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Abstract: This article reviews the application of near infrared (NIR) spectroscopy in preterm and newborn infants and its clinical value. After an overview of the commercially available instrumentation, which is able to provide absolute values of tissue haemoglobin saturation (StO(2)), we focus on the application of NIR spectroscopy to measure brain, liver, gastro-intestinal and peripheral oxygenation. From the instrumentation point of view, NIR spectroscopy has gained significantly in clinical importance, especially by being able to measure StO(2), i.e. an absolute parameter. An increasing number of commercial instruments is available today and the number of users is virtually exploding. However, the precision of the measurements is still too low from a clinical point of view and the variety of algorithms employed by the different instruments and sensors may provide quite different StO(2) values. In the future, the different instruments need to report quantitatively comparable StO(2) measurements which are more precise. The measurement of cerebral StO(2) may be useful for detecting situations where the oxygenation of the brain may be impaired and the hope is that this indicates situations which lead to brain lesions. However, the clinical utility of cerebral StO(2) still needs to be examined. Although liver and gastro-intestinal as well as peripheral measurements are still an object of research and several problems have to be overcome before clinical use, these measurements could be of high value in specific clinical situations.

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Special Issue on Medical Applications

Review

A review of near infrared spectroscopy for term and preterm newborns

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This article reviews the application of near infrared (NIR) spectroscopy in preterm and newborn infants and its clinical value. After an overview of the commercially available instrumentation, which is able to provide absolute values of tissue haemoglobin saturation (StO₂), we focus on the application of NIR spectroscopy to measure brain, liver, gastro-intestinal and peripheral oxygenation. From the instrumentation point of view, NIR spectroscopy has gained significantly in clinical importance, especially by being able to measure StO₂, i.e. an absolute parameter. An increasing number of commercial instruments is available today and the number of users is virtually exploding. However, the precision of the measurements is still too low from a clinical point of view and the variety of algorithms employed by the different instruments and sensors may provide quite different StO₂ values. In the future, the different instruments need to report quantitatively comparable StO₂ measurements which are more precise. The measurement of cerebral StO₂ may be useful for detecting situations where the oxygenation of the brain may be impaired and the hope is that this indicates situations which lead to brain lesions. However, the clinical utility of cerebral StO₂ still needs to be examined. Although liver and gastro-intestinal as well as peripheral measurements are still an object of research and several problems have to be overcome before clinical use, these measurements could be of high value in specific clinical situations.

Keywords: near infrared spectroscopy, neonate, preterm infant, brain, liver, instrumentation, tissue oxygen saturation, oximeter

Introduction

The interest in near infrared (NIR) spectroscopy as an emerging diagnostic tool for neonates and preterm infants has increased tremendously in the last few years and it is on the verge of routine clinical application, due to advances in quantification, instrumentation and the availability of commercial instruments.

Therefore the aim of this review is to:

- Give an overview of the instrumentation available and outline advantages and limitations based on the underlying principles
- Review the application of NIR spectroscopy to study the brain, with a special perspective on clinical applications

- Summarise the use of NIR spectroscopy to assess liver and gastro-intestinal oxygenation
- Describe the applications of NIR spectroscopy to investigate "peripheral", i.e. limb oxygenation

Material and methods

The authors searched for papers on the database MEDLINE (Pubmed) and/or Web of Science using the keywords: "near

infrared", "neonates" in combination with "brain", "liver oxygenation", "splanchnic circulation", "muscle", or "peripheral" up to June 2011. The references were screened and the full texts of relevant publications were retrieved. The references of reviews were hand searched. Articles concerning the description on one clinical case were rejected. Proceedings of the International Society of Oxygen Transport to Tissue (ISOTT) and the European Society of Paediatric Research were also taken into account. For non-English articles, the review was limited to the abstract. Papers were selected according to their relevance to neonatal physiology, clinical use and instrumentation.

The review of instruments was restricted to NIR spectroscopy oximetry. Web sites of commercial systems were searched and companies contacted if necessary.

Instrumentation

First, we will introduce the principles of NIR spectroscopy and then give an overview of commercially available NIR spectroscopy instruments.

Principle of near infrared spectroscopy

In the range of wavelengths from 700 nm to 1000 nm, called the near infrared (NIR) diagnostic window, it is possible to measure deep tissue, because the tissue is relatively transparent for light. At shorter wavelengths (visible spectrum) haemoglobin, and at longer wavelengths water, absorb strongly and prevent light from penetrating deep into the tissue. In the NIR spectrum, for every centimetre of additional distance between the source and the detector, light is attenuated by a factor of 10 to 100. By using sensitive detectors and safe levels of light emission up to 8 cm of tissue can be transilluminated in the NIR. In the neonate, the tissue is more transparent compared to the adult.¹ In addition, the neonatal head and other tissues have a smaller diameter and are more accessible compared to adults (for example, no hair) and, consequently, NIR spectroscopy is excellently suited specifically for the neonate. Furthermore, NIR spectroscopy employs non-ionising radiation, is non-invasive, painless and harmless and can be transported to the bedside, all important advantages for using NIR spectroscopy in neonates in a clinical setting.²

Tissue is optically characterised by two parameters: scattering and absorption. Absorption reduces the amount of light transmitted and is wavelength dependent, which allows identifying and quantifying the concentration of absorbing molecules. Scattering means that the light is deflected, i.e. a change in the direction of its propagation, without losing energy. The scattering coefficient (μ_s') is more than one order of magnitude higher than the absorption coefficient (μ_a). The scattering in tissue is strong and, thus, the light propagation is disordered after 1 mm path in tissue. Light propagation is modelled by the diffusion approximation to the Boltzmann transport equation.³⁻⁹ From μ_a measured at at least two wavelengths, the oxyhaemoglobin [O_2Hb], deoxyhaemoglobin

[HHb], total haemoglobin [$tHb = O_2Hb + HHb$] and haemoglobin oxygen saturation ($StO_2 = O_2Hb/tHb$) are calculated, because O_2Hb and HHb have different absorption spectra in the NIR range, as they do in the visible spectrum.^{5,10} NIR spectroscopy instruments, which measure optical properties at one specific location and provide absolute values at least of StO_2 , are part of this review. These are also called oximeters. The important point is that the measurement of StO_2 is absolute on a scale from 0% to 100% and can be compared between subjects or patients. Older instruments, which do not enable absolute values, but only measure relative concentrations changes, are not discussed in this review. NIR imaging instruments employ several sources and detectors at different locations and provide maps or images of changes in O_2Hb , HHb and tHb. They are also not part of this review.

There are three basic principles of operation of NIR spectroscopy/oximeters: continuous wave, frequency-domain and time-domain NIR spectroscopy. In contrast to continuous wave instruments, which only measure light intensity, frequency-domain and time-domain, NIR spectroscopy also measure the phase or time of flight, i.e. the time the light needs to penetrate the tissue. This enables absolute values of μ_a , μ_s' and, consequently, of O_2Hb , HHb, tHb and StO_2 to be determined.

Since the frequency-domain or time-domain instrumentation is more sophisticated and complicated, most commercial instruments are based on continuous wave. Some of these instruments use a multi-distance approach (Table 1: instruments 02, 04, 06, 09), meaning that light is detected at two or more different distances from the source. The multi-distance approach considerably reduces the influence of superficial layers of tissue on the StO_2 value,^{11,12} which is an important advantage in many applications, especially brain measurements. Some instruments are based on the diffusion approximation for semi-infinite boundary conditions and on some reasonable assumptions of the scattering properties at different wavelengths (for example, instruments 04, 06, 08); others are based on empirical algorithms calibrated *in vitro*, in animals, or in humans (for example, instruments 01, 02). Some instruments use multi-wavelength spectroscopy and calibration factors (instruments 01, 03, 05 and 07), meaning that more wavelengths are needed. Finally, there are fully quantitative instruments in the frequency (06) or time domain (08), which, apart from StO_2 , also determine absolute concentrations of O_2Hb , HHb and tHb.

At least two wavelengths are required to solve the spectroscopic equations for O_2Hb and HHb, but some instruments use more wavelengths, yielding a better signal-to-noise ratio or accounting for other, less absorbing chromophores such as cytochrome aa3¹³ or bilirubin.¹⁴ Some instruments use laser diodes, each producing a very well defined wavelength (Table 1: instruments 01, 03, 06, 07, 08). In practice, this design means that the laser diodes are placed in the instrument and light is carried to the skin through light fibres. They are switched on in sequence and thus a single detector can be used. Some instruments use light emitting diodes (Table 1: 02,

Table 1. Overview of commercial near infrared spectroscopy oximeters.

No.	Instrument	Technique	Number of channels	Neonatal sensor	Company	Website
01	FORE-SIGHT	Spectral	2	Yes	Casmed, USA	www.casmed.com
02	INVOS 5100C	Multi-distance	2 or 4	Yes	Somanetics, USA	www.somanetics.com
03	NIMO	Spectral	Up to 4	Custom	NIROX, Italy	www.nirox.it
04	NIRO-200NX	Multi-distance	2	Yes	Hamamatsu, Japan	www.hamamatsu.com
05	O2C	White light spectral	2	Yes	LEA, Germany	www.lea.de
06	OxiplexTS	Multi-distance IM	1 or 2	Yes	ISS, USA	www.iss.com
07	T.Ox	Sensor geometry	2	Yes	ViOptix, USA	www.vioptix.com
08	TRS-20	TRS	2	Yes	Hamamatsu, Japan	www.hamamatsu.com
09	EQUANOX 800xCA	Multi-distance	Up to 4	Yes	Nonin, USA	www.nonin.com

Instruments 03 measures StO₂ only in muscle and 07 is not used for the brain in neonates. Instrument 08 is currently sold only in Japan.

Abbreviations: Multi-distance=measures at more than one source-detector distance,

IM=intensity modulated frequency domain,

TRS=time resolved spectroscopy.

04, 09), which have a broader spectrum, but generally can be placed inside the sensor. Still others use a white light source and broad-band spectroscopy (Table 1: 05), which is mostly sensitive to superficial tissue.

While some manufacturers provide reusable sensors (for example, 04, 05, 06) others provide disposable sensors (for example, 01, 02), which lead to increased operation expenses.

NIR spectroscopy instruments are mostly portable and, with the rapid development of optics and electronics, have become increasingly economical and robust. The instruments in Table 1 are generally designed for easy clinical use. Methodological and technical aspects are reviewed in more detail in the literature.¹⁵

One problem is that NIR spectroscopy 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.^{16,17} In the neonate, this problem is small, because the skin, scalp and skull are thin and instruments with a multi-distance approach cancel out the influence of the superficial tissue. Furthermore, NIR spectroscopy is less sensitive to larger compared to smaller blood vessels.¹⁸ Thus, tHb measured by NIR spectroscopy reflects a slightly different measure of tissue blood volume compared to other methods. Although StO₂ is often thought to be a measure of the venous oxygen saturation, strictly speaking it is an average of arterial and venous saturation weighted by the compartment size. This weighting factor is impossible to determine precisely and may vary between tissues, in particular between healthy and diseased tissue, and over time.

In contrast to pulse oximetry, which measures arterial oxygen saturation and which can easily be validated by taking arterial blood samples, StO₂ is a new parameter for which no “gold standard” method exists. Therefore, it is also impossible to validate StO₂ *in vivo*. Thus, *in vivo* validation studies have focused on drawing arterial and venous blood samples, but were faced with the problem of needing to assume arterial

and venous compartment sizes (for example, Benni *et al.*¹⁹ and Hueber *et al.*²⁰). Since the compartment sizes are unknown and since the volume measured by the NIR spectroscopy sensor and the one interrogated by the venous blood sampling is not congruent, such *in vivo* studies cannot be considered true validations of the accuracy of StO₂ measured by a specific NIR spectroscopy device. They are merely plausibility tests, which may show that StO₂ values are in an approximately reasonable range. As pointed out above, depending on the configuration of the instrument, the tissue volume to which the sensors are sensitive may vary between instruments, the algorithms and assumption made vary substantially and consequently the values between the instruments vary and sometimes even between sensors for the same instrument.²¹ While some commendable manufacturers have published their algorithms (for example, 04 and 06), unfortunately most manufacturers have not provided this essential information. Knowing the algorithm helps the user to take into consideration the assumptions made and to understand under which conditions reasonable values will be obtained. This leads to a crucial problem: different instruments/sensors/algorithms yield different StO₂ values and findings generated with one set-up may not be directly transferred to another set-up. The problem will be particularly severe if clinicians set fixed limits for good or too low/high StO₂ values. These limits will have to be set differently for each instrument. For this reason, it would be important to be able to compare the different set-ups. Such a comparison needs to take into account the dynamic range and the level of the StO₂ value. One recommendable possibility to compare different instruments is to employ liquid phantoms, which mimic the optical properties (μ_s') of a specific tissue and to which human haemoglobin can be added. The oxygenation can be changed by adding yeast, O₂ or N₂ gas. In such phantoms, the StO₂ values can be measured with other gold standard methods (for example, pO₂ measurements) and the accuracy of the measurement can be determined.²² Another

possibility is to study the StO_2 *in vivo*, for example, in muscle during exercise or cuff occlusion, which enables a comparison of the dynamic range and level between instruments, but does not allow for a determination of accuracy.

In conclusion, a considerable number of commercial NIR spectroscopy instruments to measure StO_2 are available today. From a methodological point of view, the instrumentation, configuration and algorithms vary considerably between the different manufacturers. In the future, it will be important to build instruments with a high precision and to quantitatively compare the available instruments.

Cerebral oxygenation monitoring: clinical relevance in neonatal intensive care

Depending on the manufacturer, NIR spectroscopy determined cerebral StO_2 is also called or abbreviated differently, for example, rScO_2 measured by instrument O2 or tissue oxygenation index (TOI) measured by instrument O4, which are very comparable.^{23–25} Generally, the precision is not (yet) high enough for StO_2 to serve as a robust quantitative measure to monitor cerebral oxygenation in the immature and sick term neonate. In particular, the high intra- and inter-patient variability makes this method less eligible for this goal (precision of previous version of instrument O4²⁶ and instrument O6²⁷). However, when used as a trend monitoring method, substantial changes of cerebral StO_2 in the individual patient, larger than the limits of agreement, can provide us with important clinical information about changes in cerebral oxygenation, sometimes urging re-evaluation of clinical care.²⁸ Since the immature brain is extremely vulnerable, in particular in sick and haemodynamically unstable (preterm) neonates, monitoring cerebral oxygenation has a high priority and is increasingly combined with other brain monitoring devices such as amplitude-integrated EEG (aEEG), which is used to monitor brain function and to detect sub-clinical seizures. NIR spectroscopy-monitored cerebral StO_2 can also be used in combination with blood pressure monitoring and provide us with usable information concerning the autoregulatory ability of the cerebral vascular bed.^{29,30}

The use of StO_2 in the neonatal intensive care unit

Earlier studies which investigated the stability and reproducibility of NIR spectroscopy-monitored cerebral StO_2 in the neonatal intensive care unit (NICU) showed somewhat different results. In a small but elegant study, Menke *et al.*³¹ showed that precision of repeated cerebral StO_2 measurements (using the no longer sold Critikon 2020 instrument) was quite acceptable, even when different investigators did the measurements, whereas Sorensen and Greisen²⁶ found a precision of approximately 5.2% in StO_2 (using a precision

of the previous version of instrument O4) and were somewhat more cautious about the issue of reproducibility and precision of NIR spectroscopy to measure cerebral oxygenation in the neonate. Recent studies showed that a higher precision of 2.8% to 4.5% can be achieved by excluding tissue inhomogeneity using instrument O6 and a prototype.^{27,32}

A second issue in clinical practice, which is important with respect to reliability of the NIR spectroscopy-monitored cerebral oxygenation, is the question whether or not regional differences exist. Lemmers and van Bel³³ compared simultaneously determined left and right fronto-parietal measurements of StO_2 (instrument O2) and found similar values, albeit that during unstable arterial oxygen saturations a short-lived uneven re-oxygenation of the brain occurred during recovery of the arterial oxygen saturation. The same group also investigated the StO_2 (instrument O2) in four different regions of the brain simultaneously, left-right fronto-parietally and left-right temporo-occipitally, and found no differences between these regions, although StO_2 values were lower in all regions on day 7 as compared to day 1 of life.³⁴ This appeared to be true in (extremely) preterm infants but also in term infants. This may lead to the conclusion that measuring cerebral StO_2 in one region of the brain should be reliable for obtaining information about cerebral oxygenation. Figure 1 shows a picture of the position (fronto-parietally) and fixation (elastic band) of a NIR spectroscopy sensor as used at the University Medical Center (UMC), Utrecht. An alternative can be to glue the sensor to the desired region of the head. The head posture of infants seems to have no significant effect on cerebral StO_2 as recently pointed out by Ancora *et al.*, who measured StO_2 , during different head and body positions.³⁵

Expected or normal values of StO_2 are reported in numerous studies and when obtained with NIR spectroscopy devices of different brands showed comparable values. In adults, term infants up to six months of age and in (extremely) preterm

Figure 1. Picture of the position (fronto-parietally) and fixation (elastic band) of a NIR spectroscopy sensor (instrument O2) as used at the University Medical Center UMC Utrecht. The inset shows a sensor, which is attached to the head by special glue.

neonates, values range between 60% and 75%²⁴ in a large cohort of extremely and very preterm neonates during the first three days of life, values ranging between 55% and 85% were detected with a mean value of 71% (mean $\pm$ 2SD) (unpublished data). It must, however, be stated here that these measurements were performed with (small) adult sensors of NIR spectroscopy devices of different brands. Neonatal NIR spectroscopy sensors, which have quite recently been brought onto the market by different companies, all consistently yield 10% higher StO₂ values compared to the adult sensors (unpublished data). We speculate that this difference is due to different assumptions in the algorithm used to calculate StO₂ depending on the sensor. The algorithms all include assumptions about the optical properties of the tissue and its water content, which are both quite different for neonates compared to adults. In principle, we speculate that neonatal sensors provide more accurate values for neonates; however, there is no evidence that this is actually the case.

A final important question is the relationship between StO₂ on the one hand and the occurrence of brain damage. Two experimental studies in newborn pigs showed that long-lasting (from 30 min to 90 min) StO₂ values below 33–40% were related to mitochondrial dysfunction, hippocampal damage and energy failure of the immature brain.^{36,37} A clinical study in neonates, operated for left ventricular hypoplasia, showed that post-operative values of 40–45% for at least 120 min were related to new ischaemic regions on cranial magnetic resonance imaging.³⁸ We suggest that values lower than 45% of StO₂ should be avoided if possible. These values are based on the adult sensor of instruments

O2 and O4. For other instruments, the level of the values depends on the assumptions of the algorithm and may differ somewhat.

We suggest that there is a role for cerebral oxygenation monitoring using NIR spectroscopy-measured StO₂ in those (preterm) neonates where there is a danger of inadequate cerebral perfusion and/or where compromised oxygenation is imminent or actually exists. Among others, four conditions can be mentioned where cerebral oxygenation monitoring can be of advantage for the sick preterm infant:

- **(Severe) infant respiratory distress syndrome (RDS):** During ventilation due to (severe) RDS, systemic haemodynamics can be disturbed due to high ventilation pressures with consequent compromise of the cerebral oxygenation. Also, disturbances in arterial carbon dioxide tensions can cause undesired changes in cerebral oxygenation.^{24,39,40} StO₂ monitoring can be an important tool to avoid these complications.
- **Unstable and low blood pressure:** Low blood pressure can lead to underperfusion and hence to disturbed cerebral oxygenation with or without loss of cerebral autoregulation (Figure 2), giving cerebral oxygenation monitoring, preferably in combination with simultaneous blood pressure monitoring, an additional, but important role to avoid these potentially dangerous conditions.^{30,41–43}
- **Haemodynamically important ductus arteriosus:** A haemodynamically relevant ductus arteriosus has been known to affect perfusion of important organ systems such as the brain which may affect oxygenation of the brain.^{44,45} Particularly in long-standing ductal steal, cerebral oxygenation can be too low as indicated by the StO₂⁴⁶ (Figure 3). In

Figure 2. A preterm infant, who develops low blood pressure. Arterial oxygen saturation (SaO₂) is the top trace, cerebral tissue oxygen saturation (StO₂, instrument O2) middle trace (in blue) and the mean arterial blood pressure (MABP) the lowest trace. Here the cerebral StO₂ decreases almost parallel with the MABP, which is interpreted as a lack of cerebral auto-regulation, because the cerebral blood flow is not regulated independently of the MABP.

Figure 3. Example of a NIR spectroscopy recording in a preterm infant with an open ductus arteriosus (PDA). The red arrows indicate where indomethacin was administered to close the ductus, which was successful at the end of the tracings. Arterial oxygen saturation (SaO_2) is the top trace, cerebral tissue oxygen saturation (StO_2 , instrument O2) middle trace (in blue) and the mean arterial blood pressure (MABP) the lowest trace. It can clearly be seen that, in this infant, the cerebral StO_2 decreases to low levels on day 2 and recovers after the ductus is closed on day 4.

preterm neonates, whose duct had to be surgically closed, the combination of cerebral oxygenation, blood pressure and aEEG monitoring showed extremely low StO_2 [by instrument O2], blood pressures and brain activities in some infants, suggesting that monitoring of these critical variables helps to prevent complications.⁴⁶

■ *Conditions where lack of cerebral autoregulation is common.*

Apart from the above-mentioned conditions, potential clinical uses of NIR spectroscopy-monitored StO_2 are reported in preterm infants with recurrent apnoeas,^{47,48} to determine the optimal point of time for red blood cell transfusions,⁴⁹ to avoid hyper-oxygenation in extremely preterm babies which are very prone to oxidative stress,⁵⁰ and in the severely asphyxiated term infant where the pattern of StO_2 is used together with the simultaneously monitored aEEG background pattern of brain activity for prognostic purposes.⁵¹

Conclusion and outlook

NIR spectroscopy-monitored StO_2 of the immature brain is not precise enough yet to be used as a quantitative measure, but further innovative research is under way to achieve this goal. However, as a trend monitoring device it has the potential to become a very valuable tool in those infants who are sick and unstable. Several frequently occurring complications, especially in the extremely and very preterm neonate, are related to imminent or overt under-oxygenation or hyper-oxygenation of the immature brain. Further improvement of

long-term neurodevelopmental outcome may be achieved when using additional monitoring of the cerebral oxygenation, but further research concerning the benefits of this monitoring method should be performed to confirm this suggestion.

Liver and gastro-intestinal oxygenation and circulation studied by near infrared spectroscopy

The measurement of the liver oxygenation

The liver is irrigated by three different sources of blood supply. The portal vein drains the venous blood of the splanchnic system. It receives blood of the splenic, the superior mesenteric, the right and left gastric, the prepyloric, the cystic and the paraumbilical veins. The superior mesenteric vein drains the jejunal, ileal, ileocolic, right colic and middle colic veins. It is joined by the right gastroepiploic and the pancreaticoduodenal veins to form the portal vein. The hepatic artery and its branches join the branches of the portal vein at the level of the sinusoids and are distributed to the same territory in this way. The hepatic veins convey blood from the liver to the inferior vena cava.⁵² Taking into account that the global hepatic

blood supply is derived for 75% from the portal vein and, hence, for 25% from the hepatic artery, measuring the liver oxygenation might give extra information about the gastro-intestinal circulation. However, there is not a linear relationship due to the hepatic arterial buffer reaction. The portal venous flow is not regulated by the liver but by the gastro-intestinal circulation. The arterial blood flow is partly regulated by the adenosine concentration in the space of Mall, the minute fluid space surrounding the hepatic arterioles, bile ductuli, portal venules and sensory nerves. A decrease in portal flow will cause a decrease in the wash-out of adenosine and this increase in adenosine concentration will result in a vasodilation of the hepatic artery.⁵³ The arterial hepatic flow is thus not influenced by the oxygenation or the metabolism of the liver, but mainly by the portal flow.

NIR spectroscopy measurements of the liver are feasible because it is a homogenous organ that lies directly beneath the skin in neonates. The StO_2 can be measured non-invasively. When measuring the StO_2 of the liver, a mixture of the arterial as well as the venous oxygen saturation will be measured. Tokuka *et al.* described the distribution of the different flows to the liver and its consequences.⁵⁴ When the hepatic artery was clamped, a decrease in StO_2 was seen with a recovery later. This was explained by the “reciprocal relationship” between the hepatic artery and the portal vein, so that an increase in blood flow through one circuit leads to an increased inflow resistance in the other, thus helping to maintain a constant blood flow in the liver. However, when the portal vein was clamped, a much greater decrease in StO_2 was seen and there was no recuperation, suggesting that the hepatic artery cannot immediately compensate for a loss of portal venous inflow. This shows the great importance of the inflow of the portal vein for the hepatic oxygenation. In these studies, the NIR spectroscopy probes were placed upon the surface of the liver.

The oxygenation of the liver is regulated by oxygen extraction. Seifalian *et al.* described a decrease in O_2Hb and an increase in HHb (measured by the NIRO 500, a previous version of instrument O4) during graded hypoxia.⁵⁵ The same group found a good correlation between O_2Hb and the arterial oxygen pressure⁵⁶ and also between O_2Hb and the hepatic vein oxygen partial pressure in rabbits during graded hypoxia.⁵⁷ Different studies found a good correlation between NIR spectroscopy and other methods measuring hepatic hypoxia.^{58–60}

Measuring the oxygenation of the liver can be informative for three different domains. It can be used after liver transplantation to measure the perfusion of the liver, to measure the liver oxygenation as a parameter of the central venous oxygenation or as a reflection of the gastro-intestinal circulation and oxygenation.

NIR spectroscopy can be used to detect ischaemia in the liver after liver transplantation. El Desoky *et al.* showed a good correlation between ischaemia of the liver and the O_2Hb and cytochrome oxidase in rabbits. There was a decrease in both O_2Hb and cytochrome oxidase during ischaemia and, in the reperfusion phase after ischaemia, a biphasic change of

both parameters (first an increase and then a decrease). They described a good correlation between the parameters of intra-cellular injury and cytochrome oxidase.⁶¹ Kitai *et al.* described the evolution of the liver oxygenation during liver transplantation. Hepatic StO_2 changed from $81.2\% \pm 1.5\%$ (mean $\pm$ SEM) before donation (in the donor) to $49.7\% \pm 4.2\%$ after portal reflow, to $58.4\% \pm 5.0\%$ after arterial reflow, and then to $71.4\% \pm 3.9\%$ before closure. The mean hepatic StO_2 was positively correlated with portal flow rate as measured by duplex Doppler sonography. They concluded that NIR spectroscopy can help in the prevention of liver ischaemia during and after graft surgery.⁶² However, the same group also showed that the status of the liver (fatty liver, cirrhosis) needs to be taken into account when using the technique of NIR spectroscopy.^{63–65}

Measuring the StO_2 of the liver can help in determining the central venous oxygenation. Low cardiac output or shock dramatically reduce the intestinal perfusion and, hence, decrease portal vein oxygen saturation and increase oxygen extraction rate in the liver resulting in a decrease of liver tissue oxygenation.⁶⁶ Beilman *et al.* described a good correlation between the regional StO_2 of the liver and the arterial oxygen delivery during haemorrhagic shock in piglets.⁶⁷ This was confirmed by Nahum *et al.*, who found a good correlation between cardiac output and oxyhaemoglobin reading of the liver in an endotoxaemic shock model in piglets.⁶⁸ A good correlation was found in piglets during rewarming and hypocapnia between the StO_2 of the liver and the mixed venous oxygen saturation, measured in the pulmonary artery. A good relation was also found with CvO_2 , the mixed venous oxygen content.⁶⁹ No relation was found with the arterial oxygen saturation, which is in contrast to other studies.^{56,67} However, in these studies O_2Hb was measured during graded hypoxia and thus mainly reflected hypoxic hypoxia. Schultz *et al.* measured the hepatic StO_2 (measured by the NIRO 300, a previous version of instrument O4) transcutaneously, during cardiac catheterisations. They described a good correlation between the hepatic StO_2 and the central venous oxygen saturation, measured in the right atrium, in children during cardiac catheterisation.^{70,71} They did not find a good correlation between hepatic StO_2 and the hepatic vein oxygenation.⁷⁰ However, they performed single point measurements and no trend evaluations were done.

A third possibility is to use the measurement of hepatic StO_2 as a reflection of the gastro-intestinal circulation and oxygenation. In piglets, changes in flow were tested by increasing the temperature and the induction of hypocapnia. Arterial oxygenation remained stable so that changes in hepatic StO_2 were mainly caused by changes in splanchnic blood flow or changes in oxygen consumption.⁶⁹ Regarding the relationship with intestinal blood flow, a good correlation was found between the blood flow in the distal ileum and the mid-gut of the small bowel and the hepatic StO_2 in this study.⁶⁹ No correlation was found with the blood flow in the stomach and the proximal part of the jejunum. These correlations reflect the important role of the portal vein in the oxygenation of the liver as was described by Tokuka *et al.*⁵⁴ In a study in rabbits, where

the mesenteric artery was clamped for 30 min, a significant decrease in hepatic StO_2 was seen after 90 min of occlusion of the superior mesenteric artery reflecting the decrease in portal flow.⁷² The further decrease after reperfusion might reflect the decrease in hepatic arterial flow after the portal flow was regained. Teller *et al.*^{73,74} were the first to use the measurement of hepatic StO_2 as a possible parameter of intestinal flow in neonates. They found a decrease in hepatic StO_2 after feeding a bolus of breast milk. Whether this decrease is mainly caused by an increase in portal flow to the liver or by a decrease in the venous portal oxygen saturation or a combination of these two needs further research.

In conclusion, measurement of the liver oxygenation can give direct information on the liver perfusion during and after transplantation surgery and on the central venous oxygenation in cardiac surgery. To use this measurement as a reflection of the splanchnic circulation and oxygenation, the hepatic arterial buffer reaction and the effect of changes in portal flow to the liver oxygenation have to be taken into account.

Measurement of the abdominal venous saturation

Another way to look at the splanchnic oxygenation and circulation is to measure the oxygenation under the umbilicus. A good correlation was found between abdominal StO_2 and gastric tonometry in infants with congenital heart disease.⁷⁵ Petros and Fortune *et al.*, were the first to use this method and they specifically used the difference between the cerebral and splanchnic StO_2 , called the cerebro-splanchnic oxygen ratio (CSOR).^{76,77} They stated that the CSOR had a 90% (56–100%) sensitivity to detect splanchnic ischaemia, indicating that this might be a non-invasive method for detecting necrotising enterocolitis. Dave *et al.* looked at the CSOR during feeding and found that CSOR and splanchnic StO_2 , but not cerebral StO_2 , increased during feeding in stable infants.⁷⁸ Cortez *et al.* described a decrease in splanchnic StO_2 during the first nine days, followed by an increase from day 10 to day 14. There was a significantly lower StO_2 in infants with feeding intolerance.⁷⁹ The decrease in StO_2 over the first days was confirmed by McNeill *et al.*, who described an increase in abdominal rSO_2 with gestational age. However, they had a very high variability in abdominal StO_2 measurements (33–62%) in contrast to the cerebral and renal StO_2 measurements.⁸⁰ Further research regarding the influence of meconium, feeding fluid boluses and bilirubin needs to be performed in order to decrease this high variability. The reasons for this could be the high absorption of the meconium, which is falsely interpreted as O_2Hb and HHb by the instrument's algorithm, and the inhomogeneity of the tissue (for example, air bubbles or pieces of meconium). Both violate the assumptions made to calculate the StO_2 and, thus, the StO_2 values may very well be erroneous. In principle, it would be possible and desirable to include the meconium spectrum into the algorithms and thus remove a source of error.

A last promising method, only used in piglets for the moment, is a prototype side-illuminating NIR spectroscopy nasogastric probe to continuously measure changes in gastric

StO_2 . A good correlation was found with superior mesenteric artery flow.^{81,82}

Conclusion and outlook

NIR spectroscopy might be a promising technique to measure the splanchnic oxygenation and circulation non-invasively in neonates; however, there are various difficulties. The liver is a vast organ and can provide a good measurement of tissue oxygenation; however, measuring liver oxygenation imposes the problem of the hepatic buffer reaction, and changes in liver StO_2 need to be interpreted with caution looking at the changes in portal flow and central venous oxygenation. Measuring the bowel directly by placing the probe infra-umbilical on the abdomen and measuring StO_2 or CSOR shows some promising results; however, there is a high variability in these measurements, caused by the influence of meconium, feeding fluid boluses and bilirubin. Further clinical research is needed to determine whether these parameters can be used in clinical practice, or if new methods such as applying NIR spectroscopy in the nasogastric tube might be better in predicting gastrointestinal problems.

“Peripheral” (i.e. limb) oxygenation

Simple photometers, i.e. NIR spectroscopy instruments that measure changes in oxy- and deoxy-haemoglobin may be combined with venous or arterial occlusion of a limb to estimate venous oxygen saturation, blood flow, oxygen delivery and consumption.^{28,83} This has been applied to preterm and term newborns but this literature will not be reviewed here.

Over the last 10 years, NIR spectroscopy oximeters have also been applied and appear useful. First, StO_2 is roughly similar to the value of venous oxygen saturation measured by venous occlusion and, typically, in the range of 65–80% in clinically stable newborn infants. Second, similar values are obtained from the upper and lower limb, at least in stable infants.⁸⁴ Third, unfortunately, the limited precision of both measurements means that only a small fraction of StO_2 measurements falls within the range of SvO_2 to $\text{SvO}_2 + [0.2 \times \text{SpO}_2]$, i.e. in agreement with a reasonable arterio-venous blood volume ratio.⁸⁵ Fourth, there is a positive correlation between limb StO_2 and gestational age and birth weight in clinically stable infants.⁸⁶ Obviously, the subcutaneous fat increases with gestational age and birth weight and is also associated with StO_2 .⁸⁶ It is debatable whether the positive correlation is considered an error in StO_2 due to the optical heterogeneity between the subcutaneous fat and the deeper muscle compartment, or a result of the lesser oxygen extraction in fat tissue compared to muscle, or a true difference in resting muscle oxygen transport and utilisation between term and preterm neonates. In any event, to minimise the influence of the fat layer it is advisable to use an StO_2 measurement based on a multi-distance approach (Table 1), which cancels the influence of superficial tissue up to ~6 mm thickness.^{11,12}

Peripheral oximetry has given reasonable data in healthy neonates. Peripheral StO₂ increases over the first 10 min of life after elective caesarian section in healthy term infants.⁸⁷ The values were higher pre-ductally than post-ductally and lower than the simultaneously measured cerebral values, as expected. Peripheral StO₂ decreases during the first week of life in healthy term infants,⁸⁸ possibly related to a right shift of the oxygen dissociation curve, whereas oxygen consumption remains constant.

The effect of levosimendan—a novel cardiovascular drug—was examined by cerebral and peripheral oximetry. In an observational study of newborns with congenital heart disease given the drug for clinical reasons, the trends over the following hours were analysed.⁸⁹ Neither cerebral nor peripheral oxygenation increased. As levosimendan is an “inodilator” (i.e. it acts partly to improve cardiac contractility and partly to dilate peripheral arteries) this was a disappointing result, but the study set-up could be applied to a range of therapeutic interventions in compromised neonates.

In conclusion, peripheral StO₂ can be measured easily. At the current level of understanding, results should be interpreted with caution. Partly, absolute values may be influenced by the thickness of subcutaneous fat. The precision is not better than for cerebral use. Finally, it is possible that peripheral oxygen consumption may decrease in response to decreased peripheral oxygen delivery, making peripheral StO₂ less than ideal as a marker of peripheral circulatory compromise.

Conclusions and outlook

From the instrumentation point of view, NIR spectroscopy has gained significantly in clinical importance, especially by being able to measure StO₂, an absolute parameter. An increasing number of commercial instruments are available today and the number of users is virtually exploding. However, the precision of the measurements is still too low from a clinical point of view and the variety of algorithms employed by the different instruments may provide quite different StO₂ values. In the future, the different instruments need to be compared quantitatively and the StO₂ measurements are expected to become more precise.

The measurement of cerebral StO₂ may be useful for detecting situations where the oxygenation of the brain may be impaired and the hope is that this may enable the prevention of brain lesions. However, the clinical utility of cerebral StO₂ still needs to be examined.

Although liver and gastro-intestinal, as well as peripheral, measurements are still an object of research and several problems have to be overcome before clinical use, these measurements could be of high value in specific clinical situations.

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