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REVIEW

Definition of hypotension and assessment of hemodynamics in the preterm neonate

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The complexity of postnatal cardiovascular transition has only recently been better appreciated in the very low birth weight neonate. As blood pressure in itself poorly represents systemic blood flow, especially when the fetal channels are open and the developmentally regulated vital organ assignment may not have been completed, efforts to measure systemic blood flow have resulted in a novel, yet incomplete, understanding of the principles and clinical relevance of cardiovascular adaptation during postnatal transition in this patient population. This article describes the definition of hypotension based on the principles of cardiovascular physiology, and reviews the tools available to the clinician and researcher at the bedside to examine the complex relationship among blood pressure, systemic and organ blood flow, and tissue oxygen delivery and oxygen demand in vital and non-vital organs in the very low birth weight neonate. Only after gaining an insight into these complex relationships and processes will we be able to design clinical trials of selected treatment modalities targeting relevant patient sub-populations for the management of neonatal cardiovascular compromise. Only clinical trials based on a solid understanding of developmental cardiovascular physiology tailored to the appropriate patient sub-population hold the promise of being effective and practical, and can lead to improvements in both hemodynamic parameters and clinically relevant outcome measures.

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Introduction

The establishment of normal blood pressure ranges specific to gestational and postnatal age has remained an elusive goal.[1] In preterm infants, the complex physiology of the postnatal transition and the inherent immaturity of the cardiopulmonary and other organ systems present the most important challenge of establishing normative values, as continuous blood pressure monitoring in itself is insufficient to identify abnormal organ blood flow and tissue oxygen delivery in this patient population.[2] Furthermore, although there is an abundance of evidence showing improvement in blood pressure and other cardiovascular parameters, such as cardiac output, cerebral and non-vital organ blood flow and renal function, when 'hypotension' is treated during postnatal transition,[3–10] there are no data showing that treatment results in improvements in long-term outcome.

To adequately address the complex issue of cardiopulmonary compromise in the premature infant during the transitional period, hypotension can only be defined if continuous monitoring of essential hemodynamic parameters is carried out so that the underlying cardiovascular physiological processes can finally be determined. Without understanding the underlying cardiovascular principles of neonatal transition, appropriate interventional trials cannot be designed. Therefore, more comprehensive monitoring systems and new technologies for the assessment of organ blood flow and tissue oxygenation must be used and explored, respectively, before specific interventions addressing the underlying hemodynamic processes are designed and trialed. Only after this has been accomplished will the interventional clinical trials have a chance to guide our clinical practice away from the anecdotal and experience-based methods that are currently being used. Obviously, these trials must also be designed to investigate the impact of the interventions on clinically relevant outcome measures, including long-term neurodevelopmental outcome.

Definition of hypotension

Hypotension is defined in clinical trials and in practice as any value that falls below the fifth or tenth percentile for gestational and postnatal age. These percentiles are defined by population-based normative blood pressure values. By this definition, hypotension occurs in approximately 50% of very low birth weight infants admitted to the intensive care unit. As discussed elsewhere in detail,[11] three levels of cerebral blood flow (CBF) compromise may also be used to define hypotension (Figure 1). However, as this

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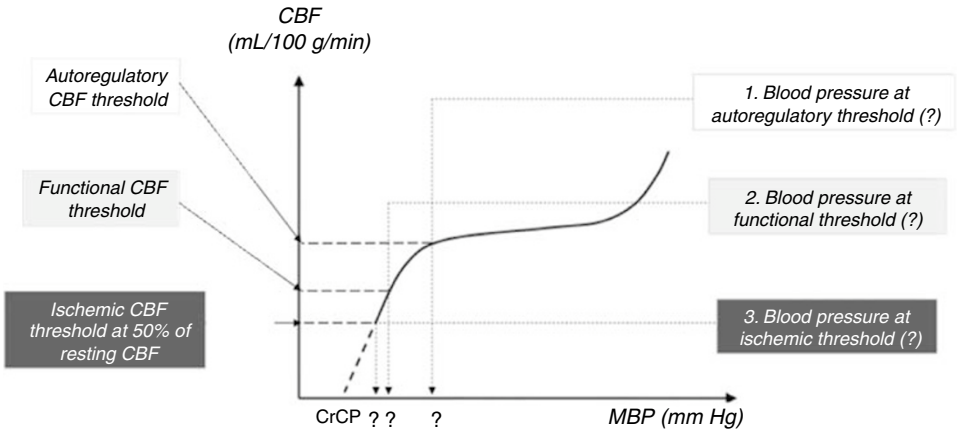

Figure 1 Definition of hypotension by three pathophysiological phenomena of increasing severity: the 'autoregulatory, functional and ischemic thresholds' of hypotension. See text for details. From McLean *et al*.[11] CBF, cerebral blood flow; MBP, mean blood pressure. CrCP, critical closing pressure.

definition is based on data extrapolated from studies in both human neonates and animal models, it cannot provide a guideline for intervention at a specific blood pressure 'threshold'. In other words, clinicians cannot infer that morbidity and mortality will improve if hypotension by this definition is rigorously avoided. Furthermore, the absolute blood pressure values at which these thresholds occur are ill-defined and are likely to vary among individual patients and the underlying pathological processes. Thus, the information available apply to the clinical definition of hypotension[1] and to a selected group of neonates, such as very preterm infants,[12–19] and not to the physiological definition itself (Figure 1).[11]

If the physiological paradigm depicted in Figure 1 is used, as blood pressure falls first, CBF autoregulation is lost, then cerebral function becomes abnormal and finally tissue ischemia occurs. Yet, we do not know at what point intervention is merited. Using this model, the point at which cerebrovascular autoregulation is lost is the most widely accepted physiological definition of clinical hypotension.[20,21] Autoregulation, which controls the constriction and dilation of arteries in response to changes in transmural pressure, is limited in preterm neonates.[21] This immaturity results in a narrow blood pressure range over which autoregulation can occur, and therefore small fluctuations around the mean are more likely to cross the lower autoregulatory threshold. We do not know the mean arterial blood pressure value at which cerebrovascular autoregulation is lost in the preterm infant, although recent studies suggest that it may be as high as 28 to 30 mm Hg in even extremely low birth weight infants (Figure 2).[22] There is an association between the loss of autoregulation, the resultant CBF fluctuations, and morbidity and mortality in preterm infants.[12,16,21] However, according to the physiological model (Figure 1), cerebral cellular function and structural integrity are not affected at the autoregulatory threshold, and association does not imply causation. Indeed, loss of autoregulation as a cause of increased morbidity and mortality in preterm neonates has yet to be scientifically proven.[11] In fact, when the autoregulatory threshold is breached, it is likely that increases in cerebral fractional oxygen extraction,[23] microvascular dilation and a shift of the hemoglobin–oxygen dissociation curve to the left will maintain tissue oxygen delivery to a certain point.[24] If the blood pressure continues to fall past that point, cerebral function will become compromised ('functional blood pressure threshold', Figure 1).[11] The mean blood pressure value at which this occurs in the very preterm infant is unknown but may be near 24 mm Hg during the initial postnatal days.[23–25] Finally, if blood pressure continues to fall, structural integrity of the brain tissue will eventually be compromised ('ischemic blood pressure threshold', Figure 1).[11] In animal models, the ischemic blood pressure threshold is reached when the corresponding CBF is approximately 50% of the resting CBF.[21] The 'ischemic blood pressure threshold' is unknown in preterm neonates and is likely to vary with the level of maturity, intercurrent or pre-existing pathophysiological conditions and physiological variables such as pH, $PaCO_2$ and PaO_2.[11]

Assessment of neonatal hemodynamics during postnatal transition

As mentioned earlier, the significant inter-individual variability in the measures of cardiovascular function, combined with the complex relationship among immaturity, postnatal transitional changes and coexisting pathological processes such as respiratory distress syndrome, sepsis or intracranial hemorrhage, makes it nearly impossible to accurately define a 'normal' blood pressure range in preterm neonates. However, this problem is not unique to neonatal hemodynamics. For example, an attempt has been made to define 'operational thresholds' rather than a 'normal range' in neonatal blood glucose monitoring.[26] In blood pressure monitoring, the operational threshold is the value (diastolic, systolic or mean) at which the clinician should consider intervention. Ideally, this threshold value is based on the best

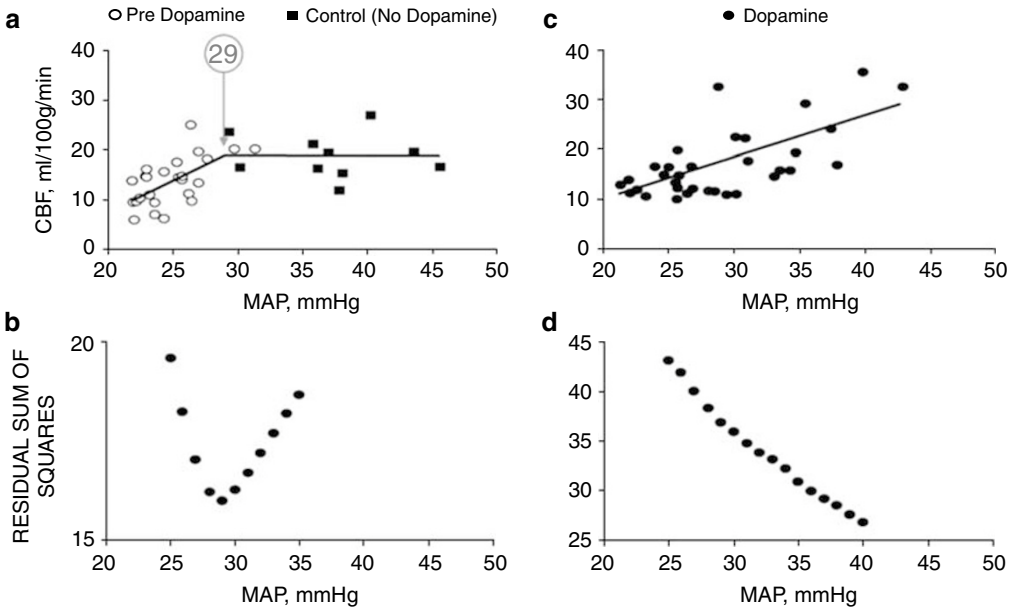

Figure 2 Relationship between cerebral blood flow (CBF) and mean arterial pressure (MAP) in hypotensive and normotensive extremely low birth weight (ELBW) neonates during the first postnatal day and the effect of dopamine on this relationship. (**a**, **b**) MAP (mm Hg) and CBF (ml per 100 g per min) measured by near-infrared spectroscopy (NIRS) in normotensive ELBW neonates not requiring dopamine (Control, closed squares; $n = 5$) and hypotensive ELBW neonates before dopamine administration (Pre-dopamine, open circles; $n = 12$). The lower threshold of the CBF autoregulatory blood pressure limit (29 mm Hg; (**a**)) is identified as the minimum of residual sum of squares of the bilinear regression analysis (**b**). (**c**, **d**) MAP (mm Hg) and CBF (ml per 100 g per min) in the formerly hypotensive ELBW neonates after dopamine treatment (closed circles). No breakpoint is evident in the CBF–MAP curve in ELBW neonates on dopamine (**c**), because there is no minimum identified by the bilinear regression analysis (**d**). From Munro MJ *et al.*[22]

evidence available in the literature and linked to improvements in organ perfusion and oxygen delivery, as well as to relevant clinical outcome measures. Not only is this threshold likely to be unique to each individual, but it will also vary with the degree of physiological maturity and the presence of any coexisting pathology. With these rigorous requirements, identifying a single blood pressure value to define an operational threshold for hypotension in preterm infants is essentially impossible. Therefore, rather than monitoring a single variable, such as systemic blood pressure, any effective hemodynamic monitoring system will need to include simultaneous assessment of blood pressure, systemic blood flow and its distribution to the different organs and regional tissue oxygenation in each patient. Only with a comprehensive approach will we be able to identify inadequate end-organ oxygen delivery and effectively treat it in the individual patient. Recent advances in near infrared spectroscopy combined with the use of functional echocardiography, continuous blood pressure monitoring and periodic assessments of indirect signs of tissue perfusion may finally enable us to obtain pertinent information regarding the elusive hemodynamic changes of postnatal transition and neonatal hemodynamic compromise.

Traditional monitoring of neonatal hemodynamics

Until recently, hemodynamic assessment was restricted to continuous heart rate, blood pressure and oxygen saturation monitoring, and to intermittent evaluation of indirect clinical and laboratory indices of perfusion, such as urine output, capillary refill time, acid-base balance and serum lactate levels. Although the information obtained from these monitoring practices is useful, it is nonspecific and non-sensitive.[2] Furthermore, it has resulted in the evolution of experience-based management of neonatal cardiovascular compromise that has little foundation in proven benefit, specifically in improved long-term outcome.

Functional echocardiography

Echocardiography in neonatology has expanded beyond its traditional application as a screening tool for structural heart disease to include intermittent assessment of systemic and organ-specific perfusion.[27] The use of functional echocardiography in recent prospective clinical trials has contributed to our better understanding of the hemodynamic changes associated with postnatal transition.[28–30] Although there is no evidence that its use is associated with better outcomes, it provides a more accurate assessment of the pathophysiology of cardiovascular compromise and is likely to become an essential part of the hemodynamic evaluation of preterm infants.[27]

Novel technologies

Techniques as diverse as electrical cardiometry (unpublished data) laser technology[31] and side-stream dark-field imaging[32] have been used in recent research studies to assess systemic and microcirculation, respectively in preterm neonates during transition. The clinical

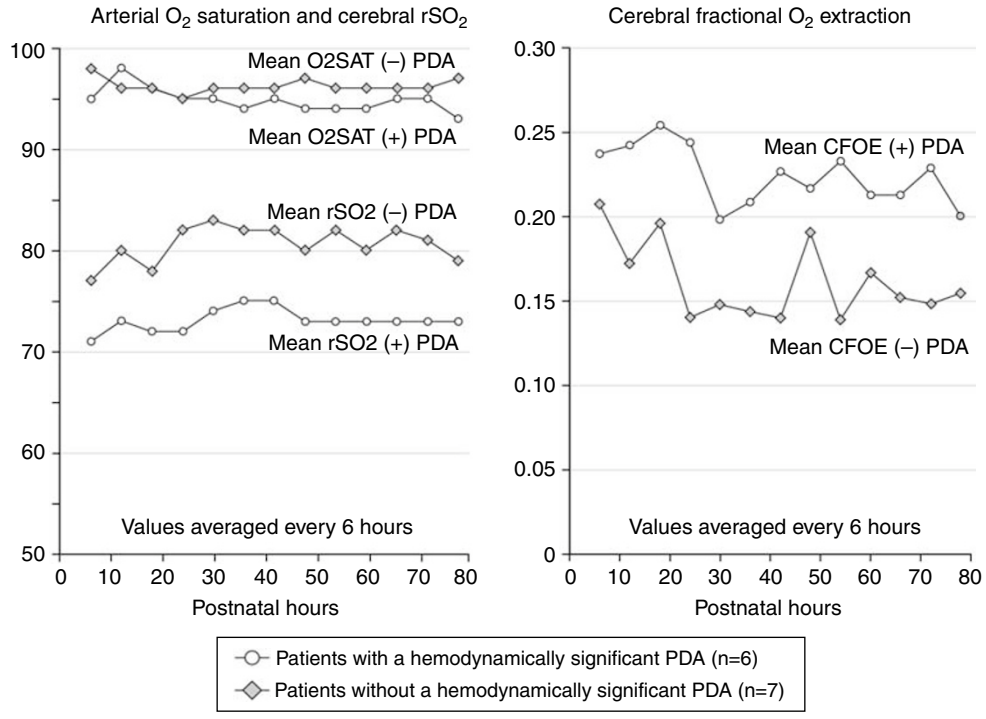

Figure 3 Our preliminary data on arterial oxygen saturation (O_2SAT; %), cerebral (C) regional tissue oxygen saturation (rSO_2, %) and cerebral fractional oxygen extraction (CFOE) in preterm neonates without (gestational age = 30 ± 2 weeks; birth weight 1318 ± 424 g; $n = 7$) and with (gestational age = 28 ± 1 weeks; birth weight 1099 ± 235 g; $n = 6$) a hemodynamically significant patent ductus arteriosus (PDA) during the first 4 postnatal days. rSO_2 was continuously monitored by near-infrared spectroscopy (NIRS) (INVOS 5100C, Somanetics Corp., Troy, MI, USA) and the values shown represent the average rSO_2 during 30 min before and 30 min after the individual time point. O_2SAT was extracted from patient records. CFOE was calculated as the difference between O_2SAT and rSO_2 for the given time point. Hemodynamic significance of the PDA was defined by echocardiographic and clinical criteria. rSO_2C and CFOE were higher and lower, respectively, in preterm neonates without a hemodynamically significant PDA compared with those with a hemodynamically significant PDA from the first hours after birth. These preliminary findings suggest that patients developing a hemodynamically significant PDA have decreased rSO_2, and thus diminished cerebral perfusion and oxygen delivery even a few hours after being born and that they compensate for the decrease in cerebral tissue oxygen delivery by increased oxygen extraction.[24] Similar findings have been reported recently.[36]

applicability of these techniques remains to be seen. Near infrared spectroscopy, on the other hand, has been applied successfully to monitor cerebral oxygen delivery and utilization,[33] as well as regional oxygen saturation in the brain and other organs.[34] Continuous, transcutaneous measurement of regional tissue saturation has an excellent correlation with central venous saturation.[35] Using this near-infrared spectroscopy technology to non-invasively and continuously monitor vital (brain) and non-vital (renal, mesenteric, muscle) organ oxygen saturation in absolute numbers at the tissue level, we can gain novel insights into the hemodynamic changes that occur during the transitional period and beyond (Figure 3).[33]

Cerebral function monitoring using amplitude-integrated EEG is gaining broader use as a part of continuous bedside assessment. In both preterm and term neonates, it can be used to assess the impact of different pathological processes and interventions on acute brain function, and ultimately on outcome.[37]

A combined approach

In the future, functional echocardiography and perhaps electrical cardiometry, near-infrared spectroscopy and cerebral function monitoring, in combination with traditional monitoring techniques and targeted intermittent clinical assessment of tissue perfusion, will be essential parts of a comprehensive bedside monitoring approach. Together, they will likely enable us to accurately identify hypotension and/or its operational thresholds in the individual patient, and to better understand the complex hemodynamic principles of postnatal adaptation and hemodynamic compromise. An improved understanding of what represents a physiological state vs a pathophysiological state will then allow us to design meaningful clinical trials. If these trials are appropriately designed and powered, and if they are able to incorporate comprehensive monitoring techniques and relevant outcome measures, they will likely lead to the development of more effective treatment modalities for neonatal cardiovascular compromise. In place of the wide range of 'experience-based' approaches currently used, there will arise a cohesive scientific approach based on the principles of developmental cardiovascular physiology and on clinically relevant long-term outcomes.

Disclosure

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