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ORIGINAL ARTICLE

Direct measurement of the tissue oxygenation in a newborn – new clinical applications

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ABSTRACT

Oxygen is a substance needed for aerobic metabolism. The process of ischemia and reperfusion are responsible for local changes in oxygen concentrations. Both subnormal and supranormal tissue oxygenations are dangerous. Monitoring of end-organ perfusion and oxygenation is essential for patients in the intensive care unit. Knowledge of the balance between supply and consumption of oxygen in the target organ tissue is necessary. An alternative possibility of measuring tissue oxygenation is near infra-red spectroscopy (NIRS) based on tissue transparency to the near infrared spectrum (NIR, wavelength 700–1000 nm), and its absorption by the relevant chromophores (oxy and deoxyhaemoglobin). The authors summarize current knowledge and practical experiences of neonatologists using NIRS in various indications – from the evaluation of immediate postpartum adaptation to its application as a part of intensive monitoring of critically ill newborns. NIRS directly and non-invasively measures the total light signal from microcirculation (from venous, arterial and capillary nets). NIRS is a modern non-invasive, continuous, real-time and bed-side monitoring of tissue oxygenation and in the future could be part of multimodal patient monitoring.

KEY WORDS: near infra-red spectroscopy; newborn; indications

ABBREVIATIONS

$artSO_2$: arterial oxygen saturation; **CAR:** cerebral autoregulation; **CBF:** cerebral blood flow; **cFTOE:** cerebral fractional tissue oxygen extraction; **cPVL:** cystic periventricular leukomalacia; **$cRSO_2$:** cerebral regional tissue oxygen saturation; **FTOE:** fractional tissue oxygen extraction; **HIE:** hypoxic-ischaemic encephalopathy; **IVH:** intraventricular haemorrhage; **MAP:** mean arterial pressure; **MRI:** magnetic resonance imaging; **NEC:** necrotising enterocolitis; **NICU:** Neonatal Intensive Care Unit; NIR: near infra-red; **NIRS:** Near Infra-Red Spectroscopy; **PDA:** persistent arterial duct; **$rRSO_2$:** renal regional tissue oxygen saturation; **RSO_2:** regional tissue oxygen saturation; **$sRSO_2$:** splanchnic regional tissue oxygen saturation; **oxyHb:** oxygenated haemoglobin; **deoxyHb:** deoxygenated haemoglobin

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Introduction

An oxygen molecule in a newborn's body can be a medicine or a poison. Oxygen is a substrate for aerobic metabolism and a source of oxidative stress at the same time – in a particular situation for a particular patient, this essential difference is only a dose issue. Both subnormal and supranormal tissue oxygenation is dangerous: regional dysoxia leads to ischemia-reperfusion tissue damage and increases the morbidity and mortality of critically ill patients (Sood *et al.*, 2015).

Monitoring of end-organ perfusion and oxygenation is essential for patients in the intensive care unit. Tissue perfusion is evaluated based on systemic blood pressure, heart rate, arterial and mixed venous oxygen saturation and hemoglobin concentration. However, such invasive and indirect measurement does not provide an accurate and comprehensive view on the hemodynamic state. Nowadays, targeted neonatal echocardiography is being used, which allows non-invasive measurement of cardiac output (contractility, superior vena cava flow) and consequently to indicate and evaluate the effect of indicated hemodynamic interventions. However, obtaining accurate measurements can be technically challenging (Baik

et al., 2015). The literature provides only a little evidence of the benefit of this method in improving the prognosis of premature infants (El-Khuffash *et al.,* 2013).

An alternative option is direct, non-invasive, non-painful, portable, continuous, real-time/bed side measurements using near infra-red spectroscopy (NIRS) (Kenosi *et al.,* 2015).

Near infra-red spectroscopy

This method was developed as early as 1977 as a non-invasive way of neuromonitoring of cardiac surgery patients during extracorporeal circulation. NIRS principle lies in the transparency of the tissues to the near infrared spectrum (wavelength 700–1000 nm) and in the differential absorption of near the infra-red (NIR) spectrum by the relevant chromophores: oxy (oxyHb) and deoxyhaemoglobin (deoxyHb) (Figure 1), described by the Beer-Lambert law (Ghosh *et al.,* 2012).

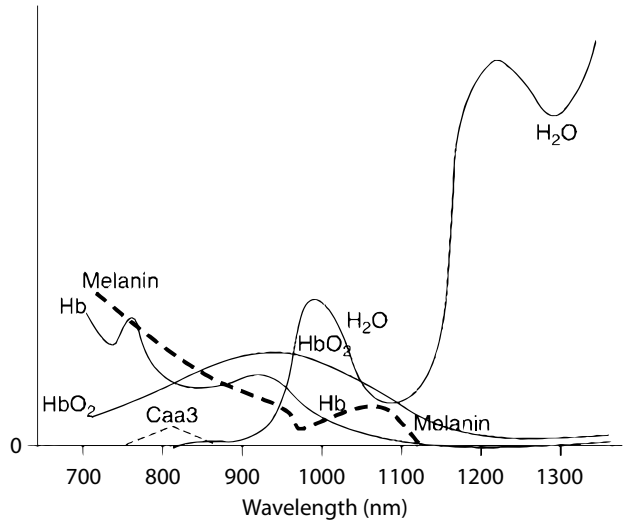

Figure 1. Near infra-red spectrum absorption by various chromophors (Murkin & Arango, 2009) HbO_2 – oxyhemoglobin, H_2O – water, Caa3 – cytochrome aa3.

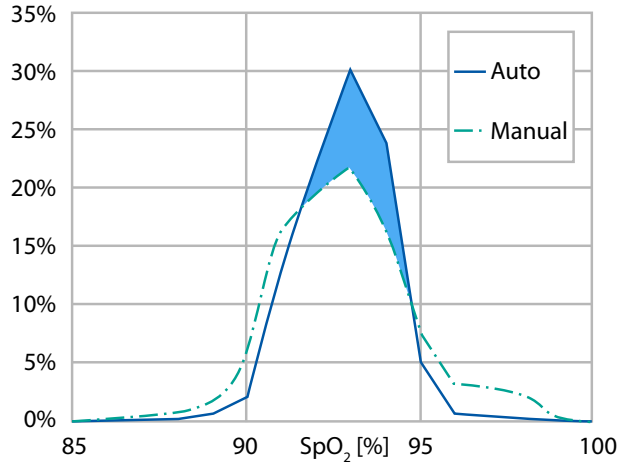

Figure 2. Effect of Predictive Intelligent Oxygenation Control on Oxygen Fraction Control. Manual- manual regulation of oxygen therapy; Auto- automatic regulation of oxygen therapy, SpO2 - oxygen saturation by pulse oximeter.

Regional tissue saturation (RSO_2) is measured from tissues 1–2 cm below the electrode, which includes a source of NIR light and two photodetectors (Vretzakis *et al.,* 2014). Assuming that tissues such as skin, muscles, or bones do not change their optical properties, then the only variables in changes of NIR light absorption are blood flow and the oxy/deoxy hemoglobin ratio in a given tissue. However, the resulting light loss on the photodetector is caused not only by hemoglobin absorption but also by NIR light scattering, which is individual and highly variable. The commonly used NIRS monitors cannot quantify it, so they do not show the absolute values of oxyHb and deoxyHb but only their ratio (oxyHb/oxyHb + deoxyHb), ranging from 0 to 100%, called regional tissue oxygenation (Korcek *et al.,* 2017).

Unlike pulse oximetry, NIRS measures the total light signal from microcirculation that includes the venous, arterial and capillary beds. 80% of the blood comes from venules, therefore NIRS best correlates with venous saturation (da Costa *et al.,* 2015).

NIRS and pulse oximetry are complementary methods. A pulse oximeter measures the saturation of arterial blood entering organs and tissues. NIRS, through RSO_2, shows the ratio between local oxygen delivery to a particular tissue and oxygen consumption in that tissue (Sood *et al.,* 2015). By simultaneous measurement of arterial oxygen saturation ($artSO_2$), we can calculate the fractional tissue oxygen extraction rate (FTOE): FTOE = ($artSO_2$ – RSO_2)/$artSO_2$. The FTOE shows the amount of oxygen extracted by the tissue and thus the ratio between regional delivery and oxygen consumption (van Bel *et al.,* 2008).

Cerebral regional delivery of oxygen to the tissue ($cRSO_2$) depends on arterial blood saturation, hemoglobin concentration and cerebral blood flow (Baik *et al.,* 2015). If there are no significant changes in tissue metabolic activity (O_2 consumption), in blood saturation or in hemoglobin concentration, then changes in $cRSO_2$ result from changes in cerebral flow (CBF), which is a function of peripheral vascular resistance and cardiac output (Liem & Greisen, 2010).

Cerebral fractional tissue oxygen extraction (cFTOE) is inversely CBF dependent and reflects the ratio between oxygen supply and brain consumption (Binder-Heschl *et al.,* 2016). Thus, it makes it possible to distinguish cerebral hypoxic hypoxia (O_2 deficiency in normal perfusion) from ischemic hypoxia (lack of O_2 due to insufficient perfusion) (Balegar *et al.,* 2014).

The recommended target saturation of arterial blood in newborns with respiratory distress or on oxygen therapy is 90 to 95%. Several studies have confirmed that both lower and higher pulse oximetry saturations increase the morbidity of premature newborns (Sweet *et al.,* 2017). Pulse oximetry is a reliable method for detecting arterial hypoxia with decrease of saturation up to 55–60%. However, as regards hyperoxia, 100% saturation in the patient on oxygen therapy implies the risk of undetected severe tissue hyperoxia.

Currently, there are several technologies that are capable of automatically regulating the oxygen fraction of patients on artificial pulmonary ventilation. One of them is "PRICO" – a system of predictive intelligent control of oxygenation. It reduces the frequency and duration of hypoxic and hyperoxic episodes, minimizes the risk of long-term unrecognized iatrogenic exposure to a high fraction of O_2, shortens the time out of the SpO_2 target range and thus increases patient´s safety (Figure 2).

However, it is interesting that, despite the reduction in the frequency of hypoxaemic episodes, the automatic oxygen therapy regulating systems in the study of Waitz *et al.* had no significant effect on $cRSO_2$ values (Waitz *et al.,* 2015).

NIRS in neonatology – clinical applications

NIRS sensor location

In neonates, we most commonly measure cerebral regional tissue oxygenation ($cRSO_2$) over the frontal lobe of the brain, renal regional tissue oxygenation ($rRSO_2$) over the kidney, and splanchnic regional tissue oxygenation ($sRSO_2$) over the intestine infraumbically (Vretzakis *et al.,* 2014).

Immediate postpartum adaptation and physiological values of regional tissue oxygenation

In term neonates, $cRSO_2$ quickly rises from about 44% in the 3rd minute of life to 76% at the age of 7 minutes, consequently, it remains stable (van Vonderen *et al.,* 2014). When compared to the physiological values of arterial saturation measured by pulse oximetry, it is clear that $cRSO_2$ increases faster and plateau reached earlier. This is caused by preferential increase in cerebral perfusion in the first minutes after delivery (Pichler *et al.,* 2013, 2014) (Figure 3).

In section-born new-borns, significantly lower oxygen saturation and heart rate are described, but $cRSO_2$ values are the same regardless of delivery mode, indicating a functioning cerebral flow autoregulation (van Vonderen *et al.,* 2014). Korček *et al.* compare the values of $cRSO_2$ during the first 15 minutes of life in healthy term new-borns with values of premature new-borns who later developed or did not develop intraventricular haemorrhage (IVH) (Figure 4) (Baik *et al.,* 2015; Korček *et al.,* 2017; Pichler *et al.,* 2013). All premature new-borns had significantly lower $cRSO_2$ values compared to term ones within the first 6 minutes of life. Subsequently, in premature neonates without IVH, $cRSO_2$ values increased and reached values of term new-borns within 15 minutes. The premature group with later development of IVH had significantly lower $cRSO_2$ values.

Several authors describe a decrease in $cRSO_2$ following a plateau of 61–84% between 7 and 10 minutes after birth (Fuchs *et al.,* 2012). This decrease in $cRSO_2$ and the increase in cFTOE is, according to the authors, due to a decrease in cerebral flow caused by significant left-to-right shunting through the arterial duct (PDA).

The lower limit of normal values during the first 3 days of life (10th percentile) is $cRSO_2$ 55% (Greisen *et al.,* 2016; Kenosi *et al.,* 2015). The following days after birth, normal cerebral RSO_2 values are about 77.9%±8.5%, and renal RSO_2 values are 86.8%±8.1% (Bernal *et al.,* 2010). Splanchnic RSO_2 is the most variable – with 75.3%±12.4% (McNeill *et al.,* 2011).

Injury of brain tissue

According to some studies, NIRS may be a predictor of neurological prognosis, which is predominantly determined by the presence and severity of IVH and cystic periventricular leukomalacia (cPVL) in premature neonates (van Vonderen *et al.,* 2014).

A key role in the pathogenesis of these diseases plays the autoregulation of cerebral haemodynamic. The functioning cerebral autoregulation (CAR) allows constant cerebral blood flow (CBF) to be maintained independently of changes in mean arterial pressure (MAP) – within

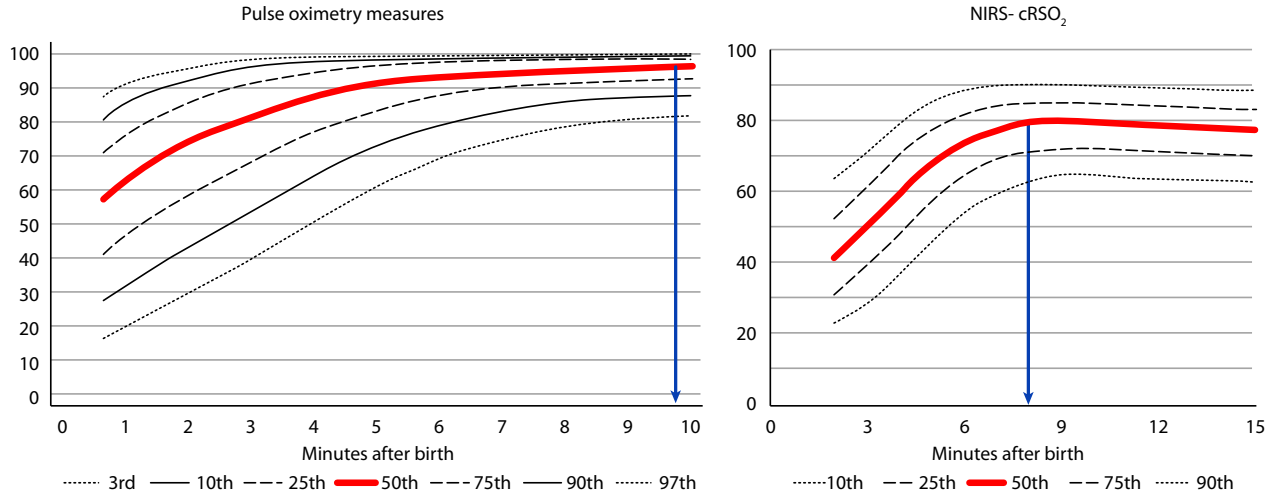

Figure 3. Newborn – postnatal adaptation, normal values (Pichler *et al.,* 2013). NIRS – Near Infra Red Spectroscopy; $cRSO_2$ – cerebral regional tissue oxygen saturation.

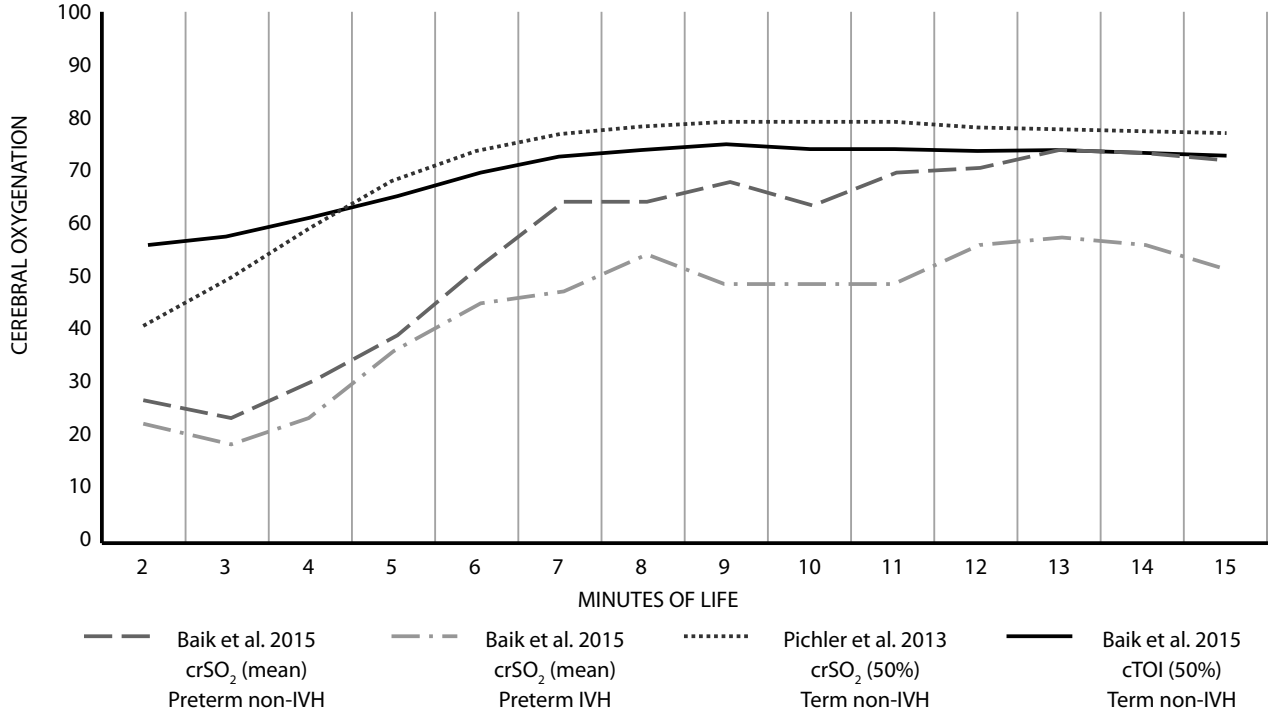

Figure 4. Comparison of cerebral regional tissue oxygenation values during the first 15 minutes of life in premature and congenital newborns (Korček *et al.,* 2017). IVH – intraventricular hemorrhage, crSO2 – cerebral regional tissue oxygenation, CTI – cerebral tissue oxygenation index

a certain range (Alderliesten *et al.,* 2013). However, in critically ill premature new-borns, CAR may be partially or totally non-functional, with an increased risk of brain injury through various mechanisms: hypoperfusion with hypoxia/ischaemia, cerebral perfusion fluctuations, hyperperfusion leading to hyperoxia and peroxidation or reperfusion injury (Alderliesten *et al.,* 2013; Balegar *et al.,* 2014; Greisen *et al.,* 2016; Noori & Seri, 2015).

On the other hand, in many NICU premature patients, functional CAR allows to maintain adequate cerebral blood flow in MAP ranging from 23–40 Torr (Tyszczuk *et al.,* 1998). Isolated hypotension in premature neonates does not impair their neurological development (Alderliesten *et al.,* 2014).

Thus, NIRS monitoring of cerebral tissue oxygenation makes it possible to detect abnormalities in cerebral perfusion and helps to identify patients at high risk of developing severe neuropathology (IVH and cPVL, respectively) (Balegar *et al.,* 2014).

In neonates with hypoxic-ischaemic encephalopathy (HIE), $cRSO_2$ at 1–2 days post insult, was significantly higher in those with poor prognosis, due to a decrease in cerebral oxygen consumption in the secondary neuronal failure phase. New-borns with HIE image on magnetic resonance imaging had higher $cRSO_2$ than new-borns with negative MRI findings (Dehaes *et al.,* 2014).

On the contrary, many studies describe reduced $cRSO_2$ values during the first hours in neonates with IVH development at 2–3 days of age. Initially low CBF – because of low minute left ventricular output, increases as myocardial contractility improves, leading to hypoperfusion-reperfusion brain injury (Noori *et al.,* 2014).

Accordingly, both reduced and elevated $cRSO_2$ values may be associated with poor neurological development of preterm infants at the age of 2–3 years. Prolonged periods with low $cRSO_2$ values in the first 2 weeks of life are associated with poorer cognitive capabilities (Verhagen *et al.,* 2015).

Blood pressure management

Regarding blood pressure management in preterm new-borns, many studies have shown poor association between low blood pressure and short- or long-term prognosis (Alderliesten *et al.,* 2014). New-borns with hypotension without signs of impaired tissue perfusion have the same short-term results as "normotensive" patients. Intravascular volume substitution or inotropic support in these children (Dopamine) does not cause significant changes in $cRSO_2$ and cFTOE (Bonestroo *et al.,* 2011). On the other hand, regardless of the definition of hypotension, less than 50% of $cRSO_2$ is associated with poor neurological prognosis, which underlines the importance of including $cRSO_2$ monitoring in therapeutic protocols (Sood *et al.,* 2015).

Some new-borns are more susceptible to sudden increases in left ventricular afterload after removal of low-pressure placental circulation and may benefit from interventions leading to increased preload and thus to stabilize the cardiac output. This may be one of the reasons why passive active placental transfusion is associated with a lower IVH/cPVL incidence (Katheria *et al.,* 2016).

NIRS and blood derivates management

Criteria for the red blood cell transfusion are traditionally a controversial topic in neonatology. Treatment protocols vary among countries. In general, erythrocyte transfusion is indicated if values of haemoglobin or haematocrit are below levels capable of adequate tissue oxygen requirements. However, individual anaemia tolerance is very variable. It is NIRS monitoring that can detect whether the oxygen requirements of tissues in a patient are adequately covered.

Monitoring of cerebral and renal tissue oxygenation at the same time is most frequently recommended in this indication. Significant improvement in $cRSO_2$, perfusion and anaemia symptoms after red blood cell transfusion was reported in children with $cRSO_2$ values below 55%, compared with patients having $cRSO_2$ above 55% (Seidel *et al.,* 2013).

The first indication of the need for haemodynamic compensation for anaemia is the reduction of renal tissue saturation. Therefore, it is recommended that transfusions be given when renal RSO_2 falls below 50% and renal FTOE rises above 40% (Ohls, 2019).

NIRS and "steal" phenomenon in persistent ductus arteriosus

Monitoring cRSO2 may also speed up the diagnosis and treatment of premature neonates with haemodynamically significant persistent arterial duct (PDA), thereby potentially reducing the risk of cerebral injury. These patients have reduced renal and cerebral RSO_2 and increased cFTOE compared to premature neonates without haemodynamically significant PDA (Lemmers, Toet, van Bel, 2008). According to another work, the diameter of the PDA correlates with the value of $cRSO_2$ – it´s low values may indicate significant PDA (Dix *et al.,* 2016).

NIRS and splanchnic RSO_2 values

Splanchnic RSO_2 values, due to peristalsis, varying intestinal contents, and the presence of coproporphyrins, are the most variable and difficult to reproduce type of regional tissue saturation (Sood *et al.,* 2014). However, mesenteric desaturation in patients with necrotising enterocolitis (NEC) has been described in several studies. In premature neonates, low splanchnic RSO_2 values and loss of variability 24–48 hours prior to NEC clinical manifestation can be observed (Cortez *et al.,* 2011).

Conclusion

NIRS is a modern non-invasive, continuous, real-time and bed-side monitoring of tissue oxygenation. It has the potential to be a biomarker of early organ dysfunction and the predictor of prognosis of critically ill new-borns as was confirmed by several observational as well as interventional studies (Pichler *et al.,* 2016; Plomgaard *et al.,* 2016). The main limitations of NIRS monitoring are interindividual variability, the existence of different types of monitors, sensors and software algorithms, and the resulting absence of general "normal" values (Sood et al., 2015). In the future, NIRS could be part of a multimodal patient monitoring NIRS in combination with electroencephalogram and/or NIRS with sonography and provide information on haemoglobin absolute saturation values, cerebral flow and blood volume index, or a relative cerebral oxygen metabolism index (Roche-Labarbe *et al.,* 2012).

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