

# Use of near-infrared spectroscopy (NIRS) in cerebral tissue oxygenation monitoring in neonates

Rene Gumulak, Lucia Casnocha Lucanova, Mirko Zibolen

Near-infrared spectroscopy (NIRS) is a technology capable of non-invasive, continuous measuring of regional tissue oxygen saturation ( $\text{StO}_2$ ).  $\text{StO}_2$  represents a state of hemodynamic stability, which is influenced by many factors. Extensive research has been done in the field of measuring  $\text{StO}_2$  of various organs. The current clinical availability of several NIRS-based devices reflects an important development in prevention, detection and correction of discrepancy in oxygen delivery to the brain and vital organs. Managing cerebral ischemia remains a significant issue in the neonatal intensive care units (NICU). Cerebral tissue oxygenation ( $\text{cStO}_2$ ) and cerebral fractional tissue extraction (cFTOE) are reported in a large number of clinical studies. This review provides a summary of the concept of function, current variability of NIRS-based devices used in neonatology, clinical applications in continuous  $\text{cStO}_2$  monitoring, limitations, disadvantages, and the potential of current technology.

**Key words:** cerebral monitoring, cerebral tissue oxygenation, near-infrared spectroscopy, neonate

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*Department of Neonatology, Jessenius Medical Faculty in Martin, Comenius University in Bratislava and University Hospital in Martin, Slovak Republic*

*Corresponding author: Rene Gumulak, e-mail: gumulak2@uniba.sk*

## INTRODUCTION

Non-invasive measurement of cerebral tissue oxygenation using near-infrared spectroscopy (NIRS) is attracting increasing attention in neonatology<sup>1</sup>. NIRS provides a continuous assessment of regional cerebral oxygenation ( $\text{cStO}_2$ ), and cerebral tissue oxygen extraction (cFTOE). Yet, it is not seen as a routine brain monitoring tool in neonatal intensive care units (NICU) (ref.<sup>2,3</sup>). The aim of this review is to provide a summary of the relationship between  $\text{cStO}_2$  and immediate postnatal adaptation, hypoxic-ischemic encephalopathy (HIE), patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), and respiratory distress syndrome (RDS), and to describe the clinical relevance of this method. Furthermore, the review summarizes the mode of function, current variability of NIRS-based devices used in neonatology, clinical applications of continuous monitoring of cerebral tissue oxygenation. It covers the limitations and disadvantages of current technology and ends with the potential of such technology if implemented in NICU environment.

### History of NIRS-based technology

Transillumination, or the passage of the light through the body, has been studied since the early 1800s (ref.<sup>4</sup>). Transillumination of the head, first described by Richard Bright in 1831, would be eventually recognized as the first light-based diagnostic technique to identify hydrocephalus<sup>4</sup>. In 1977, Jobsis reported that the tissue absorbs light (wavelength of 700–1,000 nm), and this fact can be used for vital tissue measurement in the diameter of 5–6 cm. He used a model of the myocardium and brain tissue<sup>5</sup>.

In 1985, Ferrari et al. published human cerebral oximetry studies using NIRS (ref.<sup>6</sup>). Since the first report of pediatric application of NIRS for monitoring cerebral oxygenation in sick preterm infants in 1986, the possibilities of NIRS monitoring have significantly increased<sup>7</sup>. A major milestone in terms of availability of equipment capable of continuous monitoring was the year 1993. In May 1993, INVOS 3100® (Somanetics Corporation, Troy, Mich., USA) entered the market as the first commercial cerebral oximetry device approved by the Food and Drug Administration (FDA) (ref.<sup>8</sup>). The discovery that functional activation of the human cerebral cortex can be explored by NIRS, has added a new dimension to the research. To obtain simultaneous multiple and localized information, a further major step forward was achieved by introducing NIR imaging and tomography<sup>9</sup>.

### Physical principles of NIRS

Visible light (wavelength 450–700 nm) is strongly attenuated as a result of powerful absorption and scattering by the tissue constituents<sup>10</sup>. Near Infrared Spectroscopy (NIRS) is a type of vibrational spectroscopy that employs photon energy in the energy range of  $2.65 \times 10^{-19}$  to  $7.96 \times 10^{-20}$  J (corresponding the wavelength range of 750 to 2,500 nm). This energy range is higher than necessary to promote molecules only to their lowest excited vibrational states (through a fundamental vibrational transition). On the other hand, the energy range is lower than typical values necessary for electron excitation in molecules (except for some rare earth compounds). The overall objective of spectroscopy is to probe a sample in order to acquire qualitative and/or quantitative information coming from

the interaction of near-infrared electromagnetic waves with its constituents<sup>11</sup>. Near-infrared spectroscopy has been used as a tool to determine the redox state of light absorbing molecules. This technology is based on the Beer-Lambert Law, which states that light transmission through a solution with a dissolved solute decreases exponentially as the concentration of the solute increases<sup>8</sup>. A decrement in transmitted light intensity is equivalent to the quantity of the substance and the amount of light absorbed by a unit quantity of that substance, defined as the extinction coefficient, a factor that varies with the substance and the incident - light wavelength<sup>4,8</sup>. In mammalian tissue, only three compounds change their spectra when oxygenated: cytochrome aa3, myoglobin, and hemoglobin. Because the absorption spectra of oxyhemoglobin and deoxyhemoglobin differ, their relative concentrations change within tissue with oxygenation, and the relative concentrations of the types of hemoglobin can be determined<sup>12</sup>.

All NIRS devices emit light at wavelengths within the above mentioned spectrum, and analyze photons returning to the transducer. Because the change in the intensity of the reflected light is dependent upon the oxyhemoglobin to deoxyhemoglobin ratio, oxyhemoglobin saturation can be derived<sup>13</sup>. The ratio between oxygenated and deoxygenated hemoglobin is known as a tissue oxygenation index (TOI). The value of the regional oxygenation or oxygen saturation (StO<sub>2</sub>) acquired by a NIRS-based device is a combination of intravascular oxygenated/deoxygenated venous and arterial (capillary) hemoglobin in a ratio estimated by the manufacturer<sup>8,9</sup>. Pulse oximetry deliberately considers only the arterial compartment at the time getting the measurements<sup>14</sup>. Fractional oxygen extraction (FOE) is the ratio between oxygen consumption and oxygen delivery. This is calculated using the formula  $FOE = (SpO_2 - StO_2) / SpO_2$ , without measuring the flow. Assuming constant cerebral oxygen consumption, the value will rise as oxygen delivery to the brain falls, until maximum oxygen extraction is achieved<sup>15,16</sup>. Unlike pulse oximetry, NIRS is not dependent on pulse wave, and it uses more wavelengths for spectroscopic transillumination, therefore characterizing more chromophores<sup>10,14</sup>. The extremely low level of absorption of NIR light by hemoglobin is the dominant factor in achieving measurement requiring low light intensity. While benchtop co-oximeters utilize multiple wavelengths to differentiate various dys-hemoglobins *in vitro*, noise reduction remains the most

important factor in improving accuracy and precision *in vivo*<sup>17</sup>.

### Cerebral tissue oxygenation in Neonatology

The neonatal period is very unique, as the infant undergoes dramatic physiologic changes during transition from intra to extra uterine life. This process involves changes in hemodynamics and affects oxygenation, while reflected in StO<sub>2</sub> values<sup>11</sup>. Measuring cerebral oxygenation using NIRS has taken on an increasing important role in neonatal care. Several companies have developed commercial devices, and more publications are reporting absolute boundary NIRS values or percentiles for neonates<sup>1</sup>. NIRS is sensitive to all tissues penetrated by the light, for example, on the head these represent skin, scalp, skull, sub-arachnoid space, and grey and white brain matter. The skin, the scalp and the skull are much thinner in neonates, and instruments with a multi-distance approach cancel out the influence of the superficial tissue. Furthermore, NIR spectroscopy is less sensitive in larger compared to smaller blood vessels<sup>18,19</sup>.

A large number of studies on NIRS focused on functional brain imaging has been published. Compared to electroencephalography (EEG), NIRS is less susceptible to data corruption by movement artifacts, and offers more highly spatially resolved images of activation. Blasi et al. demonstrated that spatial mapping and size of activation in infants have a high degree of reliability<sup>20</sup>. Several studies using different NIRS devices have described the changes in cerebral regional tissue oxygenation during the first minute of life. Reference ranges and centile charts have already been established for cStO<sub>2</sub> and cFTOE during the first 15 min after birth<sup>21</sup>.

### Reference ranges

The current literature indicates correlation between irreversible mitochondrial damage and the total energy disruption that lasts 30 to 120 min at values ranging from 33 to 45%. The studies were conducted on piglets models<sup>22,23</sup>. Since the premature brain is extremely vulnerable, especially in hemodynamically unstable neonates, monitoring cerebral oxygenation has a high priority and is increasingly combined with other brain monitoring devices such as amplitude-integrated EEG (ref.<sup>19</sup>). Lemmers et al. compared simultaneously determined left and right fronto-parietal measurements of cStO<sub>2</sub> with INVOS™ 5100 (Somanetics, Troy, Michigan, USA) and referred

**Table 1.** NIRS technology evolution<sup>4,6,8</sup>.

Year	Information
1831	Translumination of the head, first described by Richard Bright
1881	The first (near) infrared spectra measured by Abney and Festing
1905	W.W. Cobletz published the results of a large study using spectra measurement
1950	The first industrial applications
1975	Chemometrics
1977	Jobsis published the study using the model of the myocard and brain tissue
1985-1990	Light-fiber optics
1993	INVOS 3100® (Somanetics Corporation, Troy, Mich., USA)

similar values. Values of cerebral oxygen saturation were lower in all regions on day 7 compared to day 1 of life. However, the longitudinal study showed a slight tendency for  $cStO_2$  values to increase at the right fronto-parietal position at day 3. This pattern changed during unstable arterial oxygenation with substantial drops of  $saO_2$  with or without subsequent hyperoxemia, when extra oxygen was added for a quick recovery of arterial saturation<sup>24</sup>. In term infants at birth,  $cStO_2$  rapidly adapts to extrauterine life and after the 7<sup>th</sup> minute remains stable. The results are beneficial in terms of demonstration of cerebral oxygenation, documenting the increase in cerebral blood flow in the first minutes of life<sup>25,26</sup>. Karen et al. used NIRO-300<sup>TM</sup> (Hamamatsu Photonics, Hamamatsu, Japan) and published that newborns delivered by vacuum extraction had significantly higher tissue hemoglobin index (THI) 10 to 15 min after birth. Tissue oxygenation index (TOI) and heart rate (HR) were significantly higher in the first 5 min and  $StO_2$  in the first 10 min, but then they did not differ from those in infants after cesarean section<sup>27</sup>.

The study performed by Kratky et al. demonstrated that  $cStO_2$  increased rapidly from minute 2. Cerebral fractional oxygen extraction which was calculated for each minute, showed a significant decrease from minute 2 until min 4 and it increased within the first 14 min after delivery.  $cStO_2$  significantly showed no further changes after 5 min<sup>28</sup>.

Pichler et al. defined reference ranges and percentile charts for  $cStO_2$  and  $cFTOE$  using INVOS<sup>TM</sup> 5100 (Somanetics, Troy, Michigan, USA) in a large cohort of term and preterm neonates without any need of medical support during the first 15 min after birth, and they found no significant differences comparing term and preterm neonates<sup>29</sup>. The normal reference range of  $cStO_2$  for preterm infants depends on multiple factors such as instrument design, postnatal age, or current clinical status<sup>30</sup>. Cerebral hemoglobin oxygenation correlates with chronological age, but not with postmenstrual age.  $cStO_2$  is not correlated with postmenstrual age, but varies with chronological age and hemoglobin concentration in the blood, suggesting that it depends on systemic changes and does not reflect changes associated with brain development<sup>31</sup>. This is consistent with the findings that  $cStO_2$  may correlate with the heart and respiratory rate and with arterial  $SO_2$  in newborns<sup>32</sup>. Significantly lower  $SpO_2$  and heart rate values have been reported in infants born by cesarean section<sup>33</sup>. In the studies evaluating  $cStO_2$  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  $\pm 14\%$  and  $\pm 18\%$  (INVOS<sup>TM</sup> 5100; Somanetics, Troy, Michigan, USA) (ref.<sup>34,35</sup>). These results suggest that single site recording of the regional cerebral oxygen saturation and cerebral fractional tissue oxygen extraction 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<sup>36</sup>.

McNeill et al. confirmed that continuous, long-term  $StO_2$  monitoring of premature infants in the NICU is both

safe and feasible. Neonatal daily baseline  $StO_2$  values measured by the INVOS<sup>TM</sup> 5100 (Somanetics, Troy, Michigan, USA) not only change with postmenstrual age, but also decrease in the variability of  $StO_2$ . The group mean  $cStO_2$  fell within the expected range of 60-80%, although several subject demonstrated cerebral values consistently above 80% during the first week of life before declining<sup>37</sup>.

### Cerebral oxygenation and HIE

Neonatal HIE (hypoxic-ischemic encephalopathy) is a major cause of mortality, morbidity, and long-term neurological deficits<sup>38</sup>. Despite the progress in diagnostic modalities, accurate prediction of outcome in neonates with HIE remains a great challenge. MRI can predict outcome reliably only in severe HIE cases. Early EEG findings (24 h) do not provide additional support for outcome prediction and are nonspecific, possibly in relation to medication use<sup>38</sup>.  $cStO_2$  was significantly higher between 24 and 48 weeks of age in neonates with HIE with adverse outcomes as compared to those with favourable outcomes, suggesting a decrease in cerebral oxygen consumption during secondary energy failure. Newborns with proven brain injury caused by HIE have higher values of  $cStO_2$  than newborns without brain injury<sup>39</sup>. Plomgaard et al. investigated the benefits and harms of monitoring cerebral oxygenation by NIRS combined with an evidence-based treatment guideline versus no NIRS data and treatment as usual in the group during the first 72 h of life. Treatment guided by NIRS reduced the burden of cerebral hypoxia without affecting the selected EEG or blood biomarkers<sup>40</sup>.

### Cerebral oxygenation and patent ductus arteriosus (PDA)

The ductus arteriosus (DA) is an important vascular connection between main pulmonary artery and the aorta. After birth, the DA undergoes active constriction and eventual obliteration. PDA occurs when the ductus fails to close completely after delivery<sup>41</sup>. The incidence of hemodynamically relevant DA has been known to affect perfusion of important organ systems such as the brain. Lemmers et al. measured NIRS values in 20 infants with PDA who underwent treatment with indomethacin (gestational age under 32 weeks). The mean arterial blood pressure and  $cStO_2$  were significantly lower, and  $FTOE$  was significantly higher before the treatment of PDA compared to the control group. Indomethacin had no additional negative effect on cerebral oxygenation. Hemodynamically significant PDA had a negative effect on cerebral oxygenation in the premature infant<sup>42</sup>. NIRS can be used as a screening tool for PDA, it shows encouraging efficiency in identifying ELBW infants who are likely to benefit from early echocardiography and subsequent intervention to close a PDA (ref.<sup>43</sup>).

Vanderheagen et al. analysed a significant increase in  $cStO_2$  with concomitant decrease in  $FTOE$  at the time of surgical ligation followed by return to baseline values. As a result, the ductal clipping has no negative effect on the cerebral oxygenation<sup>44</sup>. Ductal ligation poses a risk for a further decrease in already compromised cerebral oxygenation in preterm infants. During surgery, median range of  $cStO_2$  dropped very slightly. Eleven infants showed a

drop in blood pressure and 13 infants a drop in  $cStO_2$  during surgery accompanied by a decrease in EEG amplitude<sup>45</sup>.

### Cerebral oxygenation and respiratory distress syndrome (RDS)

During artificial ventilation due to RDS, systemic hemodynamics can be disturbed with consequent compromise of cerebral oxygenation. RDS is strongly related to low and fluctuating arterial blood pressure<sup>18</sup>. Lemmers et al. investigated the relationship between mean arterial blood pressure (MABP),  $cStO_2$  and FTOE, during the first 72 h of life. RDS infants showed more periods of positive correlation between MABP and  $cStO_2$ , and negative correlation between MABP and FTOE. Although Lemmers et al. found that the patterns of cerebral oxygenation and extraction in RDS infants were not different when compared to infants without RDS. They suggested that the frequent periods with possible lack of cerebral autoregulation in RDS infants may cause these infants to be more vulnerable to cerebral damage<sup>46</sup>. Because cerebral oxygenation is essential,  $cStO_2$  monitoring can be an important tool to avoid disturbances between carbon dioxide tensions and impact on complications of this process<sup>29</sup>.

### Cerebral oxygenation and peri/intraventricular hemorrhage

Sorensen et al. found that there was a significant negative correlation between the severity of the intraventricular hemorrhage and the cerebral oxygenation<sup>47</sup>. Zhang et al. investigated the relationship between intraventricular hemorrhage (IVH) and  $cStO_2$  in preterm infants. They founded higher  $cStO_2$  values in the first 3 h after birth in neonates who later developed IVH (ref.<sup>48</sup>). Higher  $cStO_2$  and lower cFTOE values within 24 h before detection of IVH have been reported in another study referring compliant results in very preterm infants<sup>49</sup>. It has been proposed that monitoring of  $cStO_2$  can potentially reduce the damage to the vulnerable preterm brain.

## CONCLUSION

NIRS is a fascinating and dynamically evolving technology with over 40 years of history. This non-invasive bedside method is both safe and feasible. It enables continuous, long-term  $cStO_2$  monitoring of NICU patients. Currently available NIRS based devices use the above technology principles. They only differ is in the number of absolute values of wavelength, as well as in computational algorithms translating measured changes into light attenuation. The use of various optical probes complicates comparison of the results referred in older NIRS studies with the currently published data.

Because large infant population-based normative data are lacking, further studies are needed in order to establish normative data for newly available commercial NIRS instruments. In the future, it is essential to provide the  $StO_2$  measurement by means of NIRS based devices with improved quantitative precision, so that this technology will become consistent and usable for NICU worldwide.

However, NIRS provides a unique insight into the possibilities of diagnosing and treating diseases which are typically initially asymptomatic. This promising technology can be used in combination with EEG and ultrasonography in order to provide coherent information, thus improving non-invasive monitoring.

### Search strategy and selection criteria

Scientific databases (PubMed and/or Web of Science) were searched for articles describing methods and applications of NIRS in continuous monitoring in neonates. Articles were searched from 1999 to April 2016 and were selected according to their relevance to clinical use, results and devices used. Articles describing the historical evolution and physical principles of NIRS, which were published earlier, were also included. Only English language papers were reviewed.

## ABBREVIATIONS

cFTOE, Cerebral fractional tissue oxygen extraction;  $cStO_2$ , Regional cerebral oxygen saturation; DA, Ductus arteriosus; EEG, Electroencephalography; ELBW, Extremely low birth weight; FDA, Food and drug administration; FTOE, Fractional tissue oxygen extraction; HIE, Hypoxic-ischemic encephalopathy; IVH, Intraventricular hemorrhage; HR, Heart rate; MABP, Mean arterial blood pressure; MRI, Magnetic resonance; NICU, Neonatal intensive care unit; NIRS, Near-infrared spectroscopy; PDA, Patent ductus arteriosus; RDS, Respiratory distress syndrome;  $SpO_2$ , Arterial oxygen saturation measured by pulse oximetry;  $StO_2$ , Regional oxygen saturation;  $SO_2$ , Oxygen saturation; THI, Tissue hemoglobin index; TOI, Tissue oxygenation index; USA, United States of America.

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