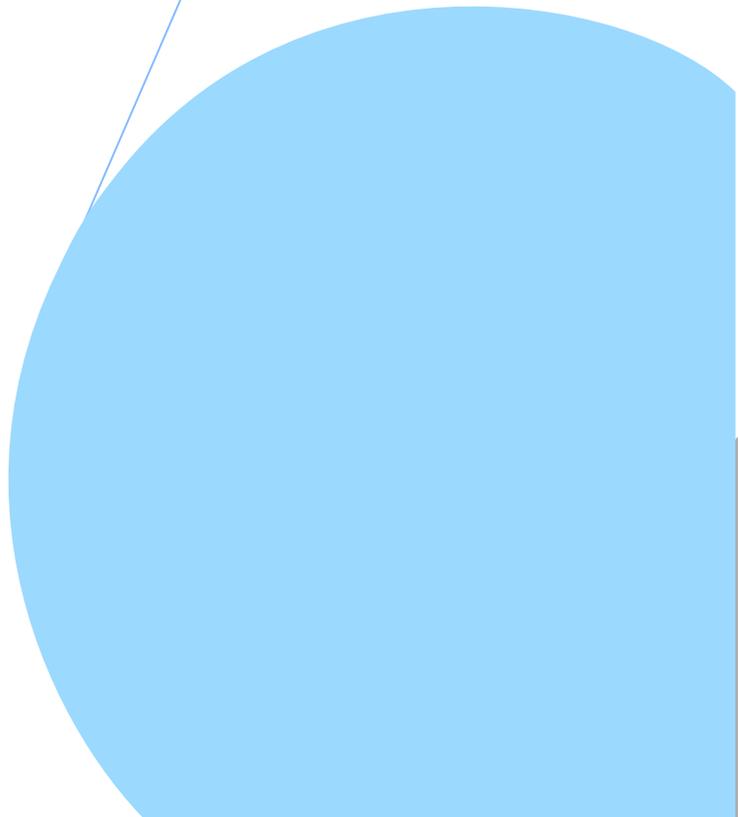
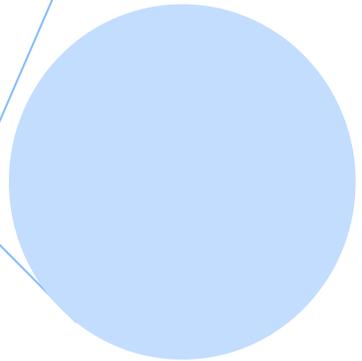
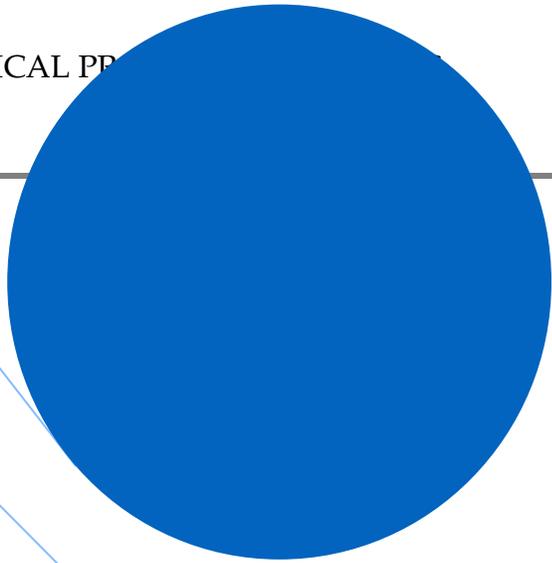


**PEDIATRIC NEWBORN MEDICINE CLINICAL  
PRACTICE GUIDELINES**

**Clinical NIRS (Near Infra-Red  
Spectroscopy) in the NICU**



Implementation Date: February 01, 2018





## **Clinical Practice Guideline: Clinical NIRS (Near Infra-Red Spectroscopy) in the NICU**

### **Points of emphasis/Primary changes in practice:**

- 1- To outline the indications of the clinical use of NIRS in the NICU.
- 2- To implement an algorithm for incorporating NIRS in the clinical care of neonates.
- 3- To standardize the process of ordering, applying and documenting NIRS data.

### **Rationale for change:**

Near-infrared spectroscopy (NIRS) is a non-invasive technique which allows for continuous monitoring of tissue oxygen saturation 2-3 cm directly below its sensors e.g., in brain, or kidneys. Feasibility and benefit of continuous NIRS has been demonstrated in neonates with congenital heart disease (CHD), term infants with neonatal encephalopathy, as well as premature infants in the determination of cerebral oxygenation and cerebral autoregulation in the context of systemic hypotension, a hemodynamically significant PDA and blood transfusion management.

A recent clinical trial has shown that continuous monitoring of cerebral NIRS has led to decreased burden of cerebral hypoxia. In the same study, cerebral hypoxia was associated with low brain electrical activity and severe intracranial hemorrhage.

**Questions? Please contact: Director of Neonatal Neurocritical Care, Department of Pediatric Newborn Medicine, BWH.**



<b>Clinical Guideline Name</b>	Clinical NIRS (Near Infra-Red Spectroscopy) in the NICU
<b>Effective Date</b>	
<b>Revised Date</b>	
<b>Contact Person</b>	Director of Neonatal Neurocritical Care
<b>Approved By</b>	Pediatric Newborn Medicine Clinical Practice Council <u>12/14/17</u> CWN PPG _____ BWH SPP Steering _____ Nurse Executive Board/CNO _____
<b>Keywords</b>	NIRS- Cerebral oximetry - Neuromonitoring

**This is a clinical practice guideline. While the guideline is useful in approaching the use of NIRS in the intensive care unit, clinical judgment and / or new evidence may favor an alternative plan of care, the rationale for which should be documented in the medical record.**

**I. Purpose**

- 1- To outline the indications of the clinical use of NIRS in the NICU.
- 2- To implement an algorithm for incorporating NIRS in the clinical care of neonates.
- 3- To standardize the process of ordering, applying and documenting NIRS data

**II.** All CPGs will rely on the [NICU Nursing Standards of Care](#).

**III. Patient population**

This protocol applies to neonates admitted to the BWH Neonatal Intensive Care Unit who are critically ill and at risk of neurologic compromise. This includes but is not limited to extremely premature infants, those with suspected hypoxic ischemic injury, or stroke, and infants at risk of cerebral injury from cardio-pulmonary risk factors.

**IV. Background/Summary Information**

**NIRS Background**

Near-infrared spectroscopy (NIRS) is used to measure tissue oxygen saturation 2-3 cm directly below its sensors e.g., in brain, kidney. Like a peripheral oxygen saturation monitor, NIRS uses the relative transparency of biological tissue to near-infrared light and the wavelength dependent absorption characteristics of hemoglobin, which vary with oxygenation.

By monitoring the intensity of light passing through the brain at two wavelengths, changes in attenuation can be converted into changes in the cerebral concentrations of oxyhemoglobin (HbO<sub>2</sub>) and deoxyhemoglobin (Hb). These two measures provide a regional oxygen saturation measurement (rSO<sub>2</sub>) [rSO<sub>2</sub>%=HbO<sub>2</sub>/(HbO<sub>2</sub>+Hb)\*100, essentially a mixed tissue saturation, which is approximately 70% venous and 30% arterial. When NIRS is used on the scalp, cerebral regional oxygen saturation (CrSO<sub>2</sub>) measurement can be established.



Feasibility and benefit of continuous NIRS have been demonstrated in neonates with congenital heart disease (CHD), term infants with neonatal encephalopathy, as well as premature infants in the determination of cerebral oxygenation and cerebral autoregulation in the context of systemic hypotension, a hemodynamically significant PDA and blood transfusion management.

**Factors that affect NIRS measurement:**

- 1- **Sensor type:** Normal CrSO<sub>2</sub> ranges from 55% to 85% when adult sensors were used (most of available clinical studies). When compared to the newer neonatal sensor, the neonatal sensor measured 10% higher than the adult sensor. [1]
- 2- **Sensor position:** Although the right to left difference in CrSO<sub>2</sub> is small, when used at 4 different sites a difference of up to  $\pm 18\%$  was detected. This variability signifies the importance of using CrSO<sub>2</sub> as a trend rather than an absolute number. [2]
- 3- **Gestational age:** CrSO<sub>2</sub> in the first day of life is increased in very premature infants when compared to term infants. [3, 4].  
However, in contrast, looking specifically within preterm infants < 32 weeks, a positive correlation was noted between GA and CrSO<sub>2</sub> measured during the first 3 days of life (1% per week GA) [5].
- 4- **Time after birth:** Immediately after birth CrSO<sub>2</sub> is low and rapidly increases from an average of 44% at 3 min to an average of 76% at 7 minutes of life, after which CrSO<sub>2</sub> remains stable. [6]. Alderliesten et al., described an increase in CrSO<sub>2</sub> followed by a decrease, creating a parabolic curve with a peak at about 36 h of life. [5] With weekly measurement in premature infants it was noted that CrSO<sub>2</sub> decreases, reaching the lowest level at six to eight weeks. [7]
- 5- **Head position:** Brief changes in head position do not cause significant changes in CrSO<sub>2</sub>. [8]
- 6- **Day to day interventions:** ETT suctioning, handling and diaper change can cause significant fluctuation in CrSO<sub>2</sub>. [9]

## Pathological conditions affecting CrSO<sub>2</sub> in Preterm Neonates

### Factors associated with decreased CrSO<sub>2</sub>

#### 1- Hypocarbica

Hypocarbica is associated with cerebral vasoconstriction and periventricular leukomalacia, perhaps secondary to cerebral ischemia and. [10-13] Acute decrease in end-tidal CO<sub>2</sub> was associated with decreased CrSO<sub>2</sub>. [14]

#### 2- Anemia

The hemoglobin concentration correlates with CrSO<sub>2</sub> [15, 16]. PRBCs transfusion is associated with increased CrSO<sub>2</sub> in anemic premature neonates. [15, 17] Improvement in CrSO<sub>2</sub> and symptoms of desaturation spells was more significant in preterm infants with a pre-transfusion CrSO<sub>2</sub> < 55% [18].

#### 3- Hypotension with lack of autoregulation

The finding of a positive correlation between cerebral oxygenation and arterial pressure has been used as a marker of cerebrovascular pressure passivity with is common in sick premature infants and is associated with intracranial hemorrhage. [19-23] A decrease of absolute mean blood pressure is not always associated with lower CrSO<sub>2</sub> and is not necessarily associated with worse neurodevelopmental outcome. However CrSO<sub>2</sub> < 50% is associated with worse neurodevelopmental outcome. [24] Whether CrSO<sub>2</sub> can be used as a marker to treat low blood pressure needs to be studied. However, when used, it must be combined with other parameters to fully evaluate the significance of the low BP, e.g., blood lactate, capillary refill, urine output, and cardiac output. [25]

#### 4- Thoracic Hyperinflation

Since mechanical ventilation can alter intrathoracic pressure, affect venous return and thereby cardiac output, it can have significant effect on the cerebral circulation. [26, 27] NIRS has a potential to detect the affects of mechanical respiratory support on the cerebral circulation. [28-30]

#### 5- PDA

Although studies have shown that hemodynamically significant PDA is associated with decreased CrSO<sub>2</sub> [31, 32], reports regarding the effect of either medical or surgical treatments of PDA on CrSO<sub>2</sub> have been inconsistent. [33-35]

#### 6- Apnea

CrSO<sub>2</sub> decreased significantly during apneic spells associated with bradycardia compared to spells with no bradycardia. [36]

#### 7- Germinal Matrix-Intraventricular Hemorrhage GM-IVH

Multiple studies have reported increased CrSO<sub>2</sub> in the first hours of life in premature infants who later developed GM-IVH [37-39]. However, patients already identified with IVH are noted to have lower CrSO<sub>2</sub>. [40-42]

#### 8- Hydrocephalus

In preterm infants with post-hemorrhagic ventricular dilatation (PHVD), ventricular decompression was associated with an increase in CrSO<sub>2</sub>. [43, 44]

## Factors associated with increased CrSO<sub>2</sub>

### 1- Hypercarbia

An acute increase in end-tidal CO<sub>2</sub> in premature infants was associated with increased CrSO<sub>2</sub>.

[14] Hypercarbia is associated with cerebral vasodilatation and with the development of germinal-matrix/ intraventricular hemorrhage [45, 46].

### 2- Hyperoxia

CrSO<sub>2</sub> correlates with systemic O<sub>2</sub> saturation (SaO<sub>2</sub>). Because of concern for oxygen toxicity, the FiO<sub>2</sub> should only be changed to maintain systemic SaO<sub>2</sub> within unit specific target ranges. [25]

### 3- Hypoglycemia

Hypoglycemia can be associated with increased cerebral blood flow. [47] Whether NIRS can be used as a marker of significant hypoglycemia is yet to be determined.

### 4- Inotropes with lack of autoregulation

Use of inotropes in premature infants may be associated with increased mortality and morbidity.

[48] NIRS was used to monitor increasing cerebral blood flow with the use of inotropes. [49]

NIRS can be used as a bedside tool to monitor the effect of these medications on cerebral perfusion and oxygenation and potentially could lead to interventions to limit their adverse effects.

## Full Term Neonates

### 1- Neonatal Encephalopathy

In neonates with neonatal encephalopathy increased CrSO<sub>2</sub> between 24-48 h is associated with adverse outcomes. [50] Combining CrSO<sub>2</sub> and aEEG had the highest predictive value for MRI detected brain injury and worse outcome. [51, 52] The predictive value of higher CrSO<sub>2</sub> to predict outcome is significant as early as 10 hours of life. [53]

### 2- Congenital Heart Diseases

Congenital heart disease is associated with worse long term neurodevelopmental outcomes. [54] Brain monitoring of these infants carries the potential for early detection and possible interventions to improve such outcomes. [55] Non-cyanotic CHD infants have an average CrSO<sub>2</sub> of 70% while those with cyanotic CHD have CrSO<sub>2</sub> values ranging from 40 to 70%. [56] In patients without pre-existing brain damage, decreased preoperative CrSO<sub>2</sub> is associated with worse neurodevelopmental outcome up to 3 years of age. [57]



## V. Guideline

### Indications for the use of NIRS at BWH NICU

- 1- Routine monitoring of extremely premature infants < 28 weeks GA for the first 72 hours of life
- 2- Neonates with significant anemia requiring transfusion (before, during and after)
- 3- Infants receiving inotropes or hydrocortisone for BP support (before, during and after inotropes)
- 4- Infants on significant respiratory support (e.g., high pressures, HFV, iNO)
- 5- Preterm infants with PDA to evaluate for hemodynamic significance
- 6- Infants with hydrocephalus (especially before, during and after therapeutic LP or surgical intervention)
- 7- Infants with neonatal encephalopathy receiving therapeutic hypothermia (through the period of cooling, and re-warming)
- 8- Neonates with CNS injury/ abnormality e.g., seizures, infarct/stroke, vascular malformations such as Vein of Galen malformation and AV malformation.
- 9- Case by case per NICU attending request

### Starting the NIRS Study

- Identify infants indicated for NIRS monitoring
- Provider enters an order in Epic requesting “NIRS-Continuous Monitoring” to be started with the indications outlined.

### Role of the bedside nurse in NIRS monitoring

- Equipment set up and lead placement is completed by the NICU bedside nurse
- Skin care: Can use either adhesive probe or wraps around probe to keep it in place without directly sticking to skin; will be determined based on age of neonate and skin condition (**Appendix- I**)
- Neonatal probes are placed unilaterally over the frontal cortex and can be used bilaterally if clinically indicated
- Bedside nurse documents CrSO<sub>2</sub> in EMR. NIRS can be added to the patient chart under: **Flowsheets> NICU Vitals** by using the function (**Add Rows**) and search for NIRS.
- CrSO<sub>2</sub> will be documented hourly and skin condition will be observed and documented with each routine neonatal care.
- Bedside nurse will mark significant events on the NIRS device.
- 

### NIRS Interpretation:

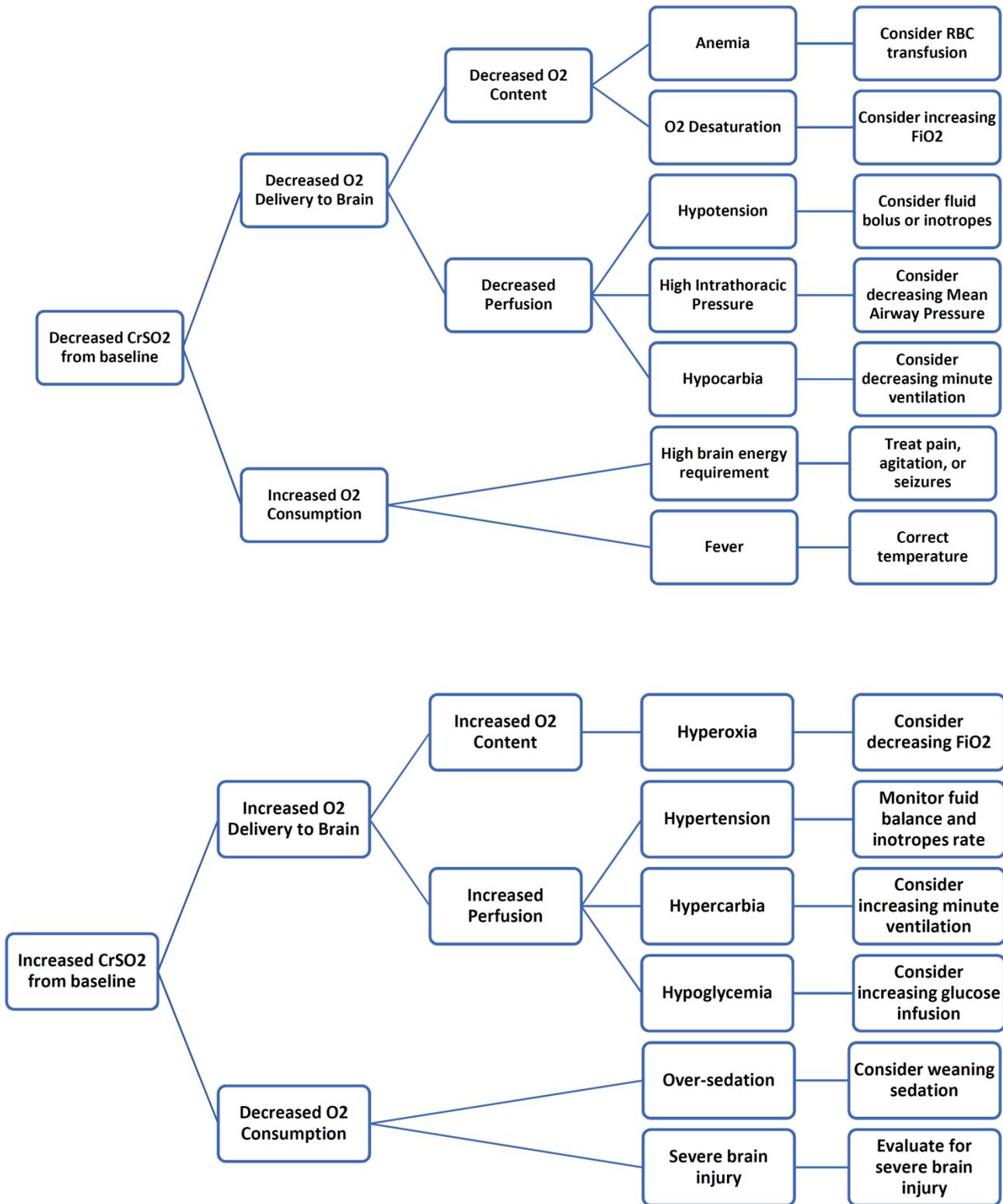
- CrSO<sub>2</sub> reflects the balance between brain tissue perfusion and oxygen extraction.
- CrSO<sub>2</sub> has a wide range of normal and is reported to be between 55% and 85% (with 10% higher if using neonatal probe). A recent clinical trial has shown that continuous monitoring of cerebral NIRS enabled a decreased burden of cerebral hypoxia. [58] Although, in the same study cerebral hypoxia was associated with low brain electrical activity and severe intracranial hemorrhage [59], it is not yet clear that maintaining premature infants within this range improves long term outcome.



- It is important to note and document the baseline measurement of each individual patient. Significant rises/falls from patient's baseline (e.g., > 20%) may represent underlying status changes more accurately than the absolute number.
- A decrease in CrSO<sub>2</sub> could be associated with decreased cerebral O<sub>2</sub> delivery/ perfusion or increased O<sub>2</sub> consumption. **A patient with significantly decreased CrSO<sub>2</sub> relative to baseline or absolute CrSO<sub>2</sub> < 60 %** needs to be evaluated for anemia, hypoxia, hypotension, chest hyperinflation, hypocarbia and treated accordingly. **(Figure 1)**
- An increase in CrSO<sub>2</sub> could be associated with increased cerebral O<sub>2</sub> delivery/ perfusion or decreased O<sub>2</sub> consumption. **A patient with significantly increased CrSO<sub>2</sub> relative to baseline or absolute CrSO<sub>2</sub> > 90%** needs to be evaluated for hyperoxia, hypercarbia, hypoglycemia, over sedation or severe brain injury. **(Figure 1)**
- **In patients with no physiologic explanation for the abnormal CrSO<sub>2</sub>, no direct interventions (e.g., manipulating FiO<sub>2</sub>) should be attempted solely to correct the CrSO<sub>2</sub> value.**



Figure 1: Suggested Algorithm for Interpreting Neonatal CrSO2



**References:**

1. Alderliesten, T., et al., *Reference values of regional cerebral oxygen saturation during the first 3 days of life in preterm neonates*. *Pediatr Res*, 2016. **79**(1-1): p. 55-64.
2. Wijbenga, R.G., P.M.A. Lemmers, and F. Van Bel, *Cerebral oxygenation during the first days of life in preterm and term neonates: Differences between different brain regions*. *Pediatric Research*, 2011. **70**(4): p. 389-394.
3. Sorensen, L.C. and G. Greisen, *The brains of very preterm newborns in clinically stable condition may be hyperoxygenated*. *Pediatrics*, 2009. **124**(5): p. e958-9e63.
4. Tina, L.G., et al., *Near Infrared Spectroscopy in healthy preterm and term newborns: correlation with gestational age and standard monitoring parameters*. *Curr Neurovasc Res*, 2009. **6**(3): p. 148-54.
5. Alderliesten, T., et al., *Reference values of regional cerebral oxygen saturation during the first 3 days of life in preterm neonates*. *Pediatric Research*, 2016. **79**(1): p. 55-64.
6. Van Vonderen, J.J., et al., *Measuring physiological changes during the transition to life after birth*. *Neonatology*, 2014. **105**(3): p. 230-242.
7. Roche-Labarbe, N., et al., *Near-infrared spectroscopy assessment of cerebral oxygen metabolism in the developing premature brain*. *Journal of Cerebral Blood Flow and Metabolism*, 2012. **32**(3): p. 481-488.
8. Ancora, G., et al., *Effect of posture on brain hemodynamics in preterm newborns not mechanically ventilated*. *Neonatology*, 2010. **97**(3): p. 212-7.
9. Limperopoulos, C., et al., *Cerebral hemodynamic changes during intensive care of preterm infants*. *Pediatrics*, 2008. **122**(5): p. e1006-e1013.
10. Liao, S.L., et al., *Effect of hypocapnia in the first three days of life on the subsequent development of periventricular leukomalacia in premature infants*. *Acta Paediatr Taiwan*, 2001. **42**(2): p. 90-3.
11. Greisen, G. and R.C. Vannucci, *Is periventricular leucomalacia a result of hypoxic-ischaemic injury? Hypocapnia and the preterm brain*. *Biology of the Neonate*, 2001. **79**(3-4): p. 194-200.
12. Murase, M. and A. Ishida, *Early hypocarbia of preterm infants: its relationship to periventricular leukomalacia and cerebral palsy, and its perinatal risk factors*. *Acta Paediatr*, 2005. **94**(1): p. 85-91.
13. Shankaran, S., et al., *Cumulative index of exposure to hypocarbia and hyperoxia as risk factors for periventricular leukomalacia in low birth weight infants*. *Pediatrics*, 2006. **118**(4): p. 1654-1659.
14. Dix, L.M.L., et al., *Carbon Dioxide Fluctuations Are Associated with Changes in Cerebral Oxygenation and Electrical Activity in Infants Born Preterm*. *J Pediatr*, 2017. **187**: p. 66-72.e1.
15. Van Hoften, J.C.R., et al., *Cerebral tissue oxygen saturation and extraction in preterm infants before and after blood transfusion*. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, 2010. **95**(5): p. F352-F358.
16. El-Dib, M., et al., *Brain Maturity and Variation of Oxygen Extraction in Premature Infants*. *Am J Perinatol*, 2016. **33**(8): p. 814-20.
17. Seidel, D., et al., *Changes in regional tissue oxygenation saturation and desaturations after red blood cell transfusion in preterm infants*. *J Perinatol*, 2013. **33**(4): p. 282-7.
18. Seidel, D., et al., *Changes in regional tissue oxygenation saturation and desaturations after red blood cell transfusion in preterm infants*. *Journal of Perinatology*, 2013. **33**(4): p. 282-287.
19. Tsuji, M., et al., *Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants*. *Pediatrics*, 2000. **106**(4): p. 625-632.
20. Soul, J.S., et al., *Fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants*. *Pediatric Research*, 2007. **61**(4): p. 467-473.



21. O'Leary, H., et al., *Elevated cerebral pressure passivity is associated with prematurity-related intracranial hemorrhage*. Pediatrics, 2009. **124**(1): p. 302-309.
22. Riera, J., et al., *New time-frequency method for cerebral autoregulation in newborns: Predictive capacity for clinical outcomes*. Journal of Pediatrics, 2014. **165**(5): p. 897-902.e1.
23. Vesoulis, Z.A. and A.M. Mathur, *Cerebral Autoregulation, Brain injury, and the Transitioning Premature infant*. Frontiers in Pediatrics, 2017. **5**: p. 7.
24. Alderliesten, T., et al., *Hypotension in preterm neonates: Low blood pressure alone does not affect neurodevelopmental outcome*. Journal of Pediatrics, 2014. **164**(5): p. 986-991.
25. Pellicer, A., et al., *The SafeBoosC phase II randomised clinical trial: A treatment guideline for targeted near-infrared-derived cerebral tissue oxygenation versus standard treatment in extremely preterm infants*. Neonatology, 2013. **104**(3): p. 171-178.
26. Skinner, J.R., et al., *Central venous pressure in the ventilated neonate*. Archives of Disease in Childhood, 1992. **67**(4 SUPPL.): p. 374-377.
27. Evans, N. and M. Kluckow, *Early determinants of right and left ventricular output in ventilated preterm infants*. Arch Dis Child Fetal Neonatal Ed, 1996. **74**(2): p. F88-94.
28. Zaramella, P., et al., *Does helmet CPAP reduce cerebral blood flow and volume by comparison with Infant Flow driver CPAP in preterm neonates?* Intensive Care Medicine, 2006. **32**(10): p. 1613-1619.
29. Palmer, K.S., et al., *Effects of positive and negative-pressure ventilation on cerebral blood-volume of newborn-infants*. Acta paediatrica, 1995. **84**(2): p. 132-139.
30. Noone, M.A., et al., *Postnatal adaptation of cerebral blood flow using near infrared spectroscopy in extremely preterm infants undergoing high-frequency oscillatory ventilation*. Acta Paediatr, 2003. **92**(9): p. 1079-84.
31. Lemmers, P.M., M.C. Toet, and F. van Bel, *Impact of patent ductus arteriosus and subsequent therapy with indomethacin on cerebral oxygenation in preterm infants*. Pediatrics, 2008. **121**(1): p. 142-7.
32. Underwood, M.A., J.M. Milstein, and M.P. Sherman, *Near-infrared spectroscopy as a screening tool for patent ductus arteriosus in extremely low birth weight infants*. Neonatology, 2007. **91**(2): p. 134-9.
33. Bhatt, M., A. Petrova, and R. Mehta, *Does treatment of patent ductus arteriosus with cyclooxygenase inhibitors affect neonatal regional tissue oxygenation?* Pediatric Cardiology, 2012. **33**(8): p. 1307-1314.
34. Vanderhaegen, J., et al., *Surgical closure of the patent ductus arteriosus and its effect on the cerebral tissue oxygenation*. Acta Paediatr, 2008. **97**(12): p. 1640-4.
35. Lemmers, P.M.A., et al., *Is cerebral oxygen supply compromised in preterm infants undergoing surgical closure for patent ductus arteriosus?* Archives of Disease in Childhood: Fetal and Neonatal Edition, 2010. **95**(6): p. F429-F434.
36. Pichler, G., B. Urlesberger, and W. Müller, *Impact of bradycardia on cerebral oxygenation and cerebral blood volume during apnoea in preterm infants*. Physiological Measurement, 2003. **24**(3): p. 671-680.
37. Alderliesten, T., et al., *Cerebral oxygenation, extraction, and autoregulation in very preterm infants who develop peri-intraventricular hemorrhage*. J Pediatr, 2013. **162**(4): p. 698-704 e2.
38. Zhang, Y., et al., *Cerebral near-infrared spectroscopy analysis in preterm infants with intraventricular hemorrhage*. Conf Proc IEEE Eng Med Biol Soc, 2011. **2011**: p. 1937-40.
39. Balegar, K.K., et al., *Early cerebral oxygen extraction and the risk of death or sonographic brain injury in very preterm infants*. J Pediatr, 2014. **164**(3): p. 475-80.e1.



40. Noori, S., et al., *Changes in cardiac function and cerebral blood flow in relation to peri/intraventricular hemorrhage in extremely preterm infants*. J Pediatr, 2014. **164**(2): p. 264-70 e1-3.
41. Sorensen, L.C., et al., *Neonatal cerebral oxygenation is not linked to foetal vasculitis and predicts intraventricular haemorrhage in preterm infants*. Acta Paediatr, 2008. **97**(11): p. 1529-34.
42. Verhagen, E.A., et al., *Cerebral oxygenation in preterm infants with germinal matrix-intraventricular hemorrhages*. Stroke, 2010. **41**(12): p. 2901-2907.
43. Norooz, F., et al., *Decompressing posthaemorrhagic ventricular dilatation significantly improves regional cerebral oxygen saturation in preterm infants*. Acta Paediatr, 2015. **104**(7): p. 663-9.
44. Soul, J.S., et al., *CSF removal in infantile posthemorrhagic hydrocephalus results in significant improvement in cerebral hemodynamics*. Pediatr Res, 2004.
45. Kaiser, J.R., et al., *Hypercapnia during the first 3 days of life is associated with severe intraventricular hemorrhage in very low birth weight infants*. Journal of Perinatology, 2006. **26**(5): p. 279-285.
46. Kaiser, J.R., C.H. Gauss, and D.K. Williams, *The effects of hypercapnia on cerebral autoregulation in ventilated very low birth weight infants*. Pediatric Research, 2005. **58**(5): p. 931-935.
47. Pryds, O., N.J. Christensen, and B. Friis-Hansen, *Increased cerebral blood flow and plasma epinephrine in hypoglycemic, preterm neonates*. Pediatrics, 1990. **85**(2): p. 172-176.
48. Wong, J., et al., *Inotrope use among extremely preterm infants in Canadian neonatal intensive care units: variation and outcomes*. Am J Perinatol, 2015. **32**(1): p. 9-14.
49. Munro, M.J., A.M. Walker, and C.P. Barfield, *Hypotensive extremely low birth weight infants have reduced cerebral blood flow*. Pediatrics, 2004. **114**(6): p. 1591-1596.
50. Toet, M.C., et al., *Cerebral oxygenation and electrical activity after birth asphyxia: Their relation to outcome*. Pediatrics, 2006. **117**(2): p. 333-339.
51. Lemmers, P.M.A., et al., *Cerebral oxygenation and brain activity after perinatal asphyxia: Does hypothermia change their prognostic value?* Pediatric Research, 2013. **74**(2): p. 180-185.
52. Goeral, K., et al., *Prediction of Outcome in Neonates with Hypoxic-Ischemic Encephalopathy II: Role of Amplitude-Integrated Electroencephalography and Cerebral Oxygen Saturation Measured by Near-Infrared Spectroscopy*. Neonatology, 2017. **112**(3): p. 193-202.
53. Peng, S., et al., *Does near-infrared spectroscopy identify asphyxiated newborns at risk of developing brain injury during hypothermia treatment?* Am J Perinatol, 2015. **32**(6): p. 555-64.
54. Massaro, A.N., et al., *Factors associated with adverse neurodevelopmental outcomes in infants with congenital heart disease*. Brain Dev, 2008. **30**(7): p. 437-46.
55. Neshat Vahid, S. and J.M. Panisello, *The state of affairs of neurologic monitoring by near-infrared spectroscopy in pediatric cardiac critical care*. Curr Opin Pediatr, 2014. **26**(3): p. 299-303.
56. Andropoulos, D.B., et al., *Neurological monitoring for congenital heart surgery*. Anesthesia and Analgesia, 2004. **99**(5): p. 1365-1375.
57. Toet, M.C., et al., *Cerebral oxygen saturation and electrical brain activity before, during, and up to 36 hours after arterial switch procedure in neonates without pre-existing brain damage: its relationship to neurodevelopmental outcome*. Exp Brain Res, 2005. **165**(3): p. 343-50.
58. Hyttel-Sorensen, S., et al., *Cerebral near infrared spectroscopy oximetry in extremely preterm infants: Phase II randomised clinical trial*. BMJ (Online), 2015. **350**.
59. Plomgaard, A.M., et al., *Early biomarkers of brain injury and cerebral hypo- and hyperoxia in the SafeBoosC II trial*. PLoS One, 2017. **12**(3): p. e0173440.