Review

Near-infrared spectroscopy: Applications in neonates

Beena G. Sood a, b, *, Kathleen McLaughlin b, Josef Cortez c

a Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Wayne State University, Children's Hospital of Michigan, Detroit, MI, USA
b Hutzel Women's Hospital, Detroit, MI, USA
c Division of Neonatology, Department of Pediatrics, University of Florida Health Jacksonville, Jacksonville, FL, USA

Keywords:
Near-infrared spectroscopy
Neonates
Preterm
Oximetry
Ischemia

SUMMARY

Near-infrared spectroscopy (NIRS) offers non-invasive, in-vivo, real-time monitoring of tissue oxygenation. Changes in regional tissue oxygenation as detected by NIRS may reflect the delicate balance between oxygen delivery and consumption. Originally used predominantly to assess cerebral oxygenation and perfusion perioperatively during cardiac and neurosurgery, and following head trauma, NIRS has gained widespread popularity in many clinical settings in all age groups including neonates. However, more studies are required to establish the ability of NIRS monitoring to improve patient outcomes, especially in neonates. This review provides a comprehensive description of the use of NIRS in neonates.

© 2015 Published by Elsevier Ltd.

1. Introduction

Adequate tissue oxygenation is a prerequisite for aerobic metabolism [1]. Occult regional dysoxia associated with ischemia—reperfusion is a major contributor to morbidity and mortality in critically ill patients, with both subnormal and supranormal tissue oxygenation being detrimental. End-organ perfusion and oxygenation is indirectly monitored by means of systemic blood pressure, heart rate, arterial oxygen saturation, hemoglobin concentration, and mixed venous oxygen saturation (SvO2). Direct, non-invasive, real-time assessment of tissue oxygenation is desirable in critically ill neonates. In 1999, a workshop convened by the NICHD and NINDS recommended that near-infrared spectroscopy (NIRS) can be used to conveniently quantitate cerebral oxygenation continuously at the bedside without the risk associated with traditional invasive studies [2]. NIRS has the potential to monitor regional oxygen saturation (RSO2) in multiple organs, with cerebral (cRSO2), renal (rRSO2), and splanchnic (sRSO2) oxygenation being the most frequently monitored in neonates [3]. This article provides a brief synopsis of the principles of NIRS and clinical applications in neonates.

2. Principles of near-infrared spectroscopy

NIRS, introduced in 1977 as a technology that is capable of continuous non-invasive monitoring of oxygenation in living tissue, is based on the transparency of biological tissue to light in the near-infrared spectrum (700–1000 nm wavelength) and its differential absorption by chromophores including hemoglobin, myoglobin, and cytochrome aa3 [4–8]. Light absorption by hemoglobin is an order of magnitude greater than that of cytochrome aa3. NIRS devices use NIR light at wavelengths of maximal absorption for the relevant chromophores, generally 700–850 nm, where the absorption spectra of oxyhemoglobin (O2Hb) and deoxyhemoglobin (HHb) are maximally separated with minimal overlap with that of water (980 nm) [8] (Fig. 1).

Early NIRS devices used two wavelengths, limiting their use to the measurement of two chromophores, O2Hb and HHb [8]. The addition of more wavelengths, through additional light sources that emit light at discrete wavelengths, or by broadband spectroscopy systems, improves accuracy. One of the most commonly used NIRS devices, IN Vivo Optical Spectroscopy (INVOS) System [Covidien, Dublin, Ireland (formerly Somanetics, Troy, MI, USA)], has a light-emitting diode (LED) that emits NIR light of two wavelengths (730 and 810 nm), and two optodes to receive the scattered light (Fig. 2) [7]. The proximal or shallow detector receives a signal from the peripheral tissue and the distal or deep detector receives a signal from the peripheral and deep tissues; by subtracting the proximal from the distal value, tissue-specific RSO2 at a depth of about 1–2 cm is obtained [9]. Because the tissue microcirculation contains arterial, venous, and capillary components, RSO2
represent a 'weighted average', with approximately 75–85% of the signal originating from venules. As opposed to pulse-oximeters which subtract out non-pulsatile flow, NIRS devices focus on the total light signal [10]. Accordingly, pulse oximetry provides measurement of arterial oxygen saturation (SO₂) reflecting only oxygen supply to tissue, whereas NIRS-measured RSO₂ reflects the balance of local tissue oxygen supply and demand. Thus, NIRS is considered complementary to pulse oximetry.

A modification of the Beer–Lambert law \( (A = a B d C + G) \) describes the relationship between the absorption of NIR light and the absorbing chromophore's concentration in tissue, where \( A \) is the attenuation measured in units of optical density, \( a \) is the specific absorption coefficient of the chromophore at a particular wavelength (L/μmol/cm), \( B \) is the differential pathlength factor (DPF), \( d \) is the distance between NIRS optodes (cm), \( C \) is the concentration of the chromophore in the tissue (mmol/L), and \( G \) is an additive term that represents the scattering losses of NIR light as it passes through the tissue. All coefficients in the equation, except for the DPF, are known constants or can be measured. Difficulty in determination of DPF and its variation between subjects has been a major obstacle to standardization of NIRS parameters across subjects and the clinical application of NIRS [10]. Consequently, NIR spectrometers commonly used in clinical practice avoid the need to estimate optical path-length by measuring only the ratio of \( O₂ \text{Hb} \) to \( HHb \), rather than their absolute concentrations. Because the change in the intensity of the reflected light depends on the \( O₂ \text{Hb} \) to \( HHb \) ratio, an oxyhemoglobin saturation can be derived:

\[
RSO₂ = \frac{HbO₂}{(HbO₂ + HHb)}
\]

Fractional tissue oxygen extraction (FTOE), a measure for the amount of oxygen extracted by the tissue, can be computed from RSO₂ and arterial oxygen saturation (SO₂) thus: \( \text{FTOE} = (SO₂ - RSO₂)/SO₂ \) [11]. Regional FTOE gives an estimate of the balance between local oxygen delivery and consumption [6].

3. Devices

In recent years, NIRS has evolved from an experimental tool to a clinical monitoring device with broad potential use [1]. Improvements in design have resulted in smaller, cheaper, resilient monitors without the need for calibration and improved user interfaces. Specialized mini-probes are available for neonates.

NIRS monitors are available from different manufacturers (Table 1) [1,8,10,12,13]. The INVOS oximeter was the first to be approved by the US Food and Drug Administration in the 1990s, reinvigorating clinical interest in NIRS. It is the most common oximeter in clinical use today. It utilizes two LED sources and two photodetectors (described above). In contrast, the Fore-Sight cerebral oximeter (CAS Medical Systems, Branford, CT, USA) uses a four-wavelength (690, 779, 808, and 850 nm) laser source and two photodiode detectors 1.25 and 4 cm from the source, providing an absolute measurement of \( RSO₂ \). The Nonin Equanox 7600 (Nonin Medical Inc., Plymouth, MN, USA), utilizes four LEDs (730, 760, 810, and 880 nm) in a dual-emitter/dual-detector sensor. Some manufacturers are combining NIRS and other technology into devices with multimodal capability [8]. Using a combination of NIR light and ultrasound, CerOx (Ornim Medical Ltd, Lod, Israel) provides assessment of brain oxygenation and blood flow.

Existing devices incorporate the same technology but with differences in the number and absolute value of wavelengths, as well as in computational algorithms to translate measured changes in light attenuation to a physiologic measure such as changes in \( O₂ \text{Hb} \) and \( HHb \) concentrations and \( RSO₂ \). Thus, comparing devices from different manufacturers can be difficult. In a bench study to evaluate test–retest variability of NIRS-measured \( cRSO₂ \) using the INVOS 5100 and the NIRO 300 cerebral oximeters in anesthetized children [14], a wide range of values were obtained with poor agreement between the devices. Similarly, a comparison of peripheral muscle \( RSO₂ \) (pRSO₂) in adults using three NIRS oximeters showed significant pair-wise differences in median values, repeatability, and/or dynamic measurements [12]. Highly significant differences have also been reported between \( cRSO₂ \) readings obtained with different probes [15]. The large range of \( RSO₂ \) values obtained with different sensors and oximeters in otherwise healthy subjects makes it difficult to define a normal range of \( cRSO₂ \) and has limited widespread clinical implementation [14]. When \( RSO₂ \) is used for trend monitoring, the reproducibility of measurement is less important; but good reproducibility is paramount if \( RSO₂ \) is to be used as a spot measurement or if the monitoring is started when the patient status is uncertain, e.g. on admission to critical care.
decreases in rRSO2 and cRSO2 indicate decreased total-body perfusion from selective differences in total-body perfusion from selective Simultaneously measured rRSO2 can serve as a control for cRSO2 by has been reported in children with CHD and in animal studies[9,16].

been reported in children with CHD and in animal studies[9,16].

position has been used successfully for monitoring cRSO2 in pre-

be theoretically detect differential perfusion or oxygenation be-

The Society of Thoracic Surgeons (STS) has the world’s largest database of cardiothoracic cases (3.77 million) (http://www.sts.org/ national-database). Recognizing the importance of cerebral oximetry in perioperative monitoring, this database now includes seven fields related to cerebral oximetry [24]. In 23% of procedures, cerebral oximetry provided the first indication of impending clinical problems. A proposed treatment algorithm in response to changes in cRSO2 during pediatric cardiac surgery suggests maneuvers to increase cardiac output, hematocrit, inspired oxygen concentration, or PaCO2 to decrease cerebral vasoconstriction if cRSO2 decreases by >20% from a stable baseline [16,22]. If absolute cRSO2 is <30%, immediately initiating or returning to bypass with aggressive efforts to improve oxygenation is suggested. If absolute cRSO2 measures >95%, cerebral blood flow, velocity bypass flow, and PaCO2 should be examined to avoid hyperperfusion injury.

Table 1
Overview of commercial near-infrared spectroscopy oximetry instruments.

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Neonatal sensor</th>
<th>Company</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>INVOS 5100 C</td>
<td>Yes</td>
<td>Covidien, Ireland</td>
<td><a href="http://www.covidien.com">www.covidien.com</a></td>
</tr>
<tr>
<td>Fore-Sight</td>
<td>Yes</td>
<td>Casmed, USA</td>
<td><a href="http://www.casmed.com">www.casmed.com</a></td>
</tr>
<tr>
<td>Equinox 7600™</td>
<td>Yes</td>
<td>Nonin Medical, Inc., USA</td>
<td><a href="http://www.nonin.com/Model7600">www.nonin.com/Model7600</a></td>
</tr>
<tr>
<td>OxiplexTS</td>
<td>Yes</td>
<td>ISS, USA</td>
<td><a href="http://www.iss.com">www.iss.com</a></td>
</tr>
<tr>
<td>T:Ox</td>
<td>Yes</td>
<td>VioOptx, USA</td>
<td><a href="http://www.vioptx.com">www.vioptx.com</a></td>
</tr>
<tr>
<td>NIMO</td>
<td>Custom</td>
<td>NIROX, Italy</td>
<td><a href="http://www.nirox.it">www.nirox.it</a></td>
</tr>
<tr>
<td>NIRO 100, NIRO 200</td>
<td>Yes</td>
<td>Hamamatsu, Japan</td>
<td><a href="http://www.hamamatsu.com">www.hamamatsu.com</a></td>
</tr>
<tr>
<td>O2 C</td>
<td>Yes</td>
<td>LEA, Germany</td>
<td><a href="http://www.lea.de">www.lea.de</a></td>
</tr>
<tr>
<td>OM-220</td>
<td>Yes</td>
<td>Shimadzu, Japan</td>
<td><a href="http://www.shimadzu.com">www.shimadzu.com</a></td>
</tr>
<tr>
<td>TRS-20</td>
<td>Yes</td>
<td>Hamamatsu, Japan</td>
<td><a href="http://www.hamamatsu.com">www.hamamatsu.com</a></td>
</tr>
<tr>
<td>CerOx™, C-FLOW</td>
<td></td>
<td>Ornim Medical, Israel</td>
<td><a href="http://www.ornim.com">www.ornim.com</a></td>
</tr>
</tbody>
</table>


### 4. Site selection

The most common application of NIRS is the assessment of cRSO2 using sensors placed on the patient’s forehead [9]. cRSO2 derives mostly from the balance between oxygen delivery and utilization in the gray matter in the frontal region. It is recommended that the cerebral probe be placed on the right or left side of the forehead and away from nevi, sinus cavities, the superior sagittal sinus, subdural or epidural hematomas, or other anomalies such as arteriovenous malformations. Bilateral cRSO2 monitoring can theoretically detect differential perfusion or oxygenation between hemispheres — particularly important in patients without an intact Circle of Willis, which occurs in 5% of neonates [16]. Because of the small surface area available on the forehead, the midline position has been used successfully for monitoring cRSO2 in preterm neonates [17–19]. Factors that affect the accuracy of cRSO2 measurements include sensor placement at different locations on the forehead, shape of the forehead, extracranial structures and blood flow, and depth of the brain surface [20].

In neonates and infants, NIRS-measured RSO2 of deeper organs [kidneys (rRSO2), intestines (sRSO2)] is feasible due to their superficial location [9]. In addition, peripheral tissue oxygenation (pRSO2) can be measured over the forearm, calf, upper arm, and upper leg. Placement of sensor over fatty deposits, hair, bony protruberances, nevi, hematomas or broken skin, or application of pressure to the sensor may result in inaccurate readings.

Transcutaneous NIRS is non-invasive and the light intensities are not harmful to the tissue, typically not causing skin burns even if applied for a longer period [1,21].

### 5. Clinical applications

#### 5.1. Neonates with complex congenital heart disease (CHD)

Cerebral oximetry is widely used in the management of neonates undergoing cardiac surgery [22,23]. A good correlation between cRSO2 and jugular venous bulb oxygen saturation (SjvO2) has been reported in children with CHD and in animal studies [9,16]. Simultaneously measured rRSO2 can serve as a control for cRSO2 by differentiating changes in total-body perfusion from selective changes in cerebral perfusion and metabolic activity. Simultaneous decreases in rRSO2 and cRSO2 indicate decreased total-body perfusion with impaired cerebral autoregulation. A decrease in cRSO2 without a change in rRSO2 indicates selective changes in cerebral perfusion and/or oxygen extraction. cRSO2 is valuable for preoperative risk stratification and identifying patients with limited organ functional reserve. Intra- and postoperatively, real-time cRSO2 provides early indications of hypoxia undetected by conventional invasive hemodynamic monitoring. Interventions to treat cRSO2 desaturations are associated with less major organ injury and shorter intensive care unit hospitalization.

Compared to patients with normal cardiac physiology, cRSO2 is significantly lower in patients with left-to-right shunting in both cyanotic and acyanotic cardiac lesions. Baseline cRSO2 in acyanotic patients without intracardiac shunting breathing room air is ~70% compared to 40–60% in cyanotic patients [16]. Lower cRSO2 measurements correlate with poorer neurologic outcomes and increased perioperative mortality. In animal models, low cerebral oximetry measurements are associated with neuronal cell dysfunction and death.

5.2. Regional oxygenation in term neonates

Normative RSO2 data for healthy term newborns has been described in a small number of reports with small sample sizes based on short recordings in the first few days of life [3,25]. The healthy newborn has significantly different ranges of cRSO2, rRSO2, and sRSO2 values than those seen in pediatric and adult patients; in addition, values evolve over time. In a cohort of 26 healthy term neonates with an average age of 44 ± 28 h, average cRSO2 was 77.5% ± 8.3% [95% confidence intervals (CI): 64% to 89%] and rRSO2 was 86.8% ± 8.1% [95% CI: 75% to 97%] [25]. Over the first 120 h after birth, average cRSO2 decreased (P < 0.01), and rRSO2 remained unchanged. Similar results were reported by other investigators [3,26]. Bailey et al. also reported on sRSO2 with mean values of 69.9 ± 12.1% on the first day and 75.3 ± 12.4% on the second day (P = 0.02). In contrast to adults, healthy term neonates have lower sRSO2 than cRSO2; furthermore, sRSO2 increased over time, resulting in mean values similar to pediatric and adult values by the second day of life [3,27].
5.3. Regional cerebral oxygenation during transition after birth

NIRS has been used for monitoring cRSO2 in neonates during transition after birth, a period when the brain is the organ at risk for injury and dysfunction [2]. In term infants at birth, cRSO2 rapidly adapts to extraterine life with values of 44% at 3 min to 76% at 7 min, after which it remains stable [11]. cRSO2 achieves a plateau earlier than pulse oximetry (SpO2) or pRSO2 [2]. These results demonstrate the potential for preferential oxygen delivery to the brain with increasing cerebral blood flow in the first minutes after birth. Although significantly lower SpO2 and heart rate values have been reported in infants born by cesarean section [11] in the first 8 min after birth, cRSO2 was not affected by manner of birth, indicating that blood flow to the brain is possibly determined by autoregulation independent from the mode of delivery [2]. Interestingly, cRSO2 of vaginally delivered neonates shows a decrease of up to 10% accompanied by an increase of cerebral FTOE (cFTOE) after 8 min of age.

NIRS is also feasible among very-low-birthweight (VLBW) infants during immediate transition and resuscitation [2]. Pichler et al. defined reference ranges and percentile charts for cRSO2 and cFTOE in a large cohort of term and preterm neonates without any need of medical support during the first 15 min after birth (Fig. 3) [28], and found no significant difference between term and preterm neonates. It is possible that monitoring cRSO2 in neonates during transition may help guide oxygen delivery, thus avoiding cerebral hypoxia; cRSO2 may even enable prediction of neurological outcomes [11].

There is increasing evidence that cRSO2 is modified by resuscitation interventions in preterm infants [2]. In late preterm infants receiving respiratory support in the delivery room, cRSO2 values were significantly lower when compared to infants experiencing unassisted transition. In VLBW infants receiving effective sustained inflation during resuscitation at birth, an increase in heart rate and cRSO2 was followed by increase in SpO2. These were not observed among those who had ineffective sustained inflations.

![cRSO2 graph](image)

**Fig. 3.** The 10th, 25th, 50th, 75th, and 90th percentiles of cerebral regional oxygen saturation (cRSO2) in term and preterm neonates requiring no medical support after birth. (Reproduced with permission by Elsevier from: Pichler G, Binder C, Avian A, et al. Reference ranges for regional cerebral tissue oxygen saturation and fractional oxygen extraction in neonates during immediate transition after birth. J Pediatr 2013;163:1558–63.)

5.4. Cerebral oxygenation in preterm neonates

NIRS monitoring is becoming widely used in premature newborns as it has the potential to provide valuable insights on the impact of prematurity and intensive care on early brain development [29]. The normal reference range of cRSO2 for preterm infants varies between 55% and 85% depending on multiple factors such as instrument design, clinical status, and postnatal age [30]. cRSO2 in the first day of life was higher and cFTOE lower in healthy, very preterm infants in stable condition, compared with healthy term newborns [31]. There was no significant correlation between head size and cRSO2.

Tina et al. reported cRSO2 and cFTOE in the first 6 h after birth in 100 healthy newborns, 30–42 weeks’ gestation [32]. A significant negative correlation between cRSO2 and gestational age was found \( r = -0.77; P < 0.001 \). Highest cRSO2 and the lowest cFTOE \( (P < 0.001, \text{for all}) \) were found at 30–33 weeks; thereafter, cRSO2 progressively decreased and cFTOE increased, reaching their lower nadir/peak respectively \( (P < 0.001, \text{for all}) \) at 38–39 weeks. cRSO2 also correlated significantly with heart rate, respiratory rate, and SaO2 values \( (r = 0.65; P < 0.001) \). Moreover, cRSO2 values were significantly higher \( (P < 0.01) \) after cesarean section compared to vaginal delivery.

Longitudinal measurement of cRSO2 and cFTOE in stable preterm infants <29 weeks’ gestation in the first 72 h of life showed decrease in cRSO2 until 12 h and gradual increase after 18 h [33]. Reciprocal changes were observed in cFTOE. Roche-Labarbe et al. reported weekly cRSO2 in the first 15 weeks of life in preterm neonates (24–37 weeks’ GA) without diagnosis of brain injury or neurologic problems [34]. cRSO2 decreased with chronological age with a nadir at six to eight weeks of life; this decrease was steeper and occurred earlier in subjects born at a lower GA. These trends were attributed to faster decrease in hemoglobin after birth and the higher cRSO2 immediately after birth in more premature infants [32].

Brief changes in head position from midline are not associated with significant alternation in cRSO2 in stable preterm infants [35]. In critically ill preterm infants, routine caregiving procedures including endotracheal suctioning and manipulation and diaper changes are associated with major fluctuations in cRSO2 that are not readily detected by current bedside monitoring [36]. These data underscore the importance of continuous cerebral hemodynamic monitoring in critically ill preterm infants.

In an evaluation of cRSO2 measurements in different brain regions in stable preterm and term neonates in the first week of life, it was shown that limits of agreement were quite large and varied between ±14% and ±18% for four different sites of measurement [6,37]. Left-to-right differences were small between different postnatal and GAs. These results suggest that single site recording of cRSO2 and cFTOE can monitor trends in individual patients to detect changes larger than the limits of agreement but lacks the precision to be used as a robust quantitative variable of cerebral oxygenation.

5.5. Cerebral oxygenation and hypoxic-ischemic encephalopathy (HIE)

NIRS has been used to monitor cRSO2 in HIE [29]. In neonates with HIE, cRSO2 was significantly higher between 24 and 48 h of age in neonates with adverse outcomes as compared to those with favorable outcomes, suggesting a decrease in cerebral oxygen consumption during secondary energy failure [38]. These findings were validated in a newborn piglet asphyxia model [39]. Newborns with evidence of hypoxic–ischemic brain injury on MRI have higher cRSO2 than newborns without brain injury.
5.6. Cerebral oxygenation in preterm neonates with hypotension

Monitoring of cRSO₂ may have a role in the management of hypotension in preterm neonates. Several studies showed a lack of association between low blood pressure and short- or long-term outcomes [40]. Hypotensive neonates without signs of impaired tissue perfusion did not differ from normotensive neonates with regard to short-term outcomes; furthermore, volume expansion and dopamine do not cause any significant change in cRSO₂ or cFTOE in these infants [41]. Regardless of clinical diagnosis of hypotension, cRSO₂ <50% was found to be associated with adverse neurodevelopmental outcomes, suggesting the utility of inclusion of cRSO₂ in hypotension management protocols.

5.7. Cerebral oxygenation and autoregulation in neonates

Cerebral autoregulation, a complex developmentally regulated process affected by multiple pathophysiologic factors, is absent in 40% of preterm neonates [42]. Absence of cerebral autoregulation in preterm infants is associated with adverse outcomes [43]. High coherence between mean arterial blood pressure and cRSO₂ indicates cerebral pressure passivity and impaired cerebral autoregulation in clinically sick preterm infants, and is strongly associated with subsequent intracranial hemorrhage or mortality [43–45]. Verhagen et al. used correlation between cFTOE and MABP to predict cerebral autoregulation, suggesting a role for NIRS to guide interventions to improve cerebral circulation [46].

5.8. Cerebral oxygenation in preterm neonates with patent ductus arteriosus (PDA)

It has been proposed that monitoring of cRSO₂ may prompt early diagnosis and treatment of hemodynamically significant PDA (hsPDA), potentially reducing damage to the vulnerable preterm brain [47]. Neonates with hsPDA had decreased cRSO₂, rRSO₂, and/or pRSO₂ and higher cFTOE compared to those without hsPDA [47,48]. Similarly, there are conflicting reports of the effect of indomethacin; one study reported improvement in deltoid and rRSO₂ whereas another study reported a 30–40% reduction in RSO₂ more pronounced in mesenteric tissue than in cerebral or renal tissue [49].

Contradictory effects of surgical closure of hsPDA on cRSO₂ and cFTOE have also been reported in a small number of studies with small sample sizes. In three studies, there was a significant increase in cRSO₂ with concomitant decrease in cFTOE at the time of surgical ligation followed by return to baseline values, suggesting that surgical ligation has no adverse effect on cRSO₂ [50,51]. In another study, a fall in cRSO₂ (range: 2–21%) during PDA ligation with recovery at 24 h post ligation was reported [52].

5.9. Cerebral oxygenation in preterm neonates with respiratory distress syndrome (RDS)

In one study, the patterns of cerebral oxygenation and extraction in infants with RDS were not different from infants without RDS in the first 72 h of life; however, there were frequent periods with possible lack of cerebral autoregulation in infants with RDS that potentially could make these infants more vulnerable to cerebral injury [53].

5.10. Cerebral oxygenation in neonates with peri/intraventricular hemorrhage (PI/IVH)

Zhang et al. reported higher cRSO₂ and lower cFTOE in the first 3 h after birth in preterm infants who later developed IVH compared to those who did not [54]. Alderliesten et al. reported higher cRSO₂ and lower cFTOE in the first 24 h before detection of P/IVH in very preterm infants monitored during the first 72 h of life [44,55]. In contrast, three investigators reported lower cRSO₂ and/or higher cFTOE in neonates with hemorrhage/IVH compared to those without [56–58]. There was a significantly negative correlation between the severity of IVH and cRSO₂ (P = 0.002).

5.11. Cerebral oxygenation and apneas and bradycardias in neonates

NIRS has been used to identify impaired cerebral oxygenation during episodes of apnea and bradycardia among preterm neonates. Pichler et al. demonstrated that cRSO₂ and cerebral blood volume measured by NIRS decreased significantly during episodes of apnea with bradycardia, compared with those episodes without bradycardia [59].

5.12. NIRS to evaluate splanchnic perfusion

Although NIRS has been used extensively to study cRSO₂, there are fewer reports about the use of NIRS to monitor sRSO₂ to predict necrotizing enterocolitis (NEC) and to guide decisions to initiate feeds. The use of NIRS to monitor sRSO₂ has been perceived to be unreliable because of the changing gas—fluid surfaces and intraluminal fecal content [19]. It has been speculated that fecal chromophores, biliverdin and bilirubin, may interfere with sRSO₂ measurements. The peak absorption spectra for these chromophores (455 nm for bilirubin and 660 nm for biliverdin) are very different from those utilized in the INVOS monitor, suggesting nominal interference with sRSO₂ measurements. This is validated by several publications reporting the feasibility and consistency of sRSO₂ measurements in animals and human neonates. Validity of NIRS-derived sRSO₂ measurements as a means of assessing splanchnic perfusion and oxygenation is further strengthened by reports of strong correlations between sRSO₂ and gastric pH, serum lactate and systemic mixed venous saturation. NIRS devices with algorithms that take into account absorption spectra of fecal chromophores may further improve accuracy of sRSO₂ measurements.

Feasibility and safety of continuous monitoring of sRSO₂ and ranges for sRSO₂ values in healthy preterm infants have been reported previously [7]. Whereas lower sRSO₂ values and a trend of decreasing sRSO₂ measurements over the first several days followed by an increase in these values were reported by two investigators (Fig. 4), higher sRSO₂ values with peak sRSO₂ values observed on day 3 of life were reported in another study using a different NIRS device. Marked variability in sRSO₂ (16%) readings has likewise been reported; this is higher than the variability of renal (6%), cerebral (3%), and pulse oximetry (1–2%) values in that order [7,60].

In preterm neonates with NEC, a pattern of low sRSO₂ values with loss of variability at least 24–48 h before the clinical diagnosis of NEC has been described; this may be preceded or followed by high readings with exaggerated variability [7,19]. Mesenteric desaturation has been described in NEC by other investigators as well. The splanchnic—cerebral oxygenation ratio (SCOR) has been proposed as an index to predict splanchnic ischemia based on the assumption that cerebral autoregulation minimizes changes in cRSO₂ during events affecting splanchnic perfusion [19]. SCOR <0.75 was reported to be highly predictive of the need for surgical intervention [61]. However, SCOR ratios may be unreliable in the presence of IVH and in critically ill infants with impaired cerebral autoregulation [7].
Although NIRS seems promising for assessing splanchnic oxygen saturation, study-specific, device-specific, and location-specific characteristics may interfere with the reliability of the measurements [21]. Schat et al. monitored simultaneously sRSO2 over the liver and infra-umbilical regions in preterm neonates with suspect or proven NEC. Although median sRSO2 values over the liver (51–62%) were not significantly different from those measured in the infra-umbilical region (49–56%), values were highly variable in time with poor correlation between sites. Larger groups of patients are required to determine the potential value of sRSO2 to predict the onset and course of NEC in preterm infants.

5.13. NIRS as a biomarker for need for red blood cell transfusions (RBCT) and response to RBCT

Several studies have reported a temporal association between RBCTs and NEC in preterm neonates; this has been refuted by others [19,62]. These conflicting reports pose a dilemma for neonatologists in determining the need for RBCTs, predicting risk for NEC following transfusion, and decision to feed in the peri-RBCT period. An improvement in cRSO2, sRSO2, and rRSO2 and a reduction in cFTOE have been reported following RBCT in small numbers of preterm infants [19] (Fig. 5). Some investigators reported lack of correlation of pre-RBCT hematocrit with cRSO2 and sRSO2, suggesting that hematocrit level alone is a poor predictor of tissue oxygenation. Van Hoften et al. reported that cRSO2 may be at risk when hemoglobin levels decrease to <9.7 g/dL [63]. A significant improvement in cRSO2, pRSO2, perfusion, and symptoms of anemia was described following transfusion in infants with cRSO2 <55% compared to infants with cRSO2 >55% [64]. Symptomatic preterm infants with anemia were reported to have higher peripheral FTOE
In conclusion, non-invasive real-time continuous bedside RSO2 monitoring has the potential to serve as biomarkers for early organ dysfunction, to predict adverse short- and long-term outcomes in critically ill neonates, and to optimize outcomes. Further studies are needed to establish normative data, absolute cut-off values predicting adverse outcomes, and to validate targeted interventions to normalize abnormal RSO2 values to improve outcomes.

In the future, combination of NIRS with EEG, ultrasound and/or imaging into single devices will provide comprehensive information of organ health through multimodal monitoring.

**Practice points**

- NIRS can be used to conveniently and non-invasively quantitate tissue oxygenation continuously at the bedside.
- Regional tissue oxygenation measured using NIRS can be a biomarker for early organ dysfunction, predict adverse short- and long-term outcomes in critically ill neonates, and optimize outcomes.
- Although NIRS is a promising technique for monitoring neonates in the intensive care unit, there is a lack of large population-based normative data in infants.

**Research directions**

- Further studies are needed to establish normative data, absolute cut-off values predicting adverse outcomes, and to validate targeted interventions to normalize abnormal RSO2 values to improve outcomes.
- In the future, combination of NIRS with EEG, ultrasound and/or imaging into single devices will provide comprehensive information of organ health through multimodal monitoring.

**Conflict of interest statement**

Beena G. Sood has previously received research funding from Somanetics Corporation (Troy, MI, USA) and Covidien, Boulder, CO, USA.

**Funding sources**

No external funding for this article.

**References**


[34] Wybenga RG, Lemmers PM, van Bel F. Cerebral oxygenation during the first days of life in preterm and term neonates: differences between different brain regions. Pediatr Res 2011;70:389–94.


