Chapter 14

Monitoring and management of brain hemodynamics and oxygenation

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Abstract

While cardiorespiratory monitoring is standard for newborns in the NICU, monitoring of brain hemodynamics and oxygenation is usually sporadic and targeted to newborns with suspected or confirmed neurologic disorders. This is unfortunate, since critically ill newborns, both preterm and term-born, are at high risk of brain injury and would benefit from improved techniques for continuous monitoring of brain hemodynamics and oxygenation, in addition to monitoring of systemic hemodynamics and oxygenation.

Near-infrared spectroscopy (NIRS) and, to a lesser extent, Doppler ultrasound are techniques that have been used in research and increasingly for clinical purposes to measure and monitor brain hemodynamics and oxygenation in newborns. NIRS monitoring can be useful for detection of diverse pathologic conditions that occur frequently in very preterm newborns and in selected populations of term newborns at risk for brain injury related to disturbances of systemic hemodynamics. This chapter reviews the current state of the art with regard to brain-monitoring techniques and the research directed at this important area, and it concludes with suggestions for the use of currently available tools to manage newborns at high risk of neurologic injury from disturbances in brain hemodynamics and oxygenation.

INTRODUCTION

Disturbances in cerebral hemodynamics and oxygenation contribute significantly to the pathogenesis of most types of brain injury in both preterm and term-born neonates. The most common injuries include germinal matrix/intraventricular hemorrhage (GM-IVH), white matter injury (WMI) of prematurity and hypoxic–ischemic encephalopathy (HIE), and brain injury related to congenital heart disease. Physiologic and pathologic conditions commonly encountered in neonates may result in altered cerebral perfusion and/or oxygenation, including conditions such as anemia, hypoxic events, respiratory distress syndrome, mechanical ventilation, patent ductus arteriosus (PDA), and alterations in systemic carbon dioxide, oxygen, and systemic perfusion. While traditional clinical monitoring in the NICU has been limited to measures of cardiorespiratory hemodynamics and oxygenation, such as heart rate, respiratory rate, blood pressure, and peripheral oxygen saturation, monitoring of cerebral hemodynamics and oxygenation has largely been ignored, except in the realm of research. Although there are shortcomings in the technologies currently available to measure cerebral hemodynamics and oxygenation, some NICUs employ these brain-monitoring technologies in their daily care of newborns. In this chapter we will describe the...
available technologies used to monitor cerebral hemodynamics and oxygenation in neonates. We will review common neonatal physiologic and pathologic conditions that may benefit from cerebral monitoring and how these conditions are expected to affect cerebral hemodynamics and oxygenation. Finally, we suggest some practical guidelines and an algorithm that may be used to incorporate brain monitoring, mainly with near-infrared spectroscopy (NIRS) in routine NICU care.

**TOOLS TO MEASURE CEREBRAL HEMODYNAMICS AND OXYGENATION**

Near-infrared spectroscopy (NIRS) technology and measures

Near-infrared spectroscopy is a noninvasive, bedside technology capable of measuring and monitoring cerebral oxygenation and hemodynamics over hours to days. Using small optodes placed on the head, lasers transmit near-infrared light of different wavelengths (usually four) through the skin and skull to the brain tissue, where the light is absorbed, largely by the chromophores oxygenated (HbO) and deoxygenated hemoglobin (Hb), and scattered. By analyzing the light that returns to the sensor of the device, changes in the concentration of HbO and Hb in cerebral tissue can be determined, as HbO and Hb have different absorption patterns across the wavelengths of transmitted light. Using these two measured parameters, commonly used NIRS devices calculate the ratio of HbO to total hemoglobin (THb = HbO + Hb) and display the cerebral regional tissue oxygen saturation (CrSO2) value, which is sometimes referred to as tissue oxygenation index (TOI). The CrSO2 reflects the oxygenation status of the vessels within the brain tissue up to 2–3 cm underneath the sensors and represents more venous than arterial saturation (assumed venous to arterial ratio of 70:30). An increase in CrSO2 can result from increased O2 delivery, which could reflect increased cerebral perfusion or increased blood O2 content, or from decreased O2 extraction, whereas decreases in CrSO2 result from the opposite changes.

In addition to measuring cerebral oxygen saturation, measures of HbO and Hb can be used to derive other parameters, such as fractional tissue oxygen extraction (FTOE) and cerebral blood volume (CBV). FTOE can be calculated from the systemic arterial oxygen saturation measured by pulse oximeter and cerebral venous oxygen saturation (from CrSO2 measured by NIRS) (Naualers et al., 2007). CBV is estimated using THb measured by NIRS and the hemoglobin concentration in blood (H) in g/dL, as CBV = THb × 0.89/[H]. It is important to know that this formula uses a specific assumption for brain density and large vessel:cerebral hematocrit ratio (Wyatt et al., 1990, 1991).

Commercially available continuous wave NIRS monitors can only measure changes in HbO and Hb rather than absolute measures of these values. These devices are best used as trend monitors. Another NIRS technology, namely frequency domain NIRS (FDNIRS), is capable of measuring absolute values of HbO and Hb and calculating absolute values for CrSO2 and CBV (Fantini et al., 1995; Zhao et al., 2005). Finally, and most promising, diffusion correlation spectroscopy (DCS) is a technique that uses the movement of red blood cells (RBCs) inside the tissue to determine tissue perfusion and a cerebral blood flow index (CBF_i) (Boas and Yodh, 1997; Cheung et al., 2001). The combination of FDNIRS and DCS yields a reliable determination of local relative cerebral metabolic rate of oxygen (rCMRO2), which may be the most useful parameter for monitoring cerebral perfusion and oxygenation (Roche-Labarbe et al., 2010). Unfortunately, these devices are being used in research but are not yet commercially available or approved for clinical use. While this technology has the potential to be the gold standard in the future, this chapter will focus on commercially available, FDA-approved devices that can be used today in the NICU.

**Doppler US**

Doppler ultrasound (US) can be used as an intermittent measurement of cerebral blood flow velocity in large cerebral blood vessels, and to estimate cerebral perfusion and resistance to cerebral blood flow (CBF). Cerebral flow velocity increases progressively with increasing birth weight and gestational age, likely related to the developmental increase in caliber of cerebral vessels and cardiac output (Bode and Wais, 1988; Kehrer et al., 2003). Doppler US has the advantage of being a noninvasive technique that can be used at the bedside of critically ill newborns without radiation. The major drawbacks of Doppler US are that it provides only intermittent measures of CBF velocity or resistance to CBF, and the operator dependence of the technique.

There are a number of conditions where Doppler US may be useful for elucidating the pathophysiology of neonatal neurologic disorders, even helping to guide management of disorders where altered arterial CBF velocity or resistance is a useful measure to track in response to interventions. For example, fluctuation in cerebral blood flow velocity (CBFV) and absent end diastolic flow has been associated with the development of GM-IVH in premature newborns (Perlman et al., 1983; Julkunen et al., 2008). Posthemorrhagic hydrocephalus
(PHH) is a complication of large IVH in which Doppler US can be useful to guide management. Neonates with PHH who showed a large increase in resistance to CBFV with anterior fontanelle compression (which correlated with increased intracranial pressure) were the newborns who required surgical intervention for their PHH (Taylor and Madsen, 1996). Doppler US has also been shown to be useful in term neonates with HIE, as decreased CBFV and increased resistive index were seen in most newborns with severe HIE in one series (Guan et al., 2017). Unfortunately, Doppler US had a lower predictive value with respect to neurologic outcome in newborns with HIE treated with therapeutic hypothermia compared to normothermic newborns with HIE (Elstad et al., 2011).

Doppler US can also be used to interrogate the cerebral veins and sinuses. For example, absent flow in the terminal veins was found to be associated with the development of periventricular hemorrhagic infarction (also called Grade IV IVH) in newborns with large IVH (Taylor, 1995). This important study helped elucidate that the pathogenesis of periventricular hemorrhagic infarction was caused by venous obstruction from a large ipsilateral IVH, clarifying that this lesion is a complication of IVH rather than a “larger” IVH extending into the adjacent parenchyma (Taylor, 1995). Doppler US can also detect cerebral sinus venous thrombosis, both in term and preterm newborns, and provides an advantage over CT or MRI for a bedside diagnosis without transport in a critically ill newborn (Lam, 1995; Raets et al., 2013).

As described previously, Doppler US is a useful tool to address some specific questions and conditions for which intermittent measurements of cerebral hemodynamics are useful, but not as a continuous monitoring tool to detect altered hemodynamics or brain injury in neonates.

**133Xenon clearance**

One of the earliest techniques used to measure regional and global cerebral blood flow was the 133xenon clearance method, which is no longer used in newborns because of exposure to radiation. As for Doppler US, this technique also provides only intermittent measurement of CBF and requires some time to make each measurement, so it is not a means of monitoring hemodynamics continuously over prolonged time periods. It is mentioned here mainly because this technique was one of the first techniques used to provide insight into normal CBF, pressure autoregulation, CO2 vasoreactivity in newborns, and pathologic changes in cerebral perfusion related to common pathologic conditions of newborns, which are described in this chapter.

**NORMAL NIRS MEASUREMENTS AND TECHNICAL AND ENVIRONMENTAL FACTORS**

**Normal NIRS values in newborns**

Because of inherent limitations with the currently available technology and the many variables that can affect CrSO2 measurement, it is best to use NIRS as a trend monitor of CrSO2 (or other NIRS parameters), rather than using NIRS to measure absolute values of CrSO2. The largest amount of reported reference data in preterm newborns comes from a single-center study at Utrecht, The Netherlands, where CrSO2 was consistently measured in 999 neonates with birth gestation age (GA) <32 weeks during the first 3 days after birth. Using adult NIRS sensors, the average CrSO2 in the first 72h after birth ranged from 62% to 71% with SD of ~7% (Fig. 14.1) (Alderliesten et al., 2016). Based on these data and other smaller studies, the range of “normal” CrSO2 in preterm newborns has been said to range from 55% to 85%. There are small differences (~3%) in some subgroups of preterm newborns, with higher CrSO2 values in male vs. female newborns, and higher CrSO2 values in small for gestational age (SGA) neonates than in those of appropriate weight in the first 3 days after birth (Cohen et al., 2016). The critical level of CrSO2 below which the risk of brain injury is high is thought to be approximately 40%-45%, based on animal studies of EEG monitoring, lactate levels, ATP, and ischemic brain injury (Kurth et al., 2002; Hou et al., 2007). However, it should be noted that many of these studies used adult sensors to measure CrSO2, and the newer neonatal sensors measure CrSO2 values ~10% higher than the adult sensor (Alderliesten et al., 2016). Further studies using neonatal sensors in large populations of preterm and term newborns are needed to establish the normal range for different gestational and postnatal ages, and the thresholds below or above which there is risk of harm and need for intervention.

**Sensor position**

Although differences in CrSO2 measured in the right vs left cerebral hemispheres are small, a difference of as much as ±18% was detected when comparing four different sites in the same newborn (Wijbenga et al., 2011). This emphasizes the importance of using CrSO2 as a trend monitor rather than as an absolute measure of cerebral oxygenation, since sensors will inevitably need to be moved during the course of NIRS monitoring of a newborn, for changes in the baby’s position and to prevent scalp irritation.
Head position

Studies of brief changes in head position have not shown significant changes in CrSO₂ (Ancora et al., 2010); however, it should be noted that changes in head position can cause movement artifact in NIRS signals.

Day-to-day interventions

Typical daily care procedures such as endotracheal tube (ETT) suctioning, surfactant administration, handling, and diaper change can cause significant fluctuations in CrSO₂ (Kaiser et al., 2004; Limperopoulos et al., 2008). These fluctuations likely reflect real changes in cerebral perfusion and oxygenation that may accompany these interventions; however, movement artifact is also often introduced with these interventions accompanied by significant movement of the newborn’s head and/or body, so caution is needed when interpreting NIRS changes in this context.

Physiologic changes in cerebral hemodynamics/oxygenation

Neonatal cerebral hemodynamics and oxygenation are affected by normal physiologic factors such as GA, neonatal transition, chronological age, and autoregulation.

Changes during transition at delivery

Multiple studies have demonstrated the feasibility and value of NIRS monitoring during the transition immediately after birth (Pichler et al., 2017). NIRS probes have been successfully applied immediately after birth, with cerebral saturation measurement achieved within 1 min of delivery, yielding normative NIRS data during resuscitation and transition. Immediately after birth, CrSO₂ is low and then rapidly increases. Average CrSO₂ (%) was reported to be in the mid-40s at 3 min and increases to a
plateau of mid-70s at 7–8 min after birth (Fig. 14.2) (Fauchère et al., 2010; Urlesberger et al., 2010; Pichler et al., 2013; Van Vonderen et al., 2014; Ziehenberger et al., 2017). Factors that affect this transition include prematurity, mode of delivery, delayed cord clamping, and mode of respiratory support (Pichler et al., 2017). In premature newborns, lower cerebral saturation has been associated with cerebral hemorrhage (Baik et al., 2015). In a prospective randomized study, the use of NIRS during resuscitation was associated with decreased cerebral hypoxia burden and trend toward better outcome (Pichler et al., 2016).

Effect of gestational age at birth

GA at birth has a significant impact on cerebral hemodynamics and oxygenation. CrSO2 at day of birth is higher in very premature newborns when compared with term newborns (Sorensen and Greisen, 2009; Tina et al., 2009). In preterm newborns born at <32 weeks GA, a positive correlation was found between birth GA and CrSO2 measured in the first 3 days after birth, corresponding to a 1% increase in CrSO2 per week GA (Alderliesten et al., 2016). Similarly, FDNIRS and DCS measurements in preterm newborns showed that CrSO2, CBV, CBFi and rCMRO2, all increased with advancing birth GA, with notable large differences between individual newborns (Roche-Labarbe et al., 2010). These increases in cerebral perfusion and oxygen metabolism reflect increasing brain size and maturation with advancing GA.
have shown that pressure passivity is most commonly found in the very low frequency range, i.e., 0–0.4 Hz, reflecting the loss of autoregulation with slow fluctuations in MAP (over many seconds), rather than with beat-to-beat variations in BP (Tsuji et al., 2000; Soul et al., 2007). Other studies have collected simultaneous MAP and CrSO2 data and analyzed how beat-to-beat oscillations in BP are reflected in the cerebral circulation, where less dampening of the oscillations is thought to reflect less autoregulatory capacity (Vesoulis et al., 2016a). Third, wavelet coherence analysis is an approach that quantifies the dynamic relationship between spontaneous oscillations in MAP and CrSO2 to determine dynamic cerebral autoregulation and that has been studied in term newborns with hypoxic–ischemic encephalopathy (Tian et al., 2016).

These studies have shown that pressure passivity occurs frequently but intermittently in preterm newborns (Tsuji et al., 2000; Soul et al., 2007). One study of 90 critically ill preterm newborns derived a pressure-passive index (PPI) as marker of impaired autoregulation, which was a measure of the percentage of all 10-min epochs that were pressure-passive (Soul et al., 2007). That study showed that pressure passivity was very common in the first 5 days after birth, occurring in 87 of the 90 newborns, for whom a mean 20% of their time was spent with a pressure-passive cerebral circulation (Soul et al., 2007). A higher PPI was associated with lower birth GA and weight, hypotension and maternal and placental hemodynamic factors, including pregnancy-induced hypertension, hemorrhage during labor and delivery, and placental infarction (Soul et al., 2007). Interestingly, the study showed that 32% of hypotensive episodes were pressure-passive, and 20% of epochs with normal MAP were pressure-passive, showing that MAP alone is not an indicator of the presence or absence of impaired autoregulation. Lower birth GA and weight was also shown to be associated with impaired autoregulation in other studies, as shown in the study of dampening of beat-to-beat oscillations in BP (Vesoulis et al., 2016a). This latter study showed that less dampening was also associated with GM-IVH by US, but the temporal association could not be determined, i.e., it was unclear whether GM-IVH preceded or potentially resulted from impaired autoregulation (Vesoulis et al., 2016a).

A variety of pathologic conditions may contribute to impaired autoregulation, in addition to the contribution of prematurity (Tsuji et al., 2000; Soul et al., 2007). Factors associated with impaired autoregulation (other than prematurity) include hypoxic–ischemia/asphyxia (Lou et al., 1979; Massaro et al., 2015; Tian et al., 2016), hypotension (Soul et al., 2007), possibly the use of inotropic drugs (Hahn et al., 2013), and seizures (Perlman and Volpe, 1983). The major concern with regard to impaired autoregulation and a pressure-passive circulation is that fluctuations in CBF may result in or contribute to neonatal brain injury in the form of GM-IVH or WMI in preterm newborns, or hypoxic–ischemic brain injury in asphyxiated term newborns (Lou et al., 1979; Pryds et al., 1989; Vesoulis and Mathur, 2017). As described previously, greater cerebral pressure passivity has been associated with GM-IVH, but it is unclear whether impaired autoregulation precedes and contributes to brain injury or is found as a consequence of brain injury (Tsuji et al., 2000; Soul et al., 2007; O’Leary et al., 2009). Neuroimaging studies (US or MRI) are necessarily performed only occasionally, and once there is a high risk of established hemorrhagic or ischemic brain injury, it usually remains difficult to determine the degree to which impaired autoregulation contributes to such injury, particularly since impaired autoregulation is not constant, but fluctuates over time. Newer techniques to measure autoregulation in real time may help resolve this question.

**PATHOLOGIC CONDITIONS AFFECTING CEREBRAL HEMODYNAMICS/ OXYGENATION**

As expected, neonatal cerebral hemodynamics and oxygenation can be affected by many pathologic conditions and their treatment. This section discusses the most common disorders affecting cerebral hemodynamics in preterm and term newborns, with regard to how brain-monitoring technologies have helped elucidate the pathophysiology of these disorders and potentially can be used to guide management. The section reviews common respiratory and cardiovascular conditions and their management, since changes in systemic hemodynamics and oxygen metabolism obviously affect the cerebral circulation and oxygenation. Finally, neuronal activity influences cerebral hemodynamics and oxygenation, as do primary neurologic disorders and various types of brain injury, so these disorders are discussed separately, even though there is obviously an interplay in the pathophysiology of respiratory, cardiovascular, and neurologic disorders.

**Respiratory conditions and management**

**HYPOCARBIA AND HYPERCARBIA**

Carbon dioxide is a major determinant of vascular tone and hence cerebral perfusion. A positive correlation between systemic CO2 concentration and cerebral perfusion has been demonstrated in numerous animal and human studies across a wide age range (Rosenberg et al., 1982; Rosenberg, 1992; Karsli et al., 2003), such that hypocarbia causes cerebral vasoconstriction and
hence decreased cerebral perfusion, while hypercarbia does the opposite. Cerebral CO₂ vasoreactivity is influenced by factors such as duration of hypocarbia or hypercarbia, medications such as indomethacin, and other factors that can cause significant vasodilation, such as hypoglycemia or hypoxia. These findings were identified in old studies using ¹³³Xenon clearance and confirmed with NIRS measures of cerebral CO₂ vasoreactivity (Pryds et al., 1990b; Pryds, 1991; Pryds and Edwards, 1996). NIRS is a better technique to detect changes in cerebral perfusion related to changes in CO₂ than ¹³³Xenon clearance, as NIRS can measure changes in cerebral perfusion occurring over brief periods of seconds to minutes. For example, a recent study of mechanically ventilated neonates born at <32 weeks GA monitored in the first 3 days after birth showed that an acute decrease in end-tidal CO₂ was associated with an acute decrease in CrSO₂ (Dix et al., 2017). Thus NIRS could be a useful means to monitor changes in cerebral hemodynamics and oxygenation that occur with changes in ventilation that might result in hypocarbia or hypercarbia.

Neonatal hypocarbia has been associated with periventricular leukomalacia, an association that is hypothesized to be related to hypocarbia causing cerebral hypoperfusion, i.e., ischemia (Greisen and Vannucci, 2001; Liao et al., 2001). While continuous monitoring of respiratory or systemic CO₂ (e.g., transcutaneous monitoring), has been increasingly used in the NICU to ensure that CO₂ levels are kept in the normal range (Aly et al., 2016), a concurrent measurement of cerebral perfusion is still needed, as CO₂ is not the only determinant of cerebral perfusion. Continuous monitoring of CrSO₂ has the potential to improve CO₂ management in ventilated newborns by determining the degree of hypocarbia that results in decreased cerebral perfusion, thereby opening the possibility of individualized adjustment of CO₂ levels to maintain normal cerebral perfusion.

Hypercarbia of course has the opposite effect of hypocarbia, causing cerebral vasodilation, and it occurs more commonly by intention than hypocarbia in the management of preterm newborns. Permissive hypercarbia has been advocated as a safe practice in the respiratory management of premature newborns in order to decrease lung injury in very premature newborns (Ryu et al., 2012). However, by causing cerebral vasodilatation and potentially impairing pressure autoregulation, hypercarbia might increase the risk of GM-IVH, as shown by one group’s studies (Kaiser et al., 2005, 2006). This would be another situation where NIRS could add value as a monitor of increases in cerebral perfusion resulting from hypercarbia that might put a newborn at risk of GM-IVH. The same study of fluctuations in CO₂ mentioned previously also demonstrated that acute increases in end-tidal CO₂ were associated with increased CrSO₂ and decreased FTOE, indicative of increased perfusion (Dix et al., 2017). Thus NIRS monitoring of preterm newborns in the first days after birth could be very valuable for detecting the impact of fluctuations of CO₂ on cerebral hemodynamics, potentially helping clinicians adjust respiratory management to minimize brain injury and hemorrhage.

**Apnea, hypoxia and hyperoxia**

Apnea is common in premature newborns and its incidence increases significantly with decreasing GA, as it is largely related to physiologic immaturity of respiratory control. For example, apnea affects 7% of those 34–35 weeks GA and almost all those less than 29 weeks GA (Zhao et al., 2011). Apnea may also be caused or exacerbated by pathologic conditions, which are also more common with younger GA. Apneic episodes may be deleterious when they cause hypoxia severe enough to result in bradycardia with decreased cardiac output, increased CO₂, and hence decreased cerebral perfusion and oxygen delivery, as shown by Doppler US measures of CBFV (Perlman and Volpe, 1985). One study using NIRS showed that CrSO₂ did decrease significantly in apneic spells associated with bradycardia compared to spells without bradycardia (Pichler et al., 2003). Thus it has been hypothesized that significant, frequent apneic episodes could contribute to worse brain injury and neurodevelopmental outcome through their effect on cerebral perfusion and oxygenation. Although some studies report an association between more days with apnea and worse neurodevelopmental outcome (Janvier et al., 2004; Pillekamp et al., 2007), these studies do not prove causation, as apnea may also be a consequence of brain injury (Cheung et al., 1999). For example, drugs used to treat apnea may have adverse effects on the cerebral circulation, as a Doppler US study showed decreased CBF velocity following caffeine administration in preterm newborns (Hoecker et al., 2002), even though caffeine was not an independent risk factor for adverse neurologic outcome in the previously mentioned study (Janvier et al., 2004). Similarly, a small study of preterm newborns showed that increasing FiO₂ to treat desaturation episodes may result in prolonged periods of elevated CrSO₂, suggesting that this intervention may be detrimental rather than therapeutic (Baerts et al., 2011). Since most studies of apnea and neurologic outcome in preterm newborns do not include NIRS or other brain monitoring to determine the effect of apnea on cerebral hemodynamics, it is difficult to determine whether apnea is the cause or a biomarker of brain injury. NIRS has a promising role for detecting and quantifying clinically significant apnea.
affecting cerebral perfusion in order to elucidate the relationship between apnea and brain injury/neurologic outcome in preterm newborns.

Interestingly, oxygen toxicity has also been identified as a potential cause of brain injury in the immature brain, suggesting that both hypoxia and hyperoxia should be avoided. Animal studies have shown that hyperoxia is associated with oxidative stress, inflammation, apoptosis, and apoptosis of some neuronal populations. Hyperoxia is also associated with alterations in genes involved in synaptic plasticity and with hypomyelination, and has been associated with later coordination deficits, hyperactivity, and cognitive impairment (Reich et al., 2016). In humans, higher oxygen saturation in premature newborns is associated with retinopathy of prematurity (ROP) and targeting lower saturation was associated with less ROP requiring treatment (Askie et al., 2017). To date, there are no human data showing an association between hyperoxia and brain injury. For example, the large prospective trial of CrSO2 monitoring showed an association of brain injury and injury biomarkers with cerebral hypoxia but not hyperoxia (Plomgaard et al., 2017). On the other hand, a NIRS study of preterm newborns in the first 96 h after birth showed that low cerebral FTOE (as a measure of cerebral hyperoxia), but not high CrSO2 or systemic oxygen saturation, was associated with ROP (Vesoulis et al., 2019). Thus NIRS monitoring could be used to help avoid cerebral hyperoxia and potentially lessen ROP, but it remains unclear whether cerebral hyperoxia is deleterious to the preterm newborn’s brain and whether this approach would lessen brain injury.

THORACIC HYPERINFLATION

Respiratory illness and management can both have an impact on cerebral perfusion and oxygenation. Mechanical ventilation may increase intrathoracic pressure, thereby reducing both systemic and cerebral venous return and, as a consequence, decrease cardiac output (Skinner et al., 1992; Evans and Kluckow, 1996a). This decreased cardiac output and/or reduced cerebral venous return could decrease cerebral perfusion, which would be important to detect. NIRS has been used to determine the effect of various types of mechanical respiratory support on cerebral perfusion, and several studies have shown an apparent effect of ventilatory strategies on cerebral hemodynamics (Palmer et al., 1995; Noone et al., 2003; Zaramella et al., 2006). Thus NIRS monitoring of cerebral hemodynamics during changes in respiratory management might be useful to facilitate detection and prevention of deleterious effects on the cerebral circulation.

Cardiovascular conditions and management

ANEMIA AND RED BLOOD CELL TRANSFUSIONS

Anemia results in a compensatory increase in cerebral blood flow (Pryds and Greisen, 1989), which could potentially increase the risk of developing IVH. Likely more important, this compensatory mechanism of increasing cerebral perfusion will fail with severe anemia, with a possible risk of hypoxic–ischemic brain injury. There is not a clear consensus regarding the threshold at which transfusion with packed red blood cells (PRBCs) in neonates is indicated (Whyte, 2012). A post hoc analysis of a large randomized trial showed increased risk of cognitive delay at 18–21 months of age with restrictive compared with liberal transfusion practice (Whyte et al., 2009). In contrast, analysis of a different trial of restrictive vs liberal transfusion practice showed decreased brain volumes and worsened neurocognitive outcome at school age in the liberal group. Of note, this study had a low follow-up rate of about 50% of newborns, limiting interpretation of the results (McCoy et al., 2011; Nopoulos et al., 2011).

As expected, multiple studies have shown that hemoglobin concentration correlates positively with CrSO2, and that PRBC transfusion results in increased CrSO2 in preterm newborns (Van Hooft et al., 2010; Seidel et al., 2013; El-Dib et al., 2016). One study showed a significant increase in CrSO2 and decrease in desaturation episodes to <80% with transfusion overall, and that these changes were most significant for those preterm newborns with a pretransfusion CrSO2 <55% (Seidel et al., 2013). Since parameters for transfusion in neonates are an area where more data are needed to inform management, CrSO2 measurement may be a clinically meaningful parameter that can help guide decision making regarding the need for and timing of PRBC transfusions.

HYPTENSION AND INOTROPES

A number of studies have shown an association between hypotension in preterm neonates with worse neurodevelopmental outcome (Watkins et al., 1989; Low et al., 1993; Goldstein et al., 1995; Martens et al., 2003; Hunt et al., 2004; Batton et al., 2007, 2009; Kuint et al., 2009; Pellicer et al., 2009). This point remains a topic of debate, however, in part because of the lack of a consensus definition of normal blood pressure and particularly with regard to the threshold to define hypotension in preterm newborns (Cayabyab et al., 2009; Noori and Seri, 2015). Systemic hypotension is physiologically associated with relatively preserved perfusion of the brain, heart, and adrenal glands, thought to occur in the brain by changing vascular resistance that preserves...
cerebral perfusion (pressure autoregulation). At a certain (unknown) threshold, however, this mechanism fails and hypotension results in decreased cerebral perfusion. This threshold is likely different in neonates with intact vs impaired autoregulation, and autoregulation cannot currently be measured with clinically available techniques in real time. Although decreased cerebral perfusion could be the cause of brain injury in preterm newborns with hypotension, causation has not been incontrovertibly proven, especially given the presence of confounding factors such as other illnesses or even the inotropes used to treat hypotension. This may explain the observation that in some studies, hypotension alone was not always associated with decreased CrSO2 or with worse neurodevelopmental outcome (Logan et al., 2011; Batton et al., 2013; Alderliesten et al., 2014).

While many neonatologists have adopted the definition of mean BP equal to postmenstrual age as a lower limit to define and treat hypotension (Stranak et al., 2014), this definition is based only on the observed correlation between lower mean blood pressure with lower GA. Other definitions include the use of <5%–10% for age or using an absolute MAP of <28–30 mmHg in very low birth weight (VLBW) neonates, based on observed relationships between BP and CBF (Watkins et al., 1989; Munro et al., 2004; Børch et al., 2010). For example, a small study of BP and autoregulation correlating intermittent measures of CBF by NIRS with continuous MAP measures showed that MAP <30 mmHg was associated with decreased CBF, but that CBF was maintained constant at MAP >30 mmHg in preterm newborns (Munro et al., 2004). Several larger studies have addressed this question of the relationship between BP and CBF using NIRS, with variable results. A large prospective study of continuous MAP and NIRS monitoring showed that hypotension occurred frequently in critically ill preterm newborns (as did impaired autoregulation) (Soul et al., 2007), but was not associated with US evidence of brain injury (Limperopoulos et al., 2007). That study showed that hypotension was a risk factor for impaired autoregulation, but that hypotension and impaired autoregulation did not invariably occur at the same time, and instead occurred at different times in most newborns (Soul et al., 2007). A later prospective study of 66 preterm newborns showed a high correlation between time with hypotension and low CrSO2 (Alderliesten et al., 2014), suggesting that hypotension was associated with decreased cerebral perfusion and/or increased oxygen extraction. However, that study showed that CrSO2 <50% for >10% of the time, but not hypotension, was associated with a slightly worse neurodevelopmental outcome (Alderliesten et al., 2014). More studies are needed to determine whether CrSO2 can be used as an additional parameter to determine when to treat low blood pressure. Of course, the critical question is what degree of hypotension results in adverse consequences, which for the purposes of this chapter, we will define as brain injury or adverse neurologic outcome.

The other point of debate in preterm newborns is whether the inotropes used to treat preterm newborns have beneficial or harmful effects on cerebral hemodynamics, and whether some inotropes are superior to others in this regard (Cox and Groves, 2012). In a large Canadian study of 7913 neonates born at <29 weeks GA, inotropes were used in 10% of these babies and were associated with increased mortality and complications such as IVH and ROP (Wong et al., 2015). In contrast, data from the EPIPAGE-II study found that inotrope use in the first 3 days in neonates born at <29 weeks GA was associated with better short-term outcome in the form of hospital discharge with no major morbidity (Durrmeyer et al., 2017). The argument that inotropes themselves might treat BP successfully but not improve cerebral perfusion or neurologic outcome emphasizes the need for monitoring of cerebral hemodynamics together with BP monitoring (Batton et al., 2016). Note that the previously mentioned small study of NIRS monitoring within 40 h of birth showed an increase in CBF with dopamine administration in those preterm newborns with hypotension (defined as MAP <30 mmHg), but not for normotensive newborns, suggesting a beneficial effect of dopamine on cerebral perfusion (Munro et al., 2004). Larger prospective studies of the benefits or harms of inotrope treatment of hypotension are needed, and these types of questions are arguably best determined by RCTs rather than observational studies (Evans et al., 2006).

Indeed, there has been increasing interest in conducting such RCTs to address this question in newborns. One pilot, feasibility RCT of BP management in preterm newborns was prematurely stopped because of low eligibility and consent rates (NCT00874393) (Batton et al., 2012). Two ongoing randomized, placebo-controlled trials of BP management may shed light on the long-term outcome of hypotension and its treatment (NCT01434251: TOHOP study and NCT01482559: HIP study). It is important to emphasize that, based on our limited knowledge at this point, the clinical significance of hypotension must be evaluated together with parameters other than CrSO2, such as cardiac output, capillary refill, blood lactate, and urine output.

**PATENT DUCTUS ARTERIOSUS**
The management of PDA in premature newborns is one of the most controversial areas in neonatology
(Mohamed et al., 2017). Shunting blood from the right atrium and pulmonary artery to the systemic circulation is vital for fetal survival. However, prolonged persistent ductal patency after birth has been associated with increased mortality and morbidity in premature newborns, including intraventricular hemorrhage (IVH) (Evans and Kluckow, 1996b). Although no study has proven a direct cause-and-effect relationship, it is biologically plausible that significant shunting across a PDA could cause fluctuations in cerebral blood flow that contribute to the pathogenesis of IVH (Laughon et al., 2004).

The controversy regarding PDA management arises from the failure of universal PDA treatment to improve meaningful short- or long-term outcomes, such as IVH or later neurodevelopmental outcome (Peckham et al., 1984; Schmidt et al., 2006; Benitz, 2010). Additionally, medical treatment for PDA such as indomethacin has been associated with increased spontaneous gut perforation, renal failure, and disturbed cerebral circulation (Van Bel et al., 1989; Shorter et al., 1999; Watterberg et al., 2004; Fanos et al., 2005). Similarly, surgical ligation has not improved mortality or morbidity and, most importantly, is associated with increased incidence of cognitive delay and neurosensory/neurodevelopmental impairment (Lippmann et al., 1976; Chorne et al., 2007; Kabra et al., 2007; Mandhan et al., 2009; Wickremasinghe et al., 2012; Malviya et al., 2013).

Given the likelihood that both PDA and its treatment could have important effects on brain perfusion and injury, NIRS monitoring could be a valuable tool for investigating these questions.

Although some studies have shown that a hemodynamically significant PDA is associated with lower CrSO2 and higher FTOE compared to controls (Underwood et al., 2007; Lemmers et al., 2008), studies of medical or surgical treatment of PDA have shown variable effects. Most PDA treatment studies have reported an increase in CrSO2 and decrease in FTOE with PDA treatment (Vanderhaegen et al., 2008; Lemmers et al., 2010), but one study reported that ~30% of newborns had a decreased CrSO2 following treatment with indomethacin or ibuprofen, while the rest had stable or increased CrSO2 (Bhatt et al., 2012). The authors noted that newborns who had a decreased CrSO2 had a higher baseline CrSO2, and the converse was true for newborns who had increased or unchanged CrSO2 (Bhatt et al., 2012). Notably, one study of surgical ligation of PDA reported that CrSO2, together with a decrease in BP and aEEG amplitude, decreased further during surgery in about half of the newborns, before postsurgical increases in the three parameters that occurred only 24h after surgery (Lemmers et al., 2010). These studies show that measuring CrSO2 and FTOE can help elucidate alterations in cerebral perfusion with hemodynamically significant PDA and its treatment, alterations that may be opposite for various subpopulations of newborns. Further work is needed to determine if NIRS monitoring can help guide the management of PDA for individual preterm newborns.

**Congenital heart disease**

Congenital heart disease (CHD) remains a significant risk factor for neurodevelopmental disability and impairments, despite remarkable advances in surgical repair of CHD in the last decades (Massaro et al., 2008). The etiology of the neurodevelopmental disability and impairments related to CHD is multifactorial, including nonmodifiable risk factors such as genetic contributors to neurologic outcome (Rollins et al., 2017). In addition to genetic contributions, brain injury related to global and focal hypoxia and ischemia remains a common cause of adverse neurologic outcome in CHD. Disturbances in cerebral hemodynamics resulting in brain injury and altered brain development may occur in utero, and in the pre-, intra- and postoperative periods around the one or more surgeries that are often needed for repair of CHD. Thus brain monitoring during critical periods offers the potential for detection of disturbed cerebral hemodynamics and oxygen utilization and possible interventions that could improve neurologic outcome. It is for these reasons that NIRS monitoring has been incorporated for research and even clinical use in many pediatric cardiac ICUs (Hirsch et al., 2009; Neshat Vahid and Panisello, 2014).

As expected, newborns with CHD have different values of cerebral oxygen saturation and CBF compared with healthy newborns, depending on the type of CHD. Newborns with noncyanotic CHD have an average CrSO2 of ~70% while those with cyanotic CHD have CrSO2 ranging from 40% to 70% (Andropoulos et al., 2004). Monitoring CrSO2 during cardiac surgery and in the perioperative period may help identify newborns at risk of brain injury and/or adverse neurologic outcome, which could help clinicians use strategies to optimize cerebral oxygenation and perfusion and improve outcome (Lee et al., 2008). Several studies have identified that lower CrSO2 is associated with neuronal dysfunction and adverse neurologic outcome (Lee et al., 2008). For example, a study of 20 newborns with transposition of the great arteries found that lower preoperative CrSO2 was associated with worse neurodevelopmental outcome at 2–3 years of age, even though CrSO2 normalized within ~24h after surgical correction in all newborns (Toet et al., 2005). FDNIRS and DCS have the potential to help elucidate the changes in cerebral hemodynamics...
in the perioperative period, because of the ability to measure CMRO₂ and CBFᵢ in addition to CrSO₂. In that regard, a small study of neonates with single ventricle (SV) CHD showed that newborns with SV who were unstable in the postoperative period had lower CMRO₂, FTOE, and CBFᵢ than stable postop newborns with SV, although CrSO₂ values were not significantly different between the two groups (Dehaes et al., 2015). A larger study of 75 newborns (40 single ventricle, 35 two ventricle CHD) showed that a postoperative combination of lower CrSO₂ and higher lactate level was predictive of death or worse neurodevelopmental outcome (Aly et al., 2017). Given the limitations of interpreting CrSO₂ values in neonates with CHD whose hemodynamics and oxygen metabolism are affected by variable factors related to the different types of CHD and surgical repair, the addition of CBF and CMRO₂ monitoring (by FDNIRS/DCS), EEG monitoring of brain function, and indicators of systemic asphyxia (e.g., serum lactate) or other biomarkers are important for elucidating the many factors that may contribute to brain injury and adverse outcome (Hirsch et al., 2009).

**Neurologic conditions and management**

**Germinal matrix: Intraventricular hemorrhage**

GM-IVH remains a common complication of premature birth, affecting up to 36% of VLBW newborns (<1500g), with the severe forms (Grades III and IV) occurring in 16% (Stoll et al., 2010). IVH also occurs in late preterm and term newborns, but its incidence is much lower, so most of the research related to changes in perfusion in IVH is focused on preterm newborns. Although severe forms of GM-IVH understandably have a greater impact on outcome than do grades 1–2 GM-IVH, both mild and severe GM-IVH are risk factors for increased mortality and worse neurodevelopmental outcome (Mukerji et al., 2015). Studies of NIRS monitoring in the first hours–days after birth in preterm newborns showed variable results in relation to the development of IVH. One prospective study showed that 30 premature newborns who underwent continuous NIRS monitoring in the first 72 h had higher CrSO₂ and lower FTOE preceding severe IVH, and high correlation between MAP and CrSO₂ following the development of severe IVH, compared to those without IVH (Alderliesten et al., 2013). Their interpretation of the results was that newborns who developed severe GM-IVH had cerebral hyperperfusion preceding and impaired pressure autoregulation following the development of severe IVH. A similar, very small study also found higher CrSO₂ and lower FTOE in five preterm newborns who developed IVH, compared with 12 newborns without IVH (Zhang et al., 2011). In contrast, a study of 71 preterm newborns monitored intermittently with NIRS and Doppler US every 24 h in the first 72 h showed high FTOE was associated with IVH (grade 2 or higher) or death (Balegar et al., 2014). Another small study showed that 17 preterm newborns who developed any size of IVH had lower CrSO₂ and higher FTOE measured in the first few days and at 1 and 2 weeks of age compared to 17 newborns without IVH (Verhagen et al., 2010). Although there were differences in sample size and NIRS devices used in these studies, there is not a consistent difference in methodologies that easily explains the opposite results regarding CrSO₂ and FTOE changes with IVH.

An increase in CrSO₂ could be related to increased cerebral blood flow in association with developing GM/IVH, as ischemia/reperfusion is a known pathogenic mechanism for GM-IVH from animal data (Goddard-Finegold et al., 1982). A small study of preterm newborns supports this mechanism, as newborns who developed IVH had lower left ventricular output (LVO) followed by an increase in LVO and CBF velocity in the hours just prior to the detection of IVH by US (Noori et al., 2014). That study also showed a decline in CrSO₂ and increase in FTOE following development of IVH (Noori et al., 2014). In contrast, newborns who did not develop IVH had very stable systemic and cerebral hemodynamics in the first 3 days after birth. Despite some of the different results of these studies, close monitoring of CrSO₂, other NIRS measures, and systemic hemodynamics in preterm newborns during the first days after birth has the potential to detect changes in cerebral hemodynamics that herald the development of IVH. It remains to be determined if there are interventions that could be successfully applied to reduce the incidence or severity of IVH related to early disturbances in cerebral hemodynamics.

**Hydrocephalus**

Progressive posthemorrhagic ventricular dilation (PHVD, also called posthemorrhagic hydrocephalus, PHH) is a serious complication of IVH associated with significant mortality and morbidity, most commonly in preterm newborns, although it also occurs in term newborns (Adams-Chapman et al., 2008; de Vries et al., 2013). One of the mechanisms postulated to cause brain injury in PHVD is the ventricular dilation itself, with or without increased intracranial pressure, which impairs cerebral perfusion. Indeed, two retrospective studies showed that larger ventricular size is associated with worse neurodevelopmental outcome, and that early intervention when ventricles were less dilated was associated with more favorable outcome than late intervention.
Results of a two-center observational study of newborns with birth GA <30 weeks suggested that early intervention with CSF drainage in PHVD resulted in lower rates of shunt insertion and complications and better neurologic outcome at 18–24 months than late intervention (Leijser et al., 2018). Given the difficulty of determining when to initiate CSF drainage procedures, NIRS could be a promising and noninvasive means to detect important changes in cerebral perfusion/oxygenation related to PHVD that could help guide management. More than one study has demonstrated that ventricular decompression in PHVD results in an increase in oxygenated Hb and CrSO2, and decrease in FTOE, supporting the notion that ventricular decompression improves cerebral perfusion and oxygen delivery (Soul et al., 2004; Norooz et al., 2015). These studies suggest that NIRS could add valuable data to help guide PHVD management by detecting impairments in cerebral perfusion and oxygen delivery that indicate need for CSF drainage prior to the onset or worsening of brain injury related to PHVD.

Neonatal Encephalopathy

The incidence of neonatal encephalopathy caused by hypoxia–ischemia (HIE) has not changed much over the last decades and is still associated with long-term neurodevelopmental impairments for many children, despite improved outcome related to therapeutic hypothermia (Natarajan et al., 2016). NIRS can be used to monitor changes in cerebral perfusion and oxygenation related to HIE and treatment with hypothermia. Much of this research using NIRS focused on pathophysiology of HIE, differentiating severity of encephalopathy and predicting outcome. Studies decades ago identified impaired autoregulation in newborns with perinatal asphyxia and HIE (Lou et al., 1979; Pryds et al., 1990a). Prior to the introduction of therapeutic hypothermia (TH), severe encephalopathy was also found to be associated with increasing CrSO2 and decreasing FTOE over the first 2 days (Toet et al., 2006). Increased CrSO2 was associated with adverse outcome, whereas stable CrSO2 and FTOE were associated with good outcome (Toet et al., 2006).

The introduction of TH complicated the interpretation of NIRS measures in newborns with HIE, since a cooled brain is expected to have reduced metabolic demand and hence likely reduced cerebral perfusion, oxygen extraction, and metabolism. When the same group studied 39 newborns with HIE treated with TH, higher CrSO2 was still associated with adverse outcome (12 died and 1 had neurodevelopmental impairment) (Lemmers et al., 2013). Both groups had similar CrSO2 on admission, but those with favorable outcome had moderate increase in CrSO2 during hypothermia and normalized after rewarming, while those with unfavorable outcome had a larger increase in CrSO2 starting at 24 h that did not normalize with rewarming (Lemmers et al., 2013). A combination of CrSO2 and aEEG measures had a higher predictive value for MRI detected brain injury and adverse outcome than did CrSO2 alone, showing the added value of measures of brain activity/encephalopathy (aEEG/EEG) to measures of cerebral hemodynamics and oxygen metabolism (Lemmers et al., 2013; Goeral et al., 2017; Niezen et al., 2018). Similarly, subsequent studies of autoregulation in newborns with HIE in the era of hypothermia treatment showed that the severity of impaired autoregulation remained associated with brain injury (Massaro et al., 2015; Tekes et al., 2015). Thus despite the potential independent effect of therapeutic hypothermia on cerebral hemodynamics and oxygen metabolism, significant disturbances in hemodynamics and oxygen metabolism remain markers of brain injury and adverse neurodevelopmental outcome.

It would be ideal to measure CBF and oxygen metabolism (CMRO2) directly, rather than just cerebral oxygen saturation in newborns with HIE with/without TH, since CrSO2 can be affected by various changes in cerebral perfusion, oxygen extraction and metabolism, which can only be inferred from measures of CrSO2. Indeed, a small FDNIRS and DCS study showed lower cerebral oxygen metabolism (CMRO2) and lower cerebral perfusion (CBF) during TH compared with posthypothermia or with healthy control newborns, even though CrSO2 did not change with rewarming (Dehaes et al., 2014). These data showed that there was likely an effect of hypothermia on cerebral perfusion and oxygen metabolism, in addition to the effect of HIE. It is difficult to determine to what degree the lower perfusion and CMRO2 are related to decreased metabolic demand related to encephalopathy, hypothermia, medication effect (e.g., sedatives), and/or other factors, as previous measures of high CMRO2 by FDNIRS in newborns with HIE but no TH were obtained over a wider and older age range (mean ~6 days of age) (Grant et al., 2009; Dehaes et al., 2014). A smaller study of CBF and CMRO2 measured by NIRS and arterial spin labeling MRI (ASL-MRI) also showed lower measured CBF and calculated CMRO2 in newborns with moderate to severe HIE treated with TH, measured in the first 72 h after birth (Wintermark et al., 2014). This small study showed that newborns with severe HIE had lower CMRO2 than those with moderate HIE (Wintermark et al., 2014), suggesting that both encephalopathy and hypothermia contributed to lower CMRO2, but this observation requires confirmation in a larger study.
MANAGEMENT OF CEREBRAL HEMODYNAMICS/OXYGENATION

Given the previously described utility and limitations of measuring and monitoring cerebral hemodynamics and oxygenation, it is worth considering how NIRS and other brain-monitoring techniques can be used in current NICU care. A recent clinical trial has shown that continuous monitoring of cerebral NIRS with specified interventions to maintain CrSO\(_2\) within a target range resulted in a decreased burden of cerebral hypoxia (Hyttel-Sorensen et al., 2015). This might be a worthwhile goal, since cerebral hypoxia was associated with low brain electrical activity and severe intracranial hemorrhage in this study (Plomgaard et al., 2017). However, it has not yet been demonstrated that keeping premature newborns within a specific CrSO\(_2\) range will reduce brain injury or improve long-term outcome.

Suggested indications and algorithms for the use of NIRS in the NICU

Keeping in mind the limitations described throughout this chapter, we provide a suggested set of indications and algorithms for incorporating currently available NIRS devices for brain monitoring in daily NICU care. Box 14.1 represents a list of possible indications for the use of NIRS in the NICU. It is important to note and document the baseline measurement of individual newborns in order to interpret subsequent measurements accurately or the effects of any interventions. Significant rises or falls from a newborn’s baseline values are usually a more clinically important indicator of the newborn’s underlying condition than the absolute value of CrSO\(_2\). There is a wide range of normal CrSO\(_2\) values in neonates, reported to vary between 55% and 85% (10% higher if using a neonatal probe), with higher CrSO\(_2\) values in male vs female newborns, and higher CrSO\(_2\) values in SGA neonates than those of appropriate weight in the first 3 days after birth (Cohen et al., 2016). A decrease in CrSO\(_2\) could be associated with decreased cerebral O\(_2\) delivery/perfusion or increased O\(_2\) consumption. A newborn with a significant decrease in CrSO\(_2\) from baseline or absolute CrSO\(_2\)<60 should be evaluated for etiologies such as anemia, hypoxia, hypotension, chest hyperinflation, and hypocarbia and treated accordingly (Fig. 14.3A). An increase in CrSO\(_2\) could be associated with increased cerebral O\(_2\) delivery/perfusion or decreased O\(_2\) consumption. A newborn with a significant increase in CrSO\(_2\) from baseline or absolute CrSO\(_2\)>90 should be evaluated for etiologies such as hyperoxia, hypercarbia, oversedation, or severe brain injury (Fig. 14.3B). It should be kept in mind that NIRS is not yet a reliable tool for brain monitoring and CrSO\(_2\) values can be influenced by artifact as well as physiologic and pathologic factors. Thus there may not be a clear etiology for an abnormal CrSO\(_2\) value or CrSO\(_2\) change, in which case there should be consideration of errors in measurement related to artifact or the device itself. Despite some limitations, NIRS monitoring can be a valuable tool to help guide clinicians in managing critically ill newborns at risk of brain injury.

Future directions

As described throughout this chapter, it is important to be able to monitor brain hemodynamics and oxygen metabolism in critically ill newborns, in order to detect and treat deleterious changes in cerebral perfusion and oxygenation that may result in brain injury and adverse neurodevelopmental outcome. While currently available monitoring techniques are still somewhat limited, the wealth of research data and improvements in technology mean that NIRS can be used in certain clinical situations now and will likely be of greater utility in the coming years. Advances in the development of FDNIRS and DCS devices that provide continuous measurement of CMRO\(_2\) and CBF at the bedside would be more useful

**BOX 14.1. SUGGESTED INDICATIONS FOR THE USE OF NIRS IN THE NICU**

- Monitoring of extremely premature neonates <28–30 weeks GA to detect frequent disturbances in cerebral hemodynamics oxygenation occurring in the first 72h after birth
- Neonates requiring transfusion for significant anemia (before, during, and after)
- Neonates receiving fluids, inotropes, or hydrocortisone for BP support (before, during, and after administration)
- Neonates on significant respiratory support (e.g., high airway pressures, HFOV, iNO)
- Preterm neonates with PDA, to evaluate for hemodynamic significance of PDA
- Neonates with hydrocephalus (especially before, during, and after therapeutic LP or surgical intervention)
- Neonates with encephalopathy treated with hypothermia (throughout hypothermia and rewarming)
- Neonates with encephalopathy or other acute neurologic disorder, e.g., seizures, infarction, vascular malformations (e.g., vein of Galen or other types)
- Specific neonates per NICU attending discretion
Development and standard use of optodes/sensors and devices designed specifically for newborns will also improve accuracy and reliability of measures in newborns in different centers, which will be particularly important for large multicenter studies. Finally, larger prospective studies and trials using NIRS (particularly with measurement of CMRO₂ and CBF) are needed to address the controversial questions described in this chapter, since small single-center studies tend to yield variable results that cannot be generalized to larger populations and used to guide clinical management. Questions that would benefit from NIRS monitoring of cerebral perfusion and oxygenation include the best approach to transfusion, management of hypotension and respiratory disorders, and the management of neonatal HIE and CHD through better understanding of treatment of cerebral hemodynamics.

Fig. 14.3. Suggested algorithm for possible etiologies and interventions for neonates with (A) decreased or (B) increased CrSO₂.

**REFERENCES**


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