CHAPTER 2

Cerebral Circulation and Hypotension in the Premature Infant: Diagnosis and Treatment

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- Pathogenesis and Diagnosis of Pathologic Cerebral Blood Flow
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As the field of neonatology has progressed over the last few decades, better monitoring and more effective interventions have been developed for supporting the respiratory, fluid and electrolyte, and nutritional abnormalities frequently encountered in very low-birth-weight (VLBW) infants. However, the ability to effectively and continuously monitor the hemodynamic changes at the level of systemic and organ blood flow and tissue perfusion remains very limited despite the advances achieved with the use of targeted neonatal echocardiography and other bedside organ and tissue perfusion monitoring modalities, such as electrical impedance velocimetry, near-infrared spectroscopy (NIRS), visible light spectroscopy, and laser Doppler technology as well as the use of amplitude-integrated EEG (aEEG) to follow changes in brain activity. With the improvements in hemodynamic monitoring and a better understanding of the principles of developmental cardiovascular physiology has come the realization of how little is actually known about circulatory compromise and its effect on organs, especially brain, blood flow, blood flow–metabolism coupling, and long-term outcomes. Although we can continuously and reliably monitor systemic blood pressure and there are myriad interventions for "normalizing" it, blood pressure is the only dependent component among the hemodynamic parameters regulating tissue perfusion and is determined by changes in the two independent variables, cardiac output and systemic vascular resistance (SVR). Accordingly, in addition to monitoring and maintaining perfusion pressure (blood pressure), the goal is to preserve normal systemic and organ blood flow and tissue oxygenation especially to the vital organs—that is, the brain, heart, and adrenals. In this regard, when it comes to the brain, medicine is at an even greater disadvantage. For instance, measuring cerebral blood flow (CBF) is more complex than measuring systemic blood flow (left ventricular output), although continuous assessment of cardiac output in neonates at the bedside has remained a significant challenge. In addition, even assessment of systemic blood flow becomes very complicated when shunting through the fetal channels (ductus arteriosus and foramen ovale) occurs during the first few postnatal days in the VLBW neonate. Also, clinical evidence of ischemia cannot be detected in the brain as easily as in other organs—for example, the heart, liver, and kidneys. Seizures are a clear sign of a pathologic process, but they can be difficult to recognize in the VLBW population, although the use of aEEG might be helpful. In addition, by the time seizures are present, irreversible injury may have already occurred. Most importantly, the clinician faces the formidable task of effectively supporting and protecting the enormously complex developmental processes that are occurring in the brain of a VLBW infant during the postnatal transitional

period and beyond. Yet detection of changes in CBF and cerebral function in a timely manner is difficult, and the understanding of how to manage the hemodynamic disturbances that affect CBF, flow-metabolism coupling, brain function, and structure and, ultimately, neurodevelopmental outcome, is limited.

The intent of this chapter is to review the available information on the definition of systemic hypotension and the pathogenesis, diagnosis, and treatment of early cerebral perfusion abnormalities in the VLBW infant that have been shown to precede intracranial hemorrhage and periventricular white matter injury (PWMI). Because CBF, flow-metabolism coupling, and cerebral oxygenation in this population are such a complex topic, we focus our discussion on the first postnatal days, during which the cardiorespiratory transition from fetal to extrauterine life occurs. We discuss some of the modalities that are being explored for identifying changes in CBF and cerebral oxygenation at the bedside. Once a pathologic process is identified, provision of a coherent, safe, and effective means of treating that process is crucial. We present a rational treatment for the pathologic processes underlying clinically evident brain injury in the VLBW infant based on the most up-to-date monitoring and clinical evidence available. Unfortunately, only a little evidence exists with regard to the appropriateness and effectiveness of the current approaches to treatment of neonatal hypotension and cardiovascular compromise. In an area as controversial and complex as this one, it is important to always highlight what is not known. Our goal is to provide the practitioner with recommendations for diagnosis and treatment that should be considered guidelines only. Finally, although the understanding of both normal and pathologic processes in the preterm brain is improving, evidence for a definitive clinical approach remains scant.

Definition of Hypotension

Hypotension, defined by population-based normative data, occurs in up to 50% of VLBW infants admitted to the neonatal intensive care unit. Hypotension in the immediate postnatal period is thought by many to be one of the major factors contributing to central nervous system injury, eventual cerebral palsy, and poor long-term neurologic outcome in VLBW neonates. Indeed, the *association* between hypotension and brain injury and poor neurodevelopmental outcome is well documented[1-8] and forms the basis of therapeutic efforts to normalize blood pressure. However, *causation* has never been demonstrated between hypotension and poor neurodevelopment. In other words, one cannot infer that long-term neurodevelopmental outcomes will improve if hypotension is rigorously avoided.

In addition, retrospective studies have raised concerns by finding an association between treated hypotension and poor neurodevelopmental outcomes.[9,10] However, it remains unclear whether hypotension, its treatment, or both were responsible for the documented association. Indeed, a follow-up study[11] to the original randomized prospective trial[12] comparing the effectiveness of dopamine and epinephrine in increasing blood pressure and CBF in hypotensive VLBW neonates during the first postnatal day found that neonates who responded to dopamine or epinephrine had long-term neurodevelopment outcomes comparable to those of age-matched normotensive controls, and that patients who did not respond to vasopressor-inotrope treatment had worse long-term outcome. These findings suggest that treatment of neonatal hypotension, when carefully titrated, may actually be effective and not harmful. However, because the primary outcome measure of the original study[12] was not long-term neurodevelopmental outcome, the follow-up study[11] may have not been appropriately powered to put this concern definitely to rest. Finally, results of a recent study support the notion that the careful treatment of neonatal hypotension might not be harmful as it found that low blood pressure in extremely preterm infants during the first 72 hours of postnatal life, regardless of treatment, was independently associated with poor neurodevelopmental outcome.[13]

In clinical practice, hypotension is usually defined as the blood pressure value below the 5th or 10th percentile for the gestational age– and postnatal age–dependent normative blood pressure values (Fig. 2-1).[14-16] However, there is no consensus

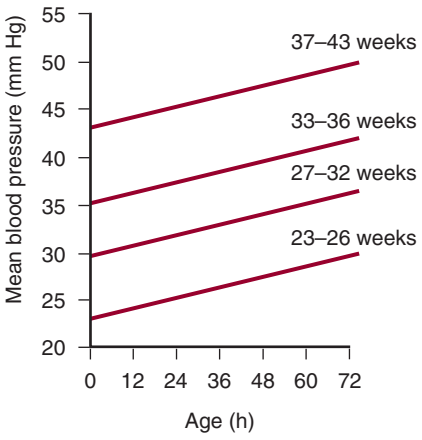

Figure 2-1 Gestational age– and postnatal age–dependent normogram for mean blood pressure values in preterm and term neonates during the first 3 postnatal days. The normogram is derived from continuous arterial blood pressure measurements obtained from 103 neonates with gestational ages between 23 and 43 weeks. Because each line represents the lower limit of 80% confidence interval of mean blood pressure for each gestational age group, 90% of infants for each gestational age group will have a mean blood pressure equal to or greater than the value indicated by the corresponding line (the lower limit of the confidence interval). (From Nuntnarumit P, Yang W, Bada-Ellzey HS. Blood pressure measurements in the newborn. *Clin Perinatol*. 1999 26:981-996.)

among neonatologists about the acceptable lower limit of systemic mean or systolic arterial blood pressure, and most units have different guidelines for the initiation of treatment of hypotension.

From a pathophysiologic standpoint, three levels of functional alterations of increasing severity can be used to guide the definition of hypotension on the basis of later findings in the literature (Fig. 2-2). However, it is important to keep in mind that no prospectively collected information is available on mortality and morbidity associated with these different blood pressure thresholds.

First, the mean blood pressure associated with the loss of CBF autoregulation is the generally accepted definition of hypotension (autoregulatory blood pressure threshold).[17] Indeed, there is considerable information in the literature indicating that CBF autoregulation is functional in normotensive but not in hypotensive VLBW neonates in the immediate postnatal period (Fig. 2-3).[5,18,19] Autoregulation is the ability of arteries to constrict or dilate in response to an increase or decrease, respectively, in the transmural pressure to maintain blood flow relatively constant within a range of arterial blood pressure changes (see Fig. 2-2). However, in the neonate, this response has a limited capacity. In addition, the autoregulatory blood pressure range is narrow in the neonatal patient population and the 50th percentile of the mean blood pressure is relatively close to the lower autoregulatory blood pressure threshold. In other words, small decreases in blood pressure may result in loss of CBF autoregulation, especially in the preterm infant.[18] Findings now suggest that the autoregulatory blood pressure threshold is around 28 to 30 mm Hg even in the extremely LBW (ELBW) neonate during the first postnatal day (Fig. 2-4).[18,19] At this blood pressure, however, cellular function and structural integrity are unlikely to be

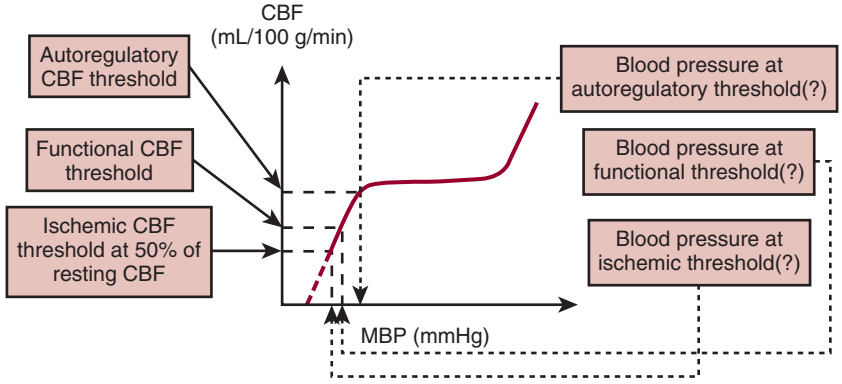

Figure 2-2 Definition of hypotension by three pathophysiologic phenomena of increasing severity: autoregulatory, functional, and ischemic thresholds of hypotension. *CBF*, Cerebral blood flow; *MBP*, mean blood pressure.

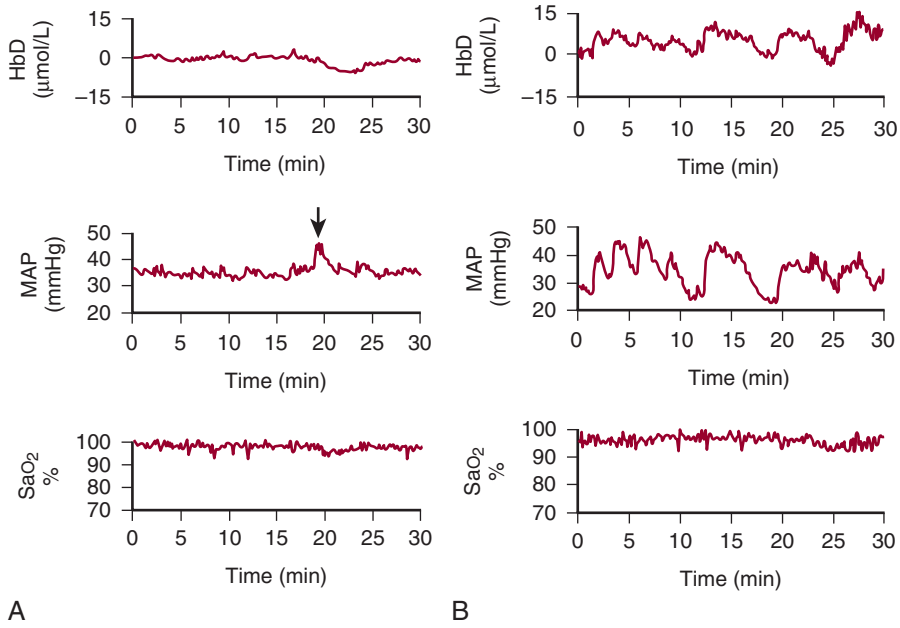

Figure 2-3 Intact and compromised cerebral blood flow (CBF) autoregulation in very low-birth-weight (VLBW) neonates in the immediate postnatal period. Changes in cerebral intravascular oxygenation (HbD = HbO_2 – Hb) correlate with changes in CBF. **A,** Changes in HbD (i.e., CBF), mean arterial pressure (MAP), and oxygen saturation (SaO_2) in a 1-day-old, 28-week gestational age (GA) preterm infant whose subsequent head ultrasound findings remained normal. No change occurs in CBF in relation to the sudden increase in MAP associated with endotracheal tube suctioning *(arrow)*. **B,** Changes in HbD (CBF), MAP, and SaO_2 in a 1-day-old 27-week GA preterm infant whose subsequent head ultrasound revealed the presence of periventricular white matter injury. Changes in blood pressure are clearly associated with changes in CBF. (From Tsuji M, Saul PJ, duPlessis A, et al. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. *Pediatrics.* 2000;106:625.)

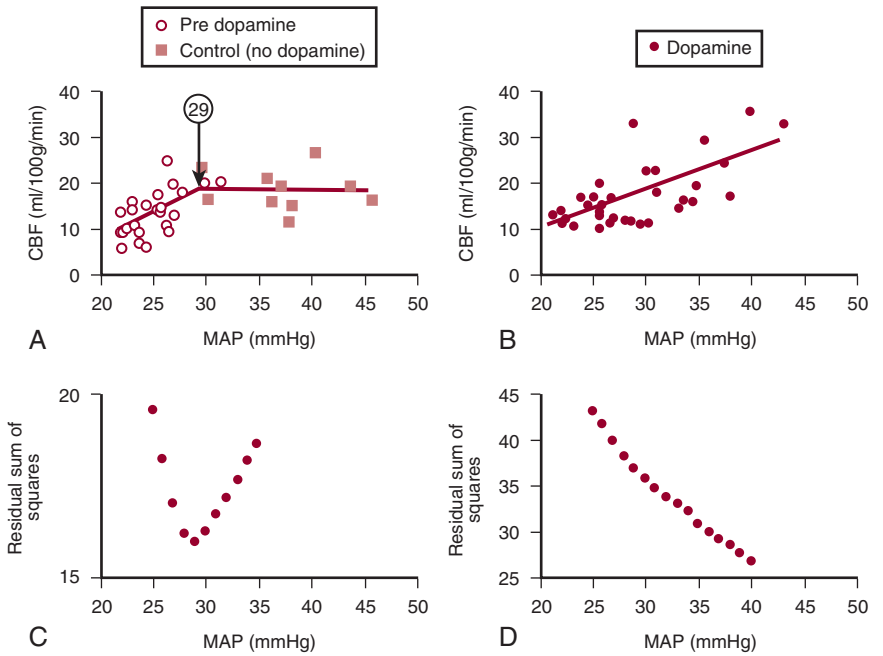

Figure 2-4 Relationship between cerebral blood flow (CBF) and mean arterial pressure (MAP) in hypotensive and normotensive extremely low-birth-weight (ELBW) neonates during the first postnatal day and the effect of dopamine on this relationship. **A** and **B,** MAP (mm Hg) and CBF (mL/100 g/min) measured by near-infrared spectroscopy (NIRS) in normotensive ELBW neonates not requiring dopamine (Control, *closed squares*; n = 5) and hypotensive ELBW neonates before dopamine administration (Predopamine, *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** and **D,** MAP (mm Hg) and CBF (mL/100 g/min) in the formerly hypotensive ELBW neonates after dopamine treatment (*filled circles*). No break point is evident in the CBF-MAP curve in ELBW neonates receiving dopamine **(C),** because no minimum is identified by the bilinear regression analysis **(D)**. (From Munro MJ, Walker AM, Barfield CP. Hypotensive extremely low birth weight infants have reduced cerebral blood flow. *Pediatrics.* 2004;114:1591.)

affected, because increased cerebral fractional oxygen extraction (CFOE), microvascular vasodilation, and a shift in the hemoglobin-oxygen dissociation curve to the left can maintain tissue oxygen delivery at levels appropriate to sustain cellular function and integrity.[20,21]

If blood pressure continues to fall, it reaches a value at which cerebral function becomes compromised (functional blood pressure threshold). Data from later reports suggest that the functional blood pressure threshold may be around 22 to 24 mm Hg in the VLBW neonate during the first postnatal days (Fig. 2-5).[21,22] However, caution is needed when interpreting these findings, which were obtained in a small number of preterm infants, because their clinical relevance is unclear. Furthermore, the relationship between cerebral electrical activity, neurodevelopmental outcome, and the threshold of CBF associated with impaired brain activity is not known.

Finally, if blood pressure decreases even further, it reaches a value at which structural integrity becomes compromised (ischemic blood pressure threshold). On the basis of findings in immature animals, it is assumed that the ischemic CBF threshold is around 50% of the resting CBF.[18] Although it is unclear what blood pressure value represents the ischemic CBF threshold in the VLBW neonate during the first postnatal day, it may be below 20 mm Hg (see Fig. 2-2).[23,24] It is important to emphasize that the situation is further complicated by the fact that these numbers represent moving targets for the individual patient. Indeed, other factors, such as $PaCO_2$ levels, the presence of acidosis, preexisting insults (asphyxia), and underlying pathophysiology (sepsis, anemia), have an impact on the critical blood pressure value at which perfusion pressure and cerebral oxygen delivery cannot satisfy cellular oxygen demand to sustain autoregulation, then cellular function, and finally structural integrity.

At present, continuous monitoring of blood pressure and assessment of indirect signs of tissue perfusion (urine output, capillary refill time, and lactic acidosis) remain the basis for identifying the presence of cardiovascular compromise. However,

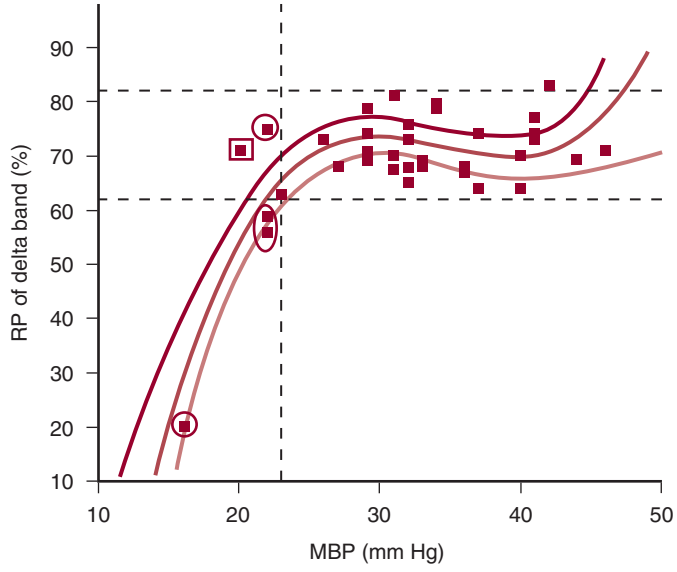

Figure 2-5 Relationship between mean blood pressure (MBP) and cerebral electrical activity in very low-birthweight neonates during the first 4 postnatal days. Shown is the relationship between MBP and the relative power (RP) of the delta band of the electroencephalogram, showing line of best fit with 95% confidence interval ($N = 35$; $R^2 = 0.627$; $P < 0.001$). *Horizontal dotted lines* represent the normal range of the relative power of the delta band (10th-90th percentile), whereas the *vertical dotted line* identifies the point of intercept. The *open square* identifies the infant with abnormal cerebral fractional oxygen extraction (CFOE), and the abnormal electroencephalogram records are *circled*. (From Victor S, Marson AG, Appleton RE, et al. Relationship between blood pressure, cerebral electrical activity, cerebral fractional oxygen extraction and peripheral blood flow in very low birth weight newborn infants. *Pediatr Res.* 2006;59:314-319.)

adequate blood pressure may not always guarantee adequate organ perfusion in VLBW neonates during the first postnatal day.[25] Indeed, blood pressure, the product of systemic blood flow and systemic vascular resistance, only weakly correlates with superior vena cava (SVC) flow in VLBW neonates during the immediate postnatal adaptation.[26] SVC flow has been used as a surrogate for systemic blood flow in the VLBW neonate during the immediate postnatal period, when shunting through the fetal channels prohibits the use of left ventricular output to assess systemic blood flow.[27] The finding that adequate blood pressure may not always guarantee adequate systemic blood flow in these patients may be explained at least in part by the notion that the cerebral vascular bed, especially of the 1-day-old ELBW neonate, may not be of high priority and thus it will constrict rather than dilate in response to a decrease in the perfusion pressure (discussed in detail later).[28-30]

Pathogenesis and Diagnosis of Pathologic Cerebral Blood Flow

Fluctuations in CBF are implicated in the pathogenesis of periventricular-intraventricular hemorrhage (P/IVH) and PWMI in the VLBW infant.[1,29,31,32] Both systemic and local (intracerebral) factors play a role in the pathogenesis of these central nervous system injuries and therefore are important in diagnosis. In addition, the level of maturity, postnatal age, and intercurrent clinical factors (e.g., infection/inflammation, vasopressor-resistant hypotension) need to be considered. In this section, we briefly discuss monitoring parameters that are currently in widespread clinical use (systemic arterial pressure and arterial blood gas sampling) and then delve into the emerging field of bedside monitoring of systemic and organ blood flow, especially CBF and brain activity. We review most of the existing technologies, including echocardiography and Doppler ultrasound, impedance electrical cardiometry (IEC), NIRS, and aEEG, and discuss the applicability and limitations of these modalities. We do not discuss the use of magnetic resonance imaging (MRI) for assessing CBF in the neonatal patient population, because this topic is addressed in Chapter 16.

A logical place to begin the discussion on monitoring CBF in the VLBW infant is to ask, "What is the normal CBF in the VLBW infant?" Several investigators have addressed this issue. It is clear from these studies that CBF is lower in preterm infants than in adults, corresponding to the lower metabolic rate of the preterm brain. Using xenon-133 clearance, Greisen[33] found that, in 42 preterm infants with a mean gestational age of 31 weeks, CBF was 15.5 ± 7.2 mL/100 g/min during the first postnatal week, a value three to four times lower than that in adults.[33] Interestingly, patients enrolled in this study who were receiving mechanical ventilation had lower CBF than their nonventilated counterparts and those receiving CPAP (11.8 ± 3.2 vs. 19.8 ± 5.3 and 21.3 ± 12 mL/100g/min, respectively). Cerebral blood flow in this study was not consistently affected by postnatal age, gestational age, birth weight, mode of delivery, $PaCO_2$, hemoglobin concentration, mean blood pressure, or phenobarbital therapy. In contrast, subsequent publications by the same group of authors investigating CBF reactivity in preterm infants during the first three postnatal days showed that, as expected, $PaCO_2$ and hemoglobin concentration significantly affect CBF in this patient population.[34-36]

Using positron emission tomography (PET) to measure CBF, Altman and colleagues[37] found lower values for CBF in preterm and term neonates compared to those obtained by the use of xenon-133 clearance.[37] More importantly, they reported that in a series of one term and five preterm infants with CBF between 4.9 and 10 mL/100g/min, the term neonate and three of the preterm infants had normal neurodevelopmental outcome at 24 months.[37] Therefore, the neurodevelopmentally safe lower limit of CBF in the neonate may be between 5 and 10 mL/100/min. Finally, because CBF is affected by many factors other than blood pressure, it is not possible to define the blood pressure value consistently associated with a decrease of CBF below this safe limit that results in ischemic brain injury.

Kluckow and Evans,[27] using SVC blood flow as a surrogate for systemic blood flow and CBF in well preterm neonates younger than 30 weeks of gestation who were receiving minimal ventilatory support, established normal values of SVC flow during the first 48 postnatal hours. Of note is that the extent to which SVC flow is representative of systemic or cerebral blood flow in preterm neonates during the first postnatal days is not known. In a subsequent study that included sick preterm infants younger than 30 weeks of gestation, the same group found that 38% of infants had a period of low SVC in the first 24 (mostly 12) postnatal hours.[25] The incidence of low SVC flow was significantly related to the level of immaturity and was more than 70% in very preterm neonates—that is, of gestational age less than 27 weeks. The sudden increase in the peripheral vascular resistance caused by the loss of the low-resistance placental circulation, the complex process of cardiorespiratory transition to the postnatal circulatory pattern, and myocardial and autonomic central nervous system immaturity have been proposed to contribute to these findings. Indeed, these factors may explain why many of these very preterm neonates struggle to maintain normal systemic blood flow during the first 12 to 24 postnatal hours. Importantly, a proportion of the very preterm babies with extremely low SVC flow were found to have systemic blood pressures in the normal range (i.e., equal to or greater than their gestational age in weeks), a finding supported by subsequent studies of this group of researchers.[26,38,39] Because normal blood pressure and decreased organ blood flow to nonvital organs are the hallmarks of the compensated phase of shock and because a portion of SVC flow represents blood returning from the brain, a vital organ, it is conceivable that the vascular beds of the cerebral cortex and white matter are low-priority vessels and function similar to those of nonvital organs in the very preterm neonate during the immediate postnatal period. This hypothesis, which is supported by earlier studies in different animal models[40,41] and observations in the human neonate,[28,29] may explain why SVC blood flow may be decreased in some very preterm neonates who have normal systemic blood pressure. Most babies with documented low SVC flow in the first 24 to 48 hours that do not go on to have P/IVH or PWMI are more mature (28 vs. 25-26 weeks of gestation). Thus, for preterm babies of less than 30 weeks of gestation, low systemic blood flow (and CBF) may be necessary but not sufficient to cause intracranial pathology. Importantly, all patients studied had an increase in SVC flow by 24 to 36 hours, and all P/IVHs occurred after the SVC flow had increased. Findings of a later prospective observational study by our group using echocardiography and NIRS confirm and expand these observations.[42] In this study, very preterm neonates who were presented with lower systemic blood flow and higher cerebral vascular resistance during the first 12 postnatal hours were at a higher risk for the development of P/IVH. Importantly, the bleeding occurred only after cardiac output and brain blood flow had increased. Taken together, these findings implicate an ischemia-reperfusion cycle in the pathogenesis of P/IVH in very preterm neonates during the immediate transitional period.

The methods used to assess systemic and cerebral blood flow in VLBW neonates in the immediate transitional period have significant limitations. When SVC flow is used to assess systemic and cerebral blood flow, measurements are operator-dependent owing to the uncertainties associated with the accurate measurement of vessel diameter and flow velocity. The fluctuations in vessel size during the cardiac cycle and the pattern of low flow velocity in the SVC are the major factors contributing to these technical difficulties. In addition, the shape of the SVC, the lack of data on the magnitude of the contribution of CBF to SVC flow, and the lack of a documented association between $PaCO_2$ and SVC flow in this patient population call for some caution in the interpretation of these findings.

Kehrer and associates[43] measured blood flow in both internal carotid and vertebral arteries and used the sum of the flow in the four arteries supplying the brain to assess the changes in CBF volume in preterm infants of 28 to 35 weeks of gestation over the first 2 postnatal weeks. Although the technique has significant limitations, the findings suggest that a steep rise in CBF occurs from the first to the second postnatal days and that this pattern is independent of gestational age. Thereafter,

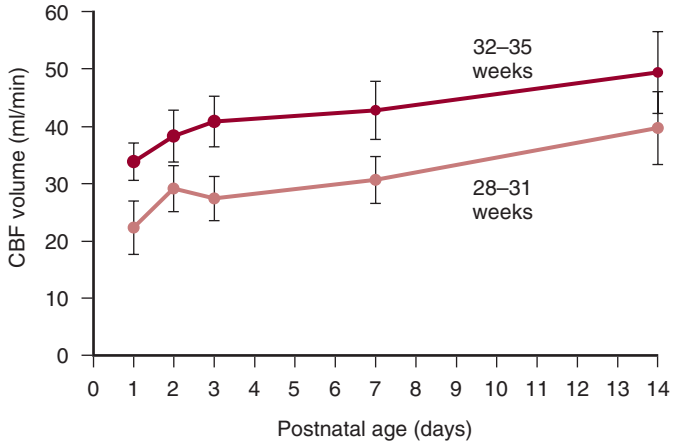

Figure 2-6 Changes in cerebral blood flow (CBF) volume in preterm neonates during the first 14 days after delivery. Shown is the development of CBF volume with increasing postnatal age in two different gestational age groups (28-31 and 32-35 weeks). The mean and 95% confidence interval are also shown (analysis of variance [ANOVA]; n = 29, $P < 0.0001$). (From Kehrer M, Blumenstock G, Ehehalt S, et al. Development of cerebral blood flow volume in preterm neonates during the first two weeks of life. *Pediatr Res.* 2005;58:927-930.)

CBF continues to rise gradually (Fig. 2-6). Because there is not a significant increase in brain weight during the first 48 postnatal hours, the investigators inferred that the observed increase in CBF during that period was secondary to increased cerebral perfusion per unit weight of tissue. On the other hand, the more gradual increase over the ensuing 2 weeks is likely due to a combination of both increased brain weight and increased perfusion.[43] The investigators studied only healthy preterm infants with normal brains, whereas the series of investigations by Evans, Kluckow, and their colleagues[25,26,38,39] included a group of preterm infants who were sicker and had a higher incidence of significant intracranial pathology. Nevertheless, the results of the two groups are complementary as they provide evidence for a decreased CBF in the first postnatal day, followed by a significant increase by the second postnatal day. It is tempting to speculate that the low CBF in the study by Kehrer and associates[43] during the first postnatal day represents a decrease from that in the fetus, but this might not be the case because findings of a later study suggest that a decrease in SVC flow and left cardiac output in very preterm neonates occurs by 12 hours of postnatal age and not immediately after birth.[44] Taken together, results of these studies suggest that low CBF in the first postnatal day and the ensuing reperfusion is a physiologic phenomenon occurring in most (if not all) very preterm neonates and that this phenomenon is a necessary but not sufficient cause of intracranial pathology (P/IVH or PWMI) in this patient population.

The ultimate goal is to improve neurodevelopmental outcome in preterm infants, and because low SVC flow in the early postnatal period has been implicated not only in the development of P/IVH and PWMI but also in impaired neurologic outcome at 3 years,[6] those infants most at risk in the immediate postnatal period must be identified. It is clear from the large number of epidemiologic and hemodynamic studies that the level of immaturity is one of the most important predisposing factors for the occurrence of more abrupt changes in CBF and the increased vulnerability during postnatal adaptation and for poor neurologic outcome. Therefore, assessment of CBF during the first 24 to 48 postnatal hours in the most immature and vulnerable patients is important. However, owing to the technical difficulties associated with reliable and continuous assessment of CBF, clinical practice currently relies on indirect measures for diagnosis of changes in cerebral perfusion. For instance, the notion that a pressure-passive cerebral circulation exists in most sick preterm neonates has led to the use of systemic blood pressure as the only surrogate measure for cerebral perfusion. However, in the compensated phase of shock, maintenance of normal systemic blood pressure is not the equivalent of adequate nonvital

organ blood flow, and the forebrain might not be a vital organ in the very preterm neonate immediately after delivery (see earlier). Therefore, the sole reliance on blood pressure in the assessment of CBF in this patient population during the first postnatal day may not be adequate.

In addition to blood pressure, monitoring of the indirect clinical indicators of tissue perfusion such as urine output, capillary refill time (CRT), and acid-base status are important. Although these indirect clinical indicators by themselves are fairly nonspecific for evaluating systemic flow, using CRT and blood pressure together results in greater sensitivity. Indeed, when blood pressure and CRT are less than 30 mm Hg and 3 seconds, respectively, the sensitivity for identifying low systemic blood flow is 86%.[45] In addition, avoidance of both hypocapnia and hypercapnia is of utmost importance because of the effect on CBF.

If the monitoring commonly used now in clinical practice at the bedside is not sufficient to tell the whole story on CBF, what can be added? Fortunately, most of the interest in organ blood flow monitoring has focused on the cerebral circulation. This interest has led to the development of a multitude of techniques for monitoring both CBF and systemic perfusion. The most frequently used techniques for CBF monitoring are Doppler ultrasound and NIRS, and aEEG has been used for monitoring cerebral function. The gold standard for monitoring systemic perfusion in the clinical practice is echocardiography, and novel approaches have recently also been developed, including IEC. We briefly discuss each of these modalities in the following sections with a primary focus on those that can be performed noninvasively at the bedside.

Doppler Ultrasound

Velocity of blood flow can be measured through the use of the Doppler principle, which states that the change in frequency of reflected sound is proportional to the velocity of the passing object (in this case, blood). The calculated velocity needs to be corrected for the angle between the vessel and the emitted sound beam (angle of insonation), and the straightforward idea is complicated by the fact that arterial blood is pulsatile and its speed varies within the vessel (i.e., it is faster in the center of the vessel). It is important to recognize that speed of blood (distance traveled per unit time) in a vessel means little by itself; we are really interested in the absolute blood flow (volume per unit time). Thus, volumetric measurements are crucial. Investigators have used several different volumetric indices, including SVC, internal carotid artery, and vertebral artery flow, as previously discussed.[27,43] The limitations of SVC flow measurements were discussed earlier. In general, major technical problems with volumetric measurements include but are not restricted to the small size of the vessels, the motion of vessel wall, and whether or not an angle of insonation of less than 20 degrees can be achieved. In addition to volumetric measurements of vessel blood flow, right ventricular and left ventricular outflow measurements have been studied. Both are fraught with pitfalls in the very preterm neonate in the immediate postnatal period, because the patent foramen ovale (PFO) and patent ductus arteriosus (PDA) create shunts that confound measurements of the right ventricular and left ventricular flows, respectively. It is believed that right ventricular output may be a more reliable indicator of systemic blood flow during the immediate postnatal period with the fetal channels open, because shunting by the patent foramen ovale is less significant than PDA shunting during the first 24 hours after delivery.[46] Indeed, right ventricular output and systemic blood pressure have been correlated with EEG parameters (brain function) in VLBW infants in the immediate postnatal period.[47]

Ultrasound techniques are noninvasive and widely accessible in the intensive care setting, and they can be done at the bedside. However, all ultrasound measurements depend on operator skill and have their significant limitations. As for the issues related to operator skills, centers utilizing these methods to diagnose pathologic CBF in neonates must have a rigorous quality control system in place with neonatologists well trained in functional echocardiography and available at the bedside at any time.[48]

With regard to the limitations to the use of vascular Doppler ultrasonography in assessing organ blood flow, the most important limitation is the small size of the artery of interest (e.g., middle or anterior cerebral artery), which precludes accurate measurement of its diameter. Because the estimation of blood flow (Q) depends on assessment of mean velocity of the blood (V) and the vessel diameter (D) ($Q = V [\pi D^2/4] \times 60$), any small error in measuring the diameter will translate into a significant error in estimating the actual blood flow. Therefore, instead of directly measuring blood flow, investigators often use changes in various Doppler-derived indices, such as mean blood flow velocity or the pulsatility or resistance index, as surrogates for changes in blood flow. This approach is based on the premise that the vessel diameter remains constant despite the changes in blood flow. However, this concept in not universally accepted.[46] Nevertheless, both animal and human studies have shown an acceptable correlation between these indices and other measures of blood flow.[49-52]

As for the technical aspect of vascular Doppler ultrasonography, one must pay special attention to consistently scan the same segment of the vessel with the same angle of insonation. Because the vessel diameter may vary at different sites, the measured velocity may also be different. With regard to the angle of insonation, one should try not to exceed 20 degrees, because with a higher angle, the velocity is significantly underestimated. Although, most new ultrasound systems have the capability to correct for the angle of insonation, using the same angle of insonation for repeated measurements will ensure better reproducibility of the data. Finally, although normative data for the Doppler ultrasonography–derived indices for various vessels are available, the previously described limitations require caution in interpretation of a single measurement. Rather, repeated measurements and the use of trends over time are thought to be more informative of the hemodynamic status and the changes in organ blood flow.

Impedance Electrical Cardiometry

Impedance electrical cardiometry is a noninvasive and continuous bedside method of measuring beat-to-beat left ventricular output on the basis of detection of changes in thoracic electrical bioimpedance (Aesculon; Cardiotronic, La Jolla, CA) caused by the changes in the orientation of the red blood cells in the ascending aorta during systole and diastole normalized for the body mass of the patient.[53] The method has been validated against thermodilution and other direct methods of cardiac output measurement and has shown excellent correlation in adults and children.[53,54] Although its clinical utility in neonates is still untested, preliminary data from our group show a very good correlation with traditional echocardiographic quantitation of left ventricular output in term[55] and preterm (unpublished data) neonates. However, further validation of this technique using cardiac output measurement methods more accurate than echocardiography, such as magnetic resonance imaging, is needed before the use of IEC can be recommended in the neonatal patient population. In conclusion, IEC represents an interesting potential means to obtain continuous, noninvasive data in absolute numbers on stroke volume and cardiac output at the bedside in neonates.

Near-Infrared Spectroscopy

NIRS has received much attention since its first use in newborns in 1985,[56] and numerous papers have been published describing its use. Basically, it involves emission of light of a specific wavelength (near-infrared range, 600-900 nm), from one optode which then travels through tissue and is detected on the other side by another optode. Because of the presence of compounds whose absorption of NIR light depends on oxygen status (chromophores such as hemoglobin and cytochrome aa_3), the absorption during passage through brain can be measured, and oxygenation indices calculated. The newborn skull and tissues overlying the brain are thin, so most of the signal received is representative of brain tissue. In the VLBW neonate, the biparietal diameter is such that essentially the whole brain can be seen by the traveling light, and results can be interpreted as global. Different wavelengths of light

can be used to assess different parameters, such as oxyhemoglobin, deoxyhemoglobin, and cytochrome aa_3 oxidase. Through induction of a small but rapid change in arterial oxygen saturation in the subject, CBF can be calculated with the use of Fick's principle. This method assumes that during the measurement period, cerebral blood volume (CBV) and cerebral oxygen extraction remain constant.

Because the measurement depends on inducing a small but sudden change in arterial oxygen concentration, the technique may not be feasible in babies with severe lung disease (in whom no change in oxygen saturation occurs with an increased FIO_2) and in infants with normal lungs in whom oxygen saturation is 100% when they breathe room air. To get around this problem, an injected tracer dye such as indocyanine green has been used instead of oxygen, with similar results.[57] Some instruments use the tissue oxygenation index (TOI), which is the weighted average of arterial, capillary, and venous oxygenation and theoretically allows the measurement of cerebral hemoglobin oxygen saturation without manipulation of FIO_2 or use of dye. However, this index also has significant potential for inaccuracy, with an intrameasurement agreement in a single subject as large as −17% to +17%.[58] Indeed, reproducibility of NIRS measurements in general has been an ongoing issue for investigators, especially in the detection of focal changes in cerebral hemodynamics. This is a significant problem, because focal hemodynamic changes are at least as likely as global changes to contribute to neuropathology.

Despite these limitations, NIRS has been validated through comparison with xenon-133 clearance in human newborns.[59] Xenon-133 clearance is the experimental model gold standard, utilizing arteriovenous differences in clearance rates of an inert radioisotope and giving a global measurement of CBF. An algorithm allowing for continuous monitoring of regional tissue oxygen saturation in absolute numbers has been developed for adult, pediatric, and neonatal use.[60] Although NIRS represents a practical solution and information on its use in neonates has been encouraging,[61] accumulation of more data and prospective studies looking at both short- and long-term outcomes are needed to provide an evidence-based utilization of NIRS in neonatal medicine.

Amplitude-Integrated EEG (Cerebral Function Monitoring)

There is evidence to support the use of aEEG in asphyxiated infants in the first several hours after birth, because it is one of the most accurate bedside methods to establish a neurologic prognosis.[62] For this reason, it has been used to select candidates for enrollment in head-cooling neuroprotection trials. This technology uses a single-channel EEG recording with biparietal electrodes. Frequencies lower than 2 Hz and higher than 15 Hz are filtered selectively, and the amplitude of the signal is integrated. The signal is then recorded semilogarithmically with slow speed, effectively compressing hours of EEG recording into shorter segments that reflect global background activity and major deviations from baseline (e.g., seizures). Studies have shown that aEEG correlates well with conventional EEG[63] and has the distinct advantage of being easily applied and interpreted by nonneurologists. In a later study, normal aEEG findings in the first 72 postnatal hours in asphyxiated term neonates have been shown to be prognostic of normal neurologic outcome at 2 years of age.[64] Coupled with early neurologic examination, simultaneous aEEG improved specificity and positive predictive value of abnormal results for abnormal neurologic outcome at 18 months of age.[65]

Significantly less information has been gathered about the use of aEEG in the preterm population. However, some typical patterns of background activity for preterm infants have been established, and a number of studies exist that point to its applicability in this group. For instance, in preterm infants with a large P/IVH, aEEG findings during the first postnatal week are predictive of survival and intermediate-term neurologic outcome.[66]

Before aEEG can be incorporated into routine clinical use, data on tracings in normal premature infants in the immediate postnatal period as well as longitudinal development of mature brain activity must be collected and evaluated. Two studies by one group of investigators have attempted to do just that.[67,68] A group of clinically

and ultrasonographically normal infants with gestational ages between 23 and 29 weeks were studied with aEEG in the first two postnatal weeks. With increasing gestational and postnatal age, the occurrence of continuous activity increased and discontinuous low-voltage activity was less likely to be seen. The number of bursts per hour also decreased with increasing gestational age. Although the investigators offered these findings as a foundation for neurodevelopmental prognosis in VLBW infants, they also represent an important starting point for cerebral function monitoring in the immediate postnatal period.

West and colleagues[47] examined the relationships among echocardiographic blood flow findings, mean arterial blood pressure, and aEEG findings in the first 48 hours after birth in preterm infants (<30 weeks of gestation). They found that low right ventricle output, used as a surrogate for systemic blood flow, in neonates with shunting across the fetal channels at 12 hours of postnatal life correlated with low aEEG amplitude whereas low mean blood pressure (<31 mm Hg) correlated with low EEG continuity. However, there was no relationship between aEEG amplitude and SVC flow. Although preliminary in nature, this study at least succeeds in drawing an association between a parameter in wide clinical use (blood pressure monitoring) and two more experimental modes of CBF monitoring (Doppler ultrasonography and aEEG). Taken together with evidence that early aEEG in preterm infants can be helpful in predicting long-term neurodevelopmental outcome, it is reasonable to suggest that aEEG merits further study in the VLBW population as a means of identifying infants at risk for low CBF and/or for pathologic fluctuations in CBF.

Summary

Methods capable of diagnosing altered CBF and the associated changes in brain function in the VLBW population in the first hours to days after delivery are still largely in the experimental arena. It is unlikely that one monitoring parameter will be sufficient to encapsulate the whole picture of real-time continuous assessment of cerebral blood flow and oxygen delivery. To do that in the future, we need to employ an approach to similar that previously and currently used in clinical practice. That is, hands-on clinical assessment must be used in combination with a variety of technologies, ranging from the conventional (heart rate, blood pressure, O_2 saturation) to the advanced (Doppler ultrasonography, IEC, NIRS, aEEG). Both systemic and cerebral blood flow, as well as oxygen delivery and extraction, will have to be evaluated simultaneously and continuously to enable more informed minute-to-minute decisions about how, when, and what to treat to be made. This goal has not been achieved, but even now experimental technologies are giving an insight into more commonly used monitoring parameters, and as the understanding of these new methods expand, it is likely that some will be incorporated into routine clinical use in the not too distant future.

Figure 2-7 shows an example of the information a comprehensive hemodynamic bedside monitoring and data acquisition system developed by our research program can convey in real time at the bedside.

Treatment Strategies

In the previous section we focused on newer experimental modalities for monitoring CBF in the VLBW neonate, with a primary emphasis on those that could be performed at the bedside noninvasively. As mentioned earlier, functional Doppler echocardiography, IEC, NIRS, and aEEG are not yet currently appropriate for widespread routine clinical use for CBF monitoring, as their application and interpretation require specialized technology and further study to determine the significance and reproducibility of results. By extension, application of these methods in clinical practice must eventually be shown to improve long-term neurologic outcome. However, results of studies using these experimental strategies can be useful for tailoring routine care because they give a glimpse of how mean arterial pressure and systemic blood flow affect CBF. This section focuses on how routinely monitored

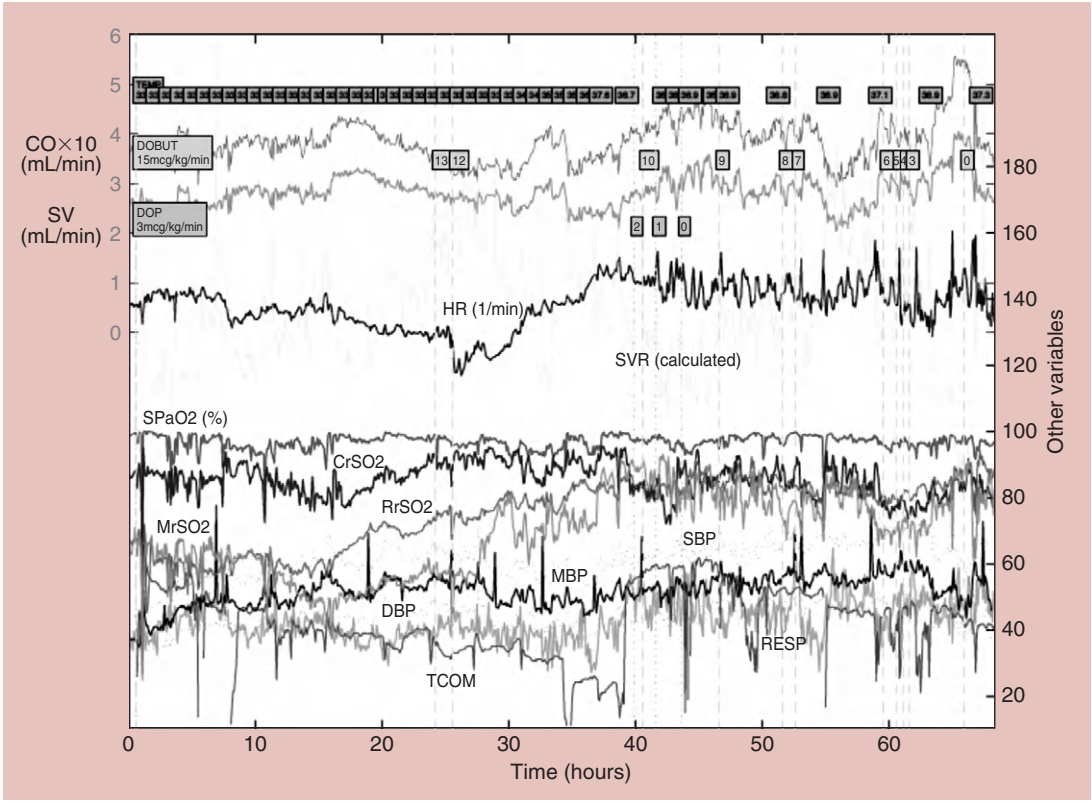

Figure 2-7 Hemodynamic parameters continuously monitored by the hemodynamic monitoring tower in a term, 3-day-old neonate with hypoxic-ischemic encephalopathy undergoing rewarming from therapeutic whole-body hypothermia. Parameters continuously monitored included arterial oxygen saturation ($SpaO_2$; %); heart rate (HR; beats/min); respiratory rate (RESP; L/min); systolic blood pressure (SBP, mm Hg), diastolic blood pressure (DBP; mm Hg), mean blood pressure (MBP; mm Hg); beat-to-beat cardiac output (CO; mL/min) and stroke volume (SV; mL/min) using impedance electrical cardiometry, cerebral ($CrSO_2$), renal ($RrSO_2$) and muscle ($MrSO_2$) mixed venous tissue oxygen saturation using near-infrared spectroscopy NIRS, and transcutaneous CO_2 (TCOM, mm Hg). These parameters are depicted on the *y*-axis, and age after delivery in hours is shown on the *x*-axis. Rewarming was started at 30 hours of monitoring. Core temperature (TEMP) is shown in *small boxes* and dopamine (DOP) and dobutamine (DOBUT) doses are depicted over the cardiac output and stroke volume data. Automatically calculated systemic vascular resistance (SVR; mm Hg × min/mL) is also depicted. See text for details.

indices, such as arterial blood pressure, acid-base status, and oxygenation, as well as commonly used medications, presence of a PDA, and intercurrent infection may affect CBF, as suggested by studies using the aforementioned CBF monitoring techniques. We discuss management options, including evidence for when and how to treat systemic hypotension and clinical signs of systemic organ hypoperfusion. Ultimately we propose a rational treatment strategy for maintaining brain perfusion and oxygenation in the VLBW infant in the first few postnatal days.

Systemic Hypotension

There are several clinical approaches to diagnosis and treatment of neonatal hypotension. First, as mentioned earlier, in a small group of ELBW infants, Munro and colleagues (see Fig. 2-4)[20] identified a mean arterial pressure of 28 to 30 mm Hg as a breakpoint, below which autoregulation appeared to be absent. Use of dopamine to raise the mean blood pressure resulted in a normalization of the CBF in these hypotensive infants. Thus, treatment of hypotension with dopamine quickly restores normal blood pressure and CBF. However, CBF autoregulation was not immediately restored. Indeed, findings of an earlier study suggest that it may take up to 1 hour for CBF autoregulation to be restored following treatment of systemic hypotension.[69]

However, if a mean blood pressure of 28 to30 mm Hg or higher is considered normal in all infants, many will be treated whose overall hemodynamic status does not indicate a need for treatment or may receive a treatment modality (volume, vasopressors/inotropes, or inotropes) that does not specifically address the underlying pathophysiology of their cardiovascular compromise.

The most widespread approach to the definition and treatment of hypotension in the VLBW neonate during the immediate transitional period is use of a mean blood pressure that equals the gestational age in numerals. There are two major concerns with this approach. First, if the autoregulatory blood pressure breakpoint is truly at 28 to 30 mm Hg for this patient population, blood pressure at the level of the gestational age in the more immature and thus vulnerable preterm neonates will be out of the autoregulatory range. Second, as discussed earlier, some of these immature neonates, even with normal blood pressure, have low systemic and presumably cerebral blood flows,[21] because their cerebral vasculature may constrict rather than dilate in the compensated phase of shock.[28-30,40,41] Because low SVC flow (used as a surrogate of CBF) in the first postnatal day is a known risk factor for P/IVH and poor neurodevelopmental outcome,[6] it is important to identify these infants at risk, and this identification cannot be accomplished with blood pressure monitoring alone. As discussed earlier, the combined use of blood pressure and indirect clinical signs of tissue hypoperfusion (blood pressure 30 mm Hg or less and CRT 3 seconds or less[45]) may help to identify patients with low systemic and thus low cerebral blood flow. If functional echocardiography is available, VLBW neonates who are normotensive (their blood pressure is equal to or higher than their gestational age in numerals) but have low systemic blood flow may be identified. As this presentation mostly occurs during the first 6 to 12 hours postnatally, targeted use of functional echocardiography to measure SVC blood flow may be the best direct approach currently available to detect low systemic perfusion. However, even if one can diagnose low systemic blood flow during the first hours after delivery, at present we do not have a truly effective treatment modality to improve systemic blood flow in this patient population. In addition, as mentioned earlier, hypotension defined by the gestational age–based criterion in VLBW neonates appears to be a risk factor for poor neurodevelopmental outcome and it is not known whether treatment with vasopressors or inotropes does[11] or does not[9] ameliorate the risk. Thus, one could speculate that some of the hypotensive infants may have been treated too late to make a difference or that the most widely applied treatment approach is ineffective in some neonates to ameliorate the hypotension- and/or low CBF–associated brain injury.

Finally, because of the uncertainties surrounding the definition of hypotension and the relationship between blood pressure and CBF in the VLBW neonate in the immediate postnatal period, as well as the potential side effects of vasopressor use and the lack of evidence that treatment of hypotension improves neurodevelopmental outcome, some authorities advocate that hypotension in the VLBW neonate during the first postnatal day(s) be treated only if there is clear evidence of organ hypoperfusion (i.e., lactic acidosis). We would argue, however, that by the time lactic acidosis can be detected, cerebral ischemia is likely to have occurred, provided that the brain has also contributed to the production of lactate. Therefore, this approach carries the theoretical risk of allowing significant cerebral hypoperfusion to occur. However, most neonatologists agree that once the fetal channels are closed and the blood pressure–CBF relationship is restored after the first few days following delivery, blood pressure becomes a more reliable indicator of vital organ perfusion even in the most immature neonate, and hypotension should be treated promptly with careful titration of the most appropriate vasopressor/inotrope or inotrope to avoid sudden changes in systemic blood pressure and blood flow.

Treatment of Hypotension Associated with PDA

A PDA with significant left-to-right shunting often manifests as hypotension,[46,70] which is a common presentation in VLBW infants in the immediate postnatal transition period. It has been demonstrated that shunting through a nonconstricting PDA

in the first 6 hours after delivery is primarily left to right and is highly associated with a low SVC flow state.[27,71] Treatment of the PDA before 6 hours of postnatal life with indomethacin induces ductal constriction by 2 hours of drug administration, but this effect is not associated with simultaneous improvements in systemic blood flow.[72] Indomethacin decreases CBF via a direct cerebrovascular vasoconstrictive effect that is independent of the drug's inhibitory action on prostaglandin synthesis.[73] It is possible that the documented decrease in severe P/IVH with early indomethacin use is due to this localized cerebral vasoconstrictive effect during a time when reperfusion may occur[72] and has less to do with improving the preceding low systemic blood flow state by closure of the ductus. However, this notion is not supported by the findings of a meta-analysis comparing the effectiveness, side effects, and hemodynamic effects of indomethacin and ibuprofen.[74] According to the findings of the meta-analysis, although ibuprofen does not induce cerebral vasoconstriction to a degree comparable to that seen with indomethacin, there is no difference in the incidence of P/IVH in VLBW neonates treated with indomethacin and those treated with ibuprofen.

Cardiovascular management of the hemodynamically unstable, hypotensive VLBW neonate with a large PDA should focus on measures that induce stepwise and reversible increases in pulmonary vascular resistance until pharmacologic or, if this fails, surgical closure of the PDA takes place. Such measures may include the avoidance of hyperventilation and respiratory (or metabolic) alkalosis and maintenance of a oxygen saturation value at the lower end of the acceptable range. It should also be remembered that high doses of vasopressors might preferentially increase systemic vascular resistance and thus left-to-right shunting through the ductus; although blood pressure may be maintained in an acceptable range, systemic perfusion could become even more compromised. Therefore, administration of high doses of dopamine or epinephrine should be avoided unless systemic blood flow can be repeatedly assessed with the use of functional echocardiography.

Treatment of Hypotension Associated with Other Causes

For hypotension due to causes such as septic shock, adrenal insufficiency, and hypovolemia, every effort should be made to treat the underlying cause and support the cardiovascular status. Although there are very little experimental data regarding the response of CBF to vasopressor medications in the hypotensive VLBW infant, some evidence is accumulating.

Dopamine is the first-line medication for many neonatologists because of its beneficial cardiovascular and renal effects.[75] It effectively increases blood pressure in the preterm infant, but its effect on organ blood flow is less well described. As mentioned earlier, evidence now indicates that despite its effect on increasing blood pressure and renal perfusion, dopamine does not have a selective vasoactive action on the cerebral circulation in normotensive VLBW neonates.[76,77] However, in hypotensive VLBW infants, the dopamine-induced increase in blood pressure is associated with an increase in CBF.[11,20,69] This finding suggests once again that cerebrovascular autoregulation is impaired in hypotensive preterm infants and that effective treatment of hypotension is associated with an increase in CBF and a delay in the restoration of CBF autoregulation (see earlier).

Are other vasopressors more effective in restoring normal CBF in this population than dopamine? A randomized controlled trial compared the cerebrovascular, hemodynamic, and metabolic effects of dopamine and epinephrine using a stepwise titration of the two medications to achieve optimum blood pressure in VLBW neonates in the first 24 postnatal hours.[11] Both medications increased cerebral perfusion in the medium-dose range, with epinephrine being slightly more effective in infants of less than 28 weeks of gestation and dopamine being more effective in those of greater than 28 weeks of gestation. Because both medications were effective at increasing blood pressure and CBF and this is the only peer-reviewed publication available on the cerebrovascular effects of epinephrine in VLBW neonates, there is no reason to choose one vasopressor over the other for this particular application.

As for inotropes and lusitropes, there has been growing interest in the potential use of milrinone, a selective phosphodiesterase III inhibitor, in neonates and infants who have undergone cardiac surgery and in VLBW neonates with low systemic blood flow during the first postnatal day. Milrinone effectively decreases the incidence of low cardiac output in infants following cardiac surgery.[78,79] Because the low-flow state in preterm infants immediately after birth is in many ways similar to the low cardiac output syndrome in postoperative cardiac patients, this drug has potential both as treatment and prophylaxis of low systemic blood flow (and presumably low CBF) in the VLBW patient population. A pilot study examined the safety, efficacy, and optimal dosing of milrinone in infants of less than 29 weeks of gestation during the first hours of postnatal life.[80] At the applied dose, milrinone appears to be relatively safe in the 1-day-old VLBW neonate. A randomized controlled trial revealed, however, that milrinone is ineffective to prevent the occurrence of low systemic blood flow in the 1-day-old VLBW neonate,[81] so the routine use of milrinone in this population cannot be recommended. Dobutamine, another sympathomimetic amine with direct positive inotropic and mild vasodilatory effects, effectively increases cardiac output and blood pressure in the VLBW neonate, especially when the cardiovascular compromise is caused by myocardial dysfunction.[82] Virtually no data are available on the cerebrovascular effects of dobutamine in the VLBW neonate.

Beyond the presentation of different forms of neonatal shock treated by vasopressors/inotropes, inotropes, and lusitropes, there has been increasing recognition that vasopressor-resistant hypotension frequently develops in the VLBW population. This presentation is thought to be due to cardiovascular adrenergic receptor downregulation and the higher incidence of relative adrenal insufficiency in the VLBW neonate.[83-86] A prospective observational study examining the hemodynamic effects of low-dose hydrocortisone administration in preterm neonates with vasopressor resistance and borderline hypotension found no independent effect of this treatment modality on CBF.[86]

Impact of Provision of Intensive Care on Systemic and Cerebral Hemodynamics

In addition to the impact of the hemodynamic changes on CBF during the postnatal transition, the effects of all interventions must be considered at all times. They include ventilatory maneuvers, the use of medications other than vasopressors/inotropes or inotropes, and invasive procedures. Premature infants with a median gestational age of 31 weeks have been reported to have a decrease in CBF velocity (and thus presumably in CBF) in response to transient hyperoxia.[87] This occurs without a decrease in $PaCO_2$, implicating hyperoxia directly in the decrease in CBF. Hypocarbia is a well-described cause of cerebral vasoconstriction, and a negative association between $PaCO_2$ and CBF and CFOE has been demonstrated in VLBW infants during the first postnatal days.[28,88,89] In addition, lower levels of $PaCO_2$ are associated with slowing of EEG activity, likely induced by decreased cerebral oxygen delivery.[89] These effects are most significant in the first 24 postnatal hours, less evident on the second day, and gone by the third postnatal day. These findings support the notion that the first hours of postnatal life represent a period of heightened vulnerability to CBF fluctuations. Not surprisingly, severe hypocapnia in VLBW neonates during the immediate transitional period is associated with PWMI and cerebral palsy.[90] Importantly, it appears that hypercapnia also has an impact on cerebral hemodynamics, in that $PaCO_2$ values higher than 45 mm Hg during the first 2 postnatal days are associated with compromised CBF autoregulation (Fig. 2-8).[91] It is tempting to speculate that this effect may, at least in part, explain the findings of retrospective studies revealing a strong independent association between hypercapnia and P/IVH in very preterm neonates.[92-94] Accordingly, the use of permissive hypercapnia during the immediate postnatal period may put the VLBW neonate at higher risk for cerebral injury.[95]

Finally, high mean airway pressures in the immediate postnatal period have also been implicated in low systemic blood flow and thus low cerebral blood flow and a predilection for PV/IVH.[26] Beyond ventilatory maneuvers and interventions,

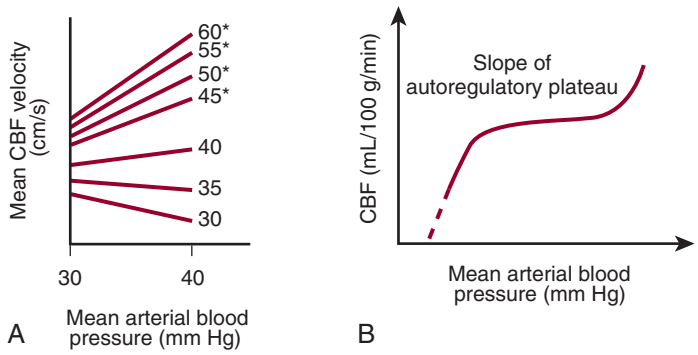

Figure 2-8 Effect of hypercapnia on cerebral blood flow (CBF) autoregulation in 43 ventilated very low-birth-weight neonates during the first 2 postnatal days. **A,** Lines represent the estimated mean slopes of the autoregulatory plateau from 30 to 60 mm Hg $PaCO_2$ with mean blood pressure values between 30 and 40 mm Hg. Horizontal line at slope zero indicates intact autoregulation, with lines at 30, 35, and 40 mm Hg being not significantly different from zero. **B,** The estimated means of the slope of the autoregulatory plateau (cm/s/mm Hg) increased as $PaCO_2$ increased from 40 mm Hg ($P = 0.004$).

commonly used medications such as midazolam and morphine have also been associated with potentially harmful changes in CBF,[96] and even umbilical arterial blood sampling could have an effect on cerebral hemodynamics in these tiny infants.[97]

The preceding paragraphs emphasize how changes in ventilatory management, administration of commonly used medications, or simple interventions in the VLBW infant, especially during the first postnatal days, can have negative and potentially devastating effects on CBF and cerebral oxygenation acutely and on neurodevelopmental outcome ultimately. The mainstays of treatment have been, and should remain at this point, maintenance of homeostasis and avoidance of potentially harmful interventions and abrupt hemodynamic changes in this most vulnerable patient population.

Summary and Recommendations

As discussed in this chapter, the management of hypotension, low systemic and cerebral blood flow, in the VLBW infant during the first postnatal days presents a significant challenge because immaturity, underlying pathology, and postnatal transition all affect the hemodynamic response to pathologic processes and interventions. Because of these factors and the lack of evidence on how treatment affect mortality and short- and long-term morbidity, straightforward recommendations on the treatment of cardiovascular compromise in the VLBW neonate during the period of transition to postnatal life cannot be given.

Therefore, the following approach to diagnosis and treatment represents our view and should be considered only as such, especially because, as discussed in this chapter, evidence on the effectiveness of the treatment of shock in the VLBW neonate during the first postnatal days is not available.

Diagnosis of Hypotension

1. We use the 5th or 10th percentile of the gestational and postnatal age-dependent population-based blood pressure values as the definition of hypotension but initiate treatment at this point only if signs of tissue hypoperfusion or echocardiographic evidence of decreased systemic perfusion or poor myocardial contractility are present. However, we attempt to maintain the mean blood pressure at 23 to 24 mm Hg even if signs of tissue hypoperfusion are not present in the most immature ELBW neonates during the first postnatal day, because cerebral electrical activity appears to be depressed at blood pressure values below this level.
2. Irrespective of the blood pressure value, whenever there is indirect or direct evidence of poor tissue perfusion, we monitor both systemic blood flow and

blood pressure closely and attempt to maintain appropriate systemic blood flow without much fluctuation in the blood pressure. Because a blood pressure breakpoint of the CBF autoregulatory curve may exist at 28 to 30 mm Hg and because more than 90% of even ELBW neonates not receiving vasopressor support maintain their mean blood pressure at 30 mm Hg or higher by the third postnatal day, we carefully attempt to slowly increase mean blood pressure during the first three postnatal days and maintain it in the 28- to 30-mm Hg range by the third postnatal day. However, it must be kept in mind that an increase in blood pressure during this period does not necessarily ensure rapid normalization of systemic and cerebral blood flow and that there are no data that this approach improves long-term neurodevelopmental outcome. Finally, the presence of a hemodynamically significant PDA affects our approach to maintaining and focusing on mean arterial blood pressure primarily and, in these cases, we carefully consider diastolic blood pressure and interrogate the cardiovascular system for evidence of systemic steal during diastole.

3. Although most neonatologists would agree with the approach described here, there is another, less frequently practiced approach that needs to be mentioned. Neonatologists using this approach initiate cardiovascular support only if there is clear evidence of poor systemic perfusion as long as mean blood pressure is at or higher than 20 mm Hg in the ELBW neonate during the first postnatal day. Because within the first 24 hours it is hard to define poor perfusion, especially without the use of functional echocardiography, and because lactic acidosis heralds the presence of (ongoing or previously present) tissue ischemia, we do not practice this diagnostic and treatment philosophy and do not allow mean arterial blood pressure to be around 20 mm Hg during the first postnatal day. However, there is no direct evidence at present that the use of permissive hypotension as an approach to diagnosis and management of cardiovascular compromise in VLBW neonates during the immediate postnatal period affects outcomes.

Treatment of Hypotension

With regard to the kind of treatment utilized, the most appropriate strategy requires identification of the underlying pathogenesis of hypotension. As described earlier, the most common etiologic factors are inappropriate peripheral vasoregulation and dysfunction of the myocardium complicated by the presence of a large PDA in VLBW neonates during the first postnatal days. Although the following approach may be recommended and we practice it, we must emphasize again that there is no evidence that treatment of hypotension in this patient population improves mortality, morbidity, or long-term neurodevelopmental outcome:

1. In the case of hypotension, because low to moderate doses of dopamine (or epinephrine) improve both blood pressure and CBF, we carefully titrate dopamine in a stepwise manner using 3- to 5-minute cycles and make every effort to avoid inducing significant rapid changes in blood pressure. If low systemic blood flow is detected with low-normal to normal blood pressure during the first postnatal day, we add dobutamine to low-dose dopamine and monitor for indirect (CRT, urine output, base deficit) and direct (functional echocardiography) signs of improvement in systemic perfusion.
2. In the presence of a hemodynamically significant PDA, we attempt to close the ductus arteriosus with a cyclooxygenase inhibitor (we use indomethacin) along with providing appropriate supportive care. If pharmacologic closure fails in the patient with a hemodynamically significant PDA, and we have evidence of ongoing or worsening systemic tissue hypoperfusion, we surgically ligate the ductus arteriosus. During the wait for surgical closure to take place, our goal is to decrease the left-to-right shunting across the ductus. As briefly described earlier, we attempt to achieve this goal by carefully increasing pulmonary resistance in a stepwise manner. Using this approach, we frequently are successful at increasing pulmonary vascular resistance,

and the associated decrease in left-to-right shunting results in improvement of systemic blood flow and blood pressure. We also use dopamine in babies with a hemodynamically significant PDA, because it has been shown that, in patients with increased pulmonary blood flow, dopamine increases pulmonary vascular resistance and systemic perfusion.[98] Interestingly, there is no evidence that dopamine preferentially increases pulmonary vascular resistance in neonates without preexisting pulmonary overcirculation. It is tempting to speculate that the increased pulmonary blood flow–associated protective upregulation of vasoconstrictive mechanisms (enhanced α-adrenergic and endothelin-1 receptor expression) and downregulation of the vasodilatory mechanisms (endogenous nitric oxide and vasodilatory prostaglandin production) in the pulmonary arteries are responsible for this observation. We add dobutamine only in the presence of impaired myocardial function, because most VLBW neonates with hemodynamically significant PDA after the first postnatal day usually have normal or hyperdynamic cardiac function. Indeed, the indiscriminate use of dobutamine in these patients may compromise myocardial filling and diastolic function. Finally, administration of fluids to increase blood volume must be restricted because excessive (or even liberal) use of volume is associated with greater mortality and morbidity in this patient population.

3. Finally, because $PaCO_2$ is a much more potent mediator of cerebral vascular tone than blood pressure, we make every effort to keep $PaCO_2$ within the

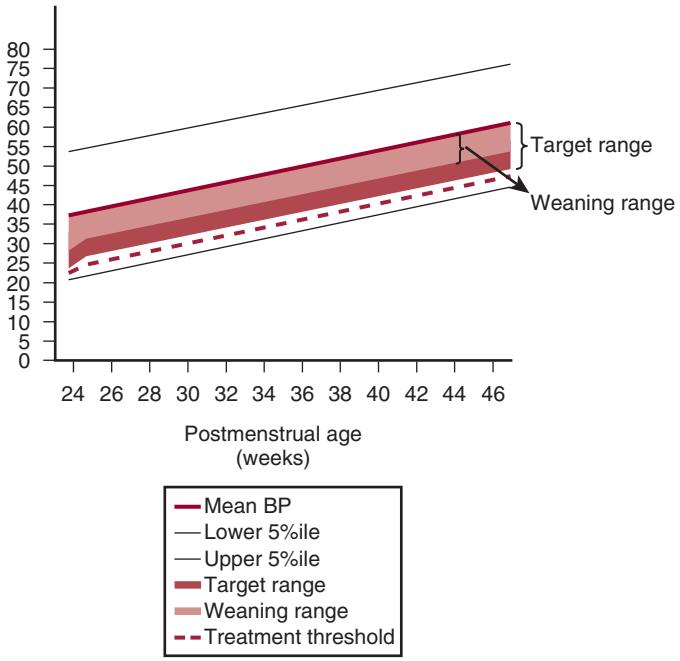

Figure 2-9 Postmenstrual age-dependent definition of hypotension and the target and weaning blood pressure ranges. *Hypotension* is defined as the treatment threshold, which is 1 to 3 points above the 5th percentile (5%ile) for postmenstrual age.[14-16] Below the treatment threshold, we usually initiate treatment of hypotension. The target range is defined as where mean blood pressure is intended to be kept. The target range is between 2 and 3 mm Hg above the treatment threshold and the 50th percentile of the mean blood pressure.[14-16] Finally, the weaning range is defined as the mean blood pressure range where careful weaning of vasopressors and/or inotropic agents is commenced. This range is between 5 mm Hg above the lower limits of target range and the 50th percentile of the mean blood pressure. Note that the upper limit of the target range does not exceed the 50th percentile of the mean blood pressure in order to decrease the risk of achieving an increase in blood pressure by causing significant increases in systemic vascular resistance and thus, potentially, decreases in cardiac output when vasopressors/inotropic agents are being administered. This graph was developed in collaboration with the Under Pressure hemodynamic group created as part of a Vermont-Oxford Network (VON) initiative for 2004 to 2006. One of us (IS) served as the VON expert on hemodynamics for this initiative.

45- to 50-mm Hg range. We hope that by keeping $PaCO_2$ relatively constant we minimize the incidence of hypocapnia-associated white matter injury and cerebral palsy and the hypercapnia-associated increased risk of P/IVH. In addition, in the presence of constant $PaCO_2$ levels, the integrity of CBF autoregulation is likely to be maximized.

Figure 2-9 illustrates our postmenstrual age–dependent approach to the diagnosis and treatment of hypotension in preterm and term neonates. It is important to note that our definition of hypotension (*dotted line*) and the target and weaning ranges have all been arbitrarily defined with the use of epidemiologic data and extrapolation of hemodynamic findings and the data on the association between blood pressure and systemic and cerebral blood flow. Because this approach, just like any other approach to manage the cardiovascular compromise in the neonatal patient population, is not evidence-based, it cannot be recommended in general and only illustrates one of the many options in the diagnosis and treatment of neonatal hypotension. We use these numbers only as guidance, carefully assess the indirect clinical signs of tissue perfusion, and perform targeted echocardiographic evaluations when more information is needed. In the future and after completion of the ongoing investigations, we plan to utilize the real-time information our comprehensive cardiovascular monitoring and data acquisition system provides.

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