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EDITORIAL

Diagnosis and treatment of the hypotensive very low birth weight infant during postnatal transition

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The vast majority of near-term and term infants successfully complete the postnatal transition from fetal to postnatal circulation. However, due to the immaturity of the cardiovascular system, very low birth weight (VLBW) neonates often have a period of systemic hypoperfusion during the first postnatal hours. The associated tissue ischemia and subsequent reperfusion result in an increased likelihood of central nervous system injury such as peri- and intraventricular hemorrhage (PIVH) and/or periventricular leukomalacia (PVL). As normal arterial pressure guarantees normal cerebral blood flow, at least in the mature cardiovascular system, neonatologists attempt to maintain arterial pressure in the perceived 'normal' range in VLBW neonates in the immediate postnatal period. However, this strategy hinges on the unproven assumption that the statistically defined normative arterial pressure range ensures normal cerebral perfusion in the $\leqslant$3-day-old VLBW neonate to the same extent as it does during later life. In addition, we do not know whether the treatment aimed at improving systemic arterial pressure results in improvements in mortality and morbidity in this patient population. Thus, the practicing neonatologist is left without much guidance as to how to diagnose and treat cardiovascular compromise in VLBW infants during the immediate transitional period.

This uncertainty in clinical practice is reflected by the findings of the study by Dempsey and Barrington[1] published in this issue of the Journal. Using a questionnaire, the authors obtained information from 95 neonatologists in Canada on their diagnostic and treatment approach to hypotension in VLBW neonates during the first 3 postnatal days. They found that around one-fourth of the neonatologists rely solely on statistically defined normative arterial pressure values to diagnose and treat hypotension while the rest use both arterial pressure and indirect clinical measures of tissue perfusion in their decision-making process. As for the treatment of hypotension in the $\leqslant$3-day-old VLBW neonate, three prevailing approaches exist. These regimes employ volume administration and dopamine, followed either by hydrocortisone, dobutamine or epinephrine if hypotension persists after dopamine administration. One reassuring finding of this study is that bicarbonate seems to be used infrequently. As the cause of lactic acidosis in patients with systemic hypotension is poor tissue perfusion and as bicarbonate administration has been shown to be detrimental or without any benefit in animal or human studies, correction of the underlying cardiovascular disturbance rather than that of the extracellular pH is the more appropriate approach. The authors conclude that the variation in the approach to diagnosis and treatment of hypotension in the $\leqslant$3-day-old VLBW neonate is a consequence of the little information available on the normal arterial pressure range in this patient population and the lack of an understanding of the pathophysiology of transitional hemodynamics. Finally, they point out that there is absolutely no evidence in favor of the use of any particular approach to circulatory support in the VLBW infant during the transitional period and that prospective studies evaluating the impact of different treatment approaches on mortality and long-term outcome are urgently needed.

So, to address the issues raised by the authors, lets begin by discussing their first question, that is what is the normal arterial pressure range in this patient population. In general, two approaches have been used to determining the normal arterial pressure range in VLBW neonates. One approach involves demonstrating an association between a 'threshold' arterial pressure and mortality and medium- and long-term morbidity. However, the studies employing this approach have been retrospective and used different 'threshold' arterial pressure values to define hypotension. For example, hypotension has been alternatively defined as a mean arterial pressure of $\leqslant$30 mm Hg,[2] a mean arterial pressure less than the 5th to 10th percentile of the gestational- and postnatal-age-dependent arterial pressure norms,[3,4] or by the 'need' for vasopressor/inotrope support.[5]

Another approach to defining hypotension in VLBW neonates relies on assessing the changes in cerebral function and/or perfusion at different arterial pressure values.[6–9] A recent study has demonstrated that changes in brain electrical activity occur when mean arterial pressure drops below 24 mm Hg in the $<$4-day-old VLBW neonate.[6] However, the findings on the relationship between cerebral perfusion and arterial pressure are contradictory, as some studies found an association between low arterial pressure and cerebral hypoperfusion[6–8] while others did not.[9] Thus, the lower limit of normal arterial pressure in the 1-day-old immature neonate remains to be determined. Finally, most studies agree that arterial pressure rapidly rises after the first 6 to 12 h and, in the vast majority of VLBW neonates, it is higher than 30 mm Hg by the third postnatal day.[10] However, it remains to be determined whether arterial pressure $\geqslant$30 mm Hg in the more that 3-day-old

VLBW neonate without a patent ductus arteriosus guarantees normal cerebral blood flow and autoregulation.

The next questions brought up by the study of Dempsey and Barrington are

> whether our knowledge of the transitional circulation of the VLBW neonate is well founded and whether a better understanding could help us design the prospective studies needed to develop an evidence-based treatment of neonatal hypotension during the first postnatal days.

Regarding our understanding of the transitional circulation, we now have evidence that the pulmonary vascular resistance drops rapidly immediately following delivery and that this process may be facilitated by surfactant administration in the VLBW neonate.[11] Thus, as long as the fetal channels are open, left-to-right shunting will dominate even the early circulatory pattern of the VLBW infant and potentially result in pulmonary overcirculation and an inability to accurately assess systemic perfusion by measuring left cardiac output. To circumvent this problem, a series of recent studies used superior vena cava (SVC) flow[12–14] and near infrared spectroscopy[6,7,15–17] to assess systemic perfusion and cerebral blood flow and oxygenation, respectively. The findings of these studies have shed light on the complexity of the transitional circulation and the impact of the initial systemic hypoperfusion on mortality and morbidity in the VLBW neonatal patient population.

Many of the neonates with low systemic flow have arterial pressures in the suspected hypotensive range and thus by definition are in uncompensated shock. However, an especially worrisome finding of the studies using SVC flow measurements is that a number of $\leqslant$1-day-old VLBW neonates with abnormally low systemic (brain) blood flow have arterial pressures in the perceived normal range, that is mean arterial pressures higher than their gestational age in weeks.[12–14] If we accept that the lower limits of normal arterial pressure range is correctly defined by these normative values, the observation that brain blood flow is decreased while arterial pressure is in the 'normal range' raises questions about whether the very principles of cardiovascular physiology apply to the VLBW patient population during the transitional period. As mentioned earlier, according to these principles, arterial pressure in the normal range should guarantee normal brain blood flow. Even as the cardiovascular status deteriorates, arterial pressure is initially maintained within the normal range to ensure normal vital organ (brain, heart, adrenal glands) perfusion ('compensated shock'). An explanation for the observed dissociation of normal arterial pressure from normal vital organ (brain) blood flow is that the vascular bed of the cerebral cortex of the very preterm neonate does not function as a high-priority vascular bed of a vital organ and responds to decreases in perfusion pressure with vasoconstriction rather than vasodilation.[12–15] According to this hypothesis, as the immature myocardium fails to immediately adapt to the increased systemic vascular resistance and tissue oxygen demand upon delivery, perfusion pressure and blood flow to the organs 'vital' at this level of immaturity (heart and adrenal glands and probably the cerebral medulla) are maintained by vasoconstriction in the nonvital organs, including the cerebral cortex.[15,18,19] As the cardiovascular status adapts beyond the first 6 to 12 postnatal hours, blood flow to nonvital organs also improves. However, the cerebral cortex, a vital organ later in life, may not be able to tolerate the hypoperfusion–reperfusion cycle as well as a 'true' nonvital organ (muscle, skin, kidneys, liver, etc) and irreversible injury such as PIVH may occur.[13]

Although the above description of the physiology of the transitional circulation is simplified and relies too heavily on indirect evidence, one can understand Dempsey and Barrington's argument[1] that the lack of a solid understanding of the physiology of neonatal cardiovascular transition is in part to blame for the enormous variation in the treatment approach and medication dosing found among the participating Canadian neonatologists. Although we have little evidence, we would suggest that there is at least as much confusion and variability among neonatologists in the US in their approach to the diagnosis and treatment of circulatory compromise in the VLBW neonate during the transitional period.

The third, and most important, point made by the authors is that

> there is no evidence that treatment aimed at improving systemic arterial pressure results in any improvement in clinically important outcomes.

Indeed, while there is some information (described earlier) on the physiology of cardiovascular adaptation, there is a complete lack of evidence from prospective, randomized, appropriately designed and powered clinical trials that hypotension itself and/or its treatment affect clinically important outcome measures such as mortality and long-term neurodevelopmental outcome. As long as such data are not available, the neonatologist is left pondering whether or not to treat the given VLBW neonate presenting with (perceived or true) cardiovascular compromise, whether the medications used for the treatment do more harm than good and whether the achieved cardiovascular response to the treatment is indeed beneficial. However, it is important to note that once postnatal transition is complete and the fetal channels have closed, the principles of cardiovascular physiology describing the close association between normal arterial pressure and vital organ perfusion are likely to apply to the VLBW neonate and the diagnosis and treatment of their cardiovascular compromise may then be less confusing. As mentioned earlier though, prospective data are lacking to substantiate even this last notion.

In summary, the issues raised by Dempsey and Barrington are a reminder that we need to approach the critical questions in perinatal–neonatal medicine in general, and in neonatal

hemodynamics in particular, in a different way than we have performed over the history of our specialty.

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