manipulation of BP, as is done in animal models, is not ethical in preterm babies who are at risk for IVH and periventricular leukomalacia.

One of the most intriguing findings is that among this cohort of 25–30-week infants, the ability to autoregulate was independent of gestational age. In contrast to animal literature (lambs), which suggests that autoregulation has not yet developed at 60% gestation,[10] some extremely low birth weight infants as young as 25 weeks gestation can effectively autoregulate cerebral blood flow. Conversely, some babies of 30 weeks gestation (relatively 'mature' for the neonatologist who cares for babies at the edge of viability) may not adequately autoregulate cerebral blood flow. The paper helps to define the lower boundary of BP for the autoregulatory plateau in preterm infants. This boundary may vary from infant to infant and over time within a given infant, and is likely somewhere between a mean arterial BP of 20 and 25 mm Hg.

There are three main limitations to this paper. First, the paper assumes that the relationships described between BP and cerebral blood flow are independent of P_aCO_2 and P_aO_2. In fact, CO_2

reactivity may be more important than BP reactivity in determining cerebral blood flow in premature infants.[11] In this study, we do not have information for a given baby about what the concurrent CO_2 is during periods of pressure passivity, nor are we told what the ventilation strategy practiced in the unit is. Kaiser *et al*.[12] have shown that CO_2 in the frequently practiced permissive hypercapnia range may actually impair autoregulation over the first few days of life. Thus, a ventilation strategy that allows for permissive hypercapnia may explain why impaired autoregulation occurred as frequently at 27–30 weeks as it did at 24–26 weeks gestation (see Gilmore *et al*., Figure 3c).

The second limitation relates to the frequent diagnosis of hypotension among study subjects (20/23 or 87% of subjects were perceived to be hypotensive by the clinicians at some point during the monitoring period) and the relatively aggressive strategy for the treatment of hypotension, with vasopressor use (19/23 or 83%) well beyond published frequency.[13] 'Hypotension' was defined as a mean arterial BP below the estimated gestational age $+5$, which may be a more inclusive definition than is used in many neonatal intensive care units. Although it is desirable to have normal-range BPs, the reader cannot distinguish the effects of BP *per se* from those of vasopressor use on autoregulatory capacity. Additionally, had the authors had a more relaxed attitude toward the treatment of hypotension, we may have gathered more information about the ability to autoregulate at mean arterial BPs in the 25–30 mm Hg range. As babies in the study spent a total of only $\sim$5% of the time at a mean BP below 30 mm Hg, we need to be cautious about making firm conclusions about the ability (or lack of ability) to autoregulate at the low BPs. It should be noted that in one of the largest studies of newborn autoregulatory capacity, in which 88 very low birth weight newborns were monitored over the first 5 days of life, the frequency of vasopressor use was similar (89%)[8] to that in the current paper. O'Leary *et al*. found a strong correlation between pressure passivity and IVH. The role that vasopressor use plays in the pathogenesis of IVH is uncertain, and one cannot tell from either of these papers whether vasopressors stabilize or impair cerebral autoregulation. It is of interest that the institutions providing us with data on cerebral autoregulation in preterm infant have a bias toward aggressive treatment of hypotension, perhaps related to an awareness of the effects of hypotension on cerebral autoregulation.

Finally, the authors give very little information on the etiology of the hypotension, and how this might relate to the impairment in autoregulation. Chorioamnionitis is associated with lower BPs and higher inflammatory mediators among newborn very low birth weight infants.[14,15] Newborn cardiac function is altered[14] and cerebral blood flow velocity may be lower in the presence of inflammation.[16] Furthermore, cerebral oxygen delivery is altered in the presence of chorioamnionitis.[17] It would be intriguing if those infants who were born following chorioamnionitis were more likely to have impaired autoregulation at 'normal' BPs.

In summary, Gilmore *et al*. highlight that autoregulatory capacity varies from individual to individual and cannot be predicted by gestational age or BP (with the caveat that it is more likely to be intact at higher BPs). There are accumulating data that low BP is associated with both ischemic and hemorrhagic brain injury among premature infants. What remains uncertain is whether it is the hypotension, *per se*, or the treatment of hypotension that can be implicated in this injury. Additionally, it is unclear what level of BP is detrimental, and what treatment of hypotension is optimal. The importance of defining the lower boundary for loss of autoregulation is that treatment of hypotension can be directed to that level of BP that results in impaired cerebral perfusion in the large majority of infants. Cerebral monitoring, as by Gilmore *et al*., will someday allow for an individual patient-directed therapeutic approach to the treatment of hypotension, targeting specific infants with impaired autoregulation and not all infants whose BP mean sits below some pre-specified number. Gilmore *et al*. describe their study as a pilot study: further work from this group may help elucidate the mechanistic interactions between these physiological factors in our critically ill very low birth weight infants.

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