

REVIEW

The light still shines, but not that brightly? The current status of perinatal near infrared spectroscopy

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Efforts have been made to find new, non-invasive methods for assessing tissue oxygenation and haemodynamics, particularly in the brain of the fetus and the newborn infant. Near infrared spectroscopy (NIRS) is a developmental technique that provides just such a method, allowing calculation of variables such as cerebral blood flow and cerebral blood volume. It can also measure peripheral oxygen consumption. This review is based on our long experience of using NIRS. Basic principles, techniques, validation, and clinical applications are highlighted. Although more than two decades have passed since its introduction, NIRS remains very much a developmental technique, despite technical progression. A great deal more research is required for NIRS to become a routine clinical tool.

Knowledge of basic mechanisms controlling oxygen transport and utilisation is essential in understanding the pathophysiology of many diseases. Maintaining adequate tissue oxygen transport could be considered a primary objective in intensive care management.¹ Inadequacy of clinical techniques for assessing tissue oxygenation may add to uncertainty surrounding the benefits of treatment modalities in acute life threatening illness.

Cerebral palsy remains a significant problem among very low birth weight (VLBW) survivors² and is strongly associated with white matter infarction. Events such as perinatal asphyxia, hypotension, and septic shock are common, adding to the vulnerability of this population.³ Pulse oximetry is commonly used to measure arterial oxygen saturation (SaO₂), supplemented by intermittent arterial gas estimations, and occasional use of transcutaneous oxygen and carbon dioxide monitors.⁴ Systemic circulation is monitored by electrocardiograph and invasive and non-invasive blood pressure monitors. Despite these measures, all continuously applicable at the cotside, cerebral damage frequently occurs, even in infants whose measured parameters have been stable.

Since conventional methods have failed to provide effective strategies for the prevention of brain injury, new methods for assessing the adequacy of the cerebral circulation, particularly of the fetus and neonate, have been sought. Near infrared spectroscopy (NIRS) allows the non-invasive monitoring of tissue oxygenation and cerebral haemodynamics. The aim of this paper is to review the clinical, research, and technical

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advances in NIRS over the past 25 years and discuss its potential as a clinically useful monitoring tool.

BACKGROUND

The use of in vivo NIRS in humans was introduced by Jobsis, in 1977,⁵ for non-invasive monitoring of tissue oxygenation, and it was first applied to neonates in 1985.⁶ Although the principles underlying NIRS are relatively straightforward, they are often poorly understood.⁷ Two important phenomena are relied on:

- (1) The relative transparency of biological tissue to near infrared (NIR) light
- (2) The presence of chromophores (compounds whose absorption of NIR is oxygen status dependent) in tissue.

The chromophore most extensively studied is haemoglobin, although cytochrome aa₃ and myoglobin are also significant. All techniques use NIR light (600–900 nm). Within this range deoxyhaemoglobin (Hb), oxyhaemoglobin (HbO₂), and oxidised cytochrome aa₃ exhibit distinguishable optical absorption characteristics, for example, Hb absorption peaks at 775 nm, whereas at 800 nm the absorption of Hb and HbO₂ is identical. The characteristics of light are therefore altered by passage through tissue containing these chromophores.

A typical NIRS trace (fig 1) shows the impact of an episode of deoxygenation. The concentration of HbO₂ falls, mirrored by an equal and opposite rise in Hb, provided that the total haemoglobin (HbT) in the tissue remains constant. HbO₂ may change because of alterations in haemoglobin saturation or volume, therefore Hbdiff ($\Delta[\text{HbO}_2 - \text{Hb}]$) is often used to track changes

Abbreviations: CBF, cerebral blood flow; CBV, cerebral blood volume; CBVR, cerebrovascular reactivity; CNEP, continuous negative extrathoracic pressure ventilation; CSvO₂, oxygen saturation of cerebral venous blood; CW, continuous wave; DO₂, oxygen delivery; DPF, differential path length factor; FIO₂, fractional inspired oxygen concentration; FOE, fractional oxygen extraction; Hb, deoxyhaemoglobin; HbO₂, oxyhaemoglobin; Hbdiff, $\Delta[\text{HbO}_2 - \text{Hb}]$; HbT, total haemoglobin; IM, intensity modulated; IPPV, intermittent positive pressure ventilation; IVH, intraventricular haemorrhage; MRS, magnetic resonance spectroscopy; NIR, near infrared; NIRS, near infrared spectroscopy; PaCO₂, partial pressure of carbon dioxide in arterial blood; PCr, phosphocreatine; Pi, inorganic phosphate; SaO₂, arterial oxygen saturation; TOI, tissue oxygenation index; TOS, tissue oxygen saturation; TPSF, temporal point spread function; TR, time resolved; VLBW, very low birth weight; VO₂, oxygen consumption

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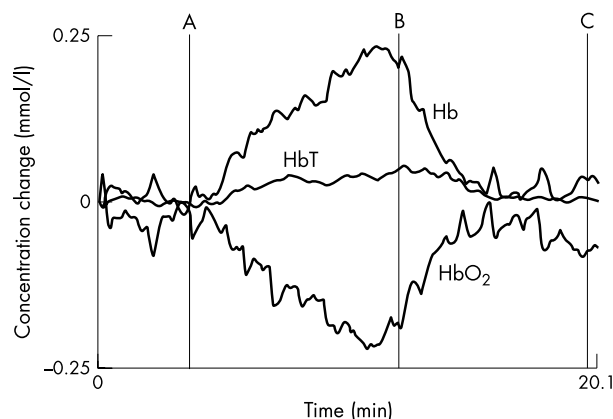


Figure 1 Effects of hypoxia on the concentration of cerebral total (HbT), deoxygenated (Hb), and oxygenated haemoglobin (HbO₂) in a preterm infant of 30 weeks gestation.¹³ Arterial saturation gradually falls from 94% at A to a lowest value of 83% at B, then rises to 93% at C.

attributable to saturation alone. At its most basic, NIRS simply shows changes from baseline, from which all other measurements are derived.

Cytochrome aa₃ is also of interest, having the potential to inform about cellular oxygenation. Studies in rats have been successful,^{8,9} but clinical studies have proven difficult.¹⁰ Haemoglobin is such a ubiquitous and powerful chromophore that a separate effect of cytochrome aa₃ has been difficult to identify.

Myoglobin may be important in muscle studies, where the relative contribution of haemoglobin versus myoglobin remains contentious.¹¹

TECHNIQUES USED

- (1) Change in absorbance: "continuous wave (CW) NIRS" uses a series of light pulses of few nanoseconds.
- (2) Change in phase, amplitude, and modulation depth: "intensity modulated (IM) NIRS" uses sinusoidal modulation of the light intensity.
- (3) Pulse width and transit time: "time resolved (TR) NIRS" uses a picosecond light pulse.

Continuous wave NIR instrument (CWNIRS)

Initially all NIRS instruments were of this type, applied to animal models at first, then used to study the circulation and oxygenation of the human brain.^{6,12,13} The sampling rate is usually 0.5 or 1.0 seconds (for example, Radiometer, Keele, Hammatsu) although sampling rates of 100 ms have been achieved and used to study cortical blood oxygenation. Multi-site NIRS¹⁴ enables investigation at four adjacent sites simultaneously (for example, four regions of the brain or two brain and two forearm regions).

Early results^{6,12} did not adjust the optical pathlength to allow for scattering of light in tissue. Accurate estimates of differential path length factors (DPF) for different tissues were later derived,¹⁵ enabling quantification of Δ Hb, Δ HbO₂, and Δ HbT using a multicompartiment model. However, this path length is itself altered by haemodynamic changes. Further, attachment method, pressure applied, and gestational age contribute to the errors when assuming a fixed DPF. Probe movement during monitoring may affect the entire study. Remarkably, despite these limitations, NIRS has provided useful evidence regarding the management of sick neonates.

A further problem is that quantifiable changes can only be observed when there is a biochemical or haemodynamic change (spontaneous or induced) in tissue. The clinical drive

for absolute values has led to the second generation of NIR instruments. CWNIRS has been adapted in several ways to achieve quantification.^{16,17} Somnatics uses a multidistance method to calculate intracerebral oxygen saturation. However, regional measurements in the brains of patients undergoing cardiac surgery correlated poorly with values obtained by co-oximetry.¹⁸ Critikon uses multiple probes to determine tissue oxygen saturation (TOS). Δ TOS in infants was found to correlate with Δ SaO₂,¹⁹ but Δ SaO₂ was considerably underestimated and a highly significant interpatient variability was observed, leaving the clinical value of TOS measurements undetermined.

Intensity modulated NIR instrument (IMNIRS)

Further contribution towards quantification of Hb and HbO₂ (hence HbT and CBV), as well as mixed arteriovenous saturation has come from IMNIR technology. This method calculates coefficients for absorption and scattering, which are required to make absolute measurements. However, artifacts caused by probe movement may affect the calculations. In pulse oximetry, specialised signal processing techniques have reduced this problem. The light intensity varies in amplitude in a sinusoidal manner. The phase, amplitude, and modulation depth of the transmitted/back scattered signal are altered by the tissue. Changes in volume of chromophores will produce changes in the coefficients.²⁰

Time resolved type (TRNIRS)

TRNIRS measures the time passage of a picosecond pulse of light through tissue. This is the temporal point spread function (TPSF), from which the necessary coefficients can be calculated, allowing quantification of oxygenation.^{21,22} The need for several wavelengths of this picosecond light source and a fast detector makes this a very expensive technique. It has expanded knowledge of tissue characteristics, but had little clinical impact.

It is now theoretically possible to measure and display tissue saturation (regional, mean, or mixed arteriovenous) as a percentage using CW and IMNIR machines. Saturation is a composite of the blood in the arteries, veins, and capillaries, and the values obtained do not equate to any known technique. IMNIR can also measure absolute concentrations of Hb, HbO₂, and HbT from which CBV can be derived. Absolute measurements, made on the assumption of homogeneity of tissue, could however be erroneous,²³ and the influence of multilayered structures warrants investigation.⁷

Optical imaging

Several groups are trying to develop a functional or biochemical optical image of the brain. Although resolution is likely to be poor, this could identify areas of hypo/hyperperfusion or relative ischaemia. However, the significant problems of light scattering and image reconstruction must be overcome in order to produce images of complex structures like the neonatal brain. Optical imaging of the brain appears feasible and achievable,²⁴ but is not yet a practical proposition at the bedside.

INDIRECT MEASUREMENTS USING CWNIRS

Cerebral blood flow and volume measurements

CWNIRS has been used to measure cerebral blood flow (CBF) using HbO₂ as a tracer. A sharp rise in HbO₂ is induced, by increasing fractional inspired oxygen concentration (FIO₂), and detected by CWNIRS. CBF is calculated by applying the Fick principle, giving neonatal values of 7–33 ml/100 g/min.²⁵ It is vital that during the manoeuvre CBF, CBV, and VO₂ remain constant.¹⁰ Unfortunately, this is not always possible to achieve.

CBV can also be estimated using CWNIRS. Quantification is achieved by inducing a fall in SaO₂ of 5–10% over five minutes

within the range 80–95%, by reducing the FIO_2 . As with the CBF method, CBF, CBV, and VO_2 are assumed to remain stable. When HbO_2 (or $Hbdiff$) is plotted against ΔSaO_2 the gradient is proportional to CBV. A mean of 2.22 (0.40) ml/100 g has been recorded in healthy infants.¹² CBV has been shown to decrease significantly during sampling from umbilical artery catheters.²⁶

These methods are only applicable to oxygen dependent babies and the required ΔSaO_2 must not affect CBV or CBF, or cause excessive desaturation. Multiple measurements are required because the repeatability is poor. This takes time, as parameters must be allowed to settle between tests. Frequently, in sick babies, changes are required for clinical reasons before the series of tests is complete.

Cerebral venous saturation

It has been assumed that any change in CBV, induced by jugular occlusion or head tilting, is due to a change in the quantity of blood in the venous sinuses. Therefore, the relative change in Hb compared with HbO_2 can be used to calculate the saturation of cerebral venous blood (CSvO₂). This methodology has been validated against invasive measurements using venous blood sampled during cardiac catheterisation.²⁷ Using NIRS with jugular venous occlusion, CSvO₂ and jugular blood flow have been measured in healthy infants.²⁸ Mean CSvO₂ was 64%, but jugular blood flow was much lower than expected, suggesting a methodological problem.

Low levels of CSvO₂ could indicate hypoxic stress and high levels a failure of oxygen uptake, as in cellular energy failure. In conjunction with SaO_2 and CBF, CSvO₂ has been used to measure cerebral VO_2 .²⁹ However, this introduces all the limitations of CBF measurements. Fractional oxygen extraction (FOE) is the ratio between VO_2 and oxygen delivery (DO_2). This can be calculated, without measuring flow, using the formula $FOE = (SaO_2 - CSvO_2) / SaO_2$. Assuming constant cerebral VO_2 , FOE will rise as DO_2 to the brain falls, until maximum oxygen extraction is achieved. Beyond this critical point, further reduction in DO_2 will cause reduction in VO_2 , increasing the risk of lactate production and ischaemic damage.

VALIDATION AND COMPARISONS OF NIRS MEASUREMENTS

Validation of NIRS measurements is difficult because there is no clinically applicable gold standard. However, CWNIRS has been compared with other methods of assessment of cerebral oxygenation and haemodynamics.

Plethysmography

Changes in CBV in preterm infants have been validated against strain gauge plethysmography.³⁰ A strain gauge placed around the infant's head detects changes in occipitofrontal circumference allowing ΔCBV to be estimated. A change in CBV induced by bilateral jugular venous occlusion in healthy preterm neonates, with NIRS and strain gauge applied simultaneously, produced two closely related sets of measurements.

Pulse oximetry

Changes in SaO_2 using pulse oximetry have been compared with changes in $Hbdiff$ using NIRS in preterm infants.³¹ During pauses in nasal airflow, a fall in SaO_2 was observed in 68% and a fall in $Hbdiff$ in 56%. Although the degree of concordance was high for large amplitude changes, in 20% no fall in $Hbdiff$ occurred despite a fall in SaO_2 and in 8% the converse was true. The authors concluded that both techniques are sensitive to changes in cerebral oxygenation. A fall of $Hbdiff > 0.3 \mu\text{mol}/100 \text{ g brain}$ is likely to be clinically significant and is associated with ΔSaO_2 of about 12%.

¹³³Xenon clearance

This is an established technique for measuring CBF. Comparison of both methods in newborn infants³² showed a good level of agreement.

Magnetic resonance spectroscopy (MRS)

MRS can detect secondary energy failure in the asphyxiated neonatal brain. A low ratio of intracellular phosphocreatine to inorganic phosphate (PCr:Pi) indicates a poor prognosis. In a comparison with NIRS, one infant, with severe birth asphyxia, had a marked alteration in cerebral haemodynamics preceding the detection of secondary cerebral energy failure by MRS.³³ Unfortunately, it has not been possible to use cytochrome aa, measurements to detect secondary energy failure in human infants, although this has been achieved in neonatal piglets.³⁴

CLINICAL APPLICATIONS

Most clinical work has been undertaken using CWNIRS. Where alternative technology has been employed this is stated.

Apnoea and hypoxia

In 1985, Jane Brazzy published the first study showing that hypoxaemia could be detected in newborn infants using NIRS applied to the cranium.⁶ Further studies indicated that a fall in SaO_2 of 5–10% usually results in a fall in HbO_2 and a rise in Hb and HbT, irrespective of whether the fall in SaO_2 was spontaneous or induced, suggesting compensatory vasodilatation.¹³

Subsequent studies confirmed the findings for Hb and HbO_2 but showed much more variable results for HbT, suggesting that a fall in HbT is more likely if there is an obstructive element to the apnoea.³⁵ Individual traces have been published clearly showing a fall in HbT with bradycardia, overshooting after recovery.¹³ Cyclical desaturation and reoxygenation of cerebral blood has also been shown during periodic breathing.³⁶

Fetal studies

A non-invasive method of detecting fetal hypoxaemia is an attractive proposition. Initial studies were very encouraging. Oxygen given to mothers could be detected by a rise in $Hbdiff$ in the fetus.³⁷ Changes in Hb and HbO_2 , resulting from contractions, were used to calculate mean cerebral saturation. It subsequently transpired that similar, contraction induced changes, occurred in a non-viable infant, thus questioning the validity of the calculations.³⁸ Currently, NIRS is insufficiently developed to allow evaluation of its use in labour by randomised trials.³⁹ However, IMNIRS may permit calculation of cerebral saturation between contractions, potentially detecting significant changes in fetal oxygen status.

Ventilation

Both intermittent positive pressure ventilation (IPPV) and continuous negative extrathoracic pressure ventilation (CNEP) have been shown to lead to reduced CBV.^{40–41} In IPPV, this reduction is attributable to a fall in HbO_2 , whereas in CNEP it results from a fall in both HbO_2 and Hb. This implies that whereas IPPV primarily reduces CBF, CNEP, by reducing intrathoracic pressure, increases cerebral venous drainage. Compared to changes during jugular venous occlusion, or apnoea and bradycardia, these changes are reassuringly small. CNEP requires a neck seal, which could theoretically cause jugular venous occlusion. NIRS has shown that this did not occur in any patients studied.⁴² The effect of endotracheal suction on cerebral haemodynamics has also been studied. As expected, during suction, $Hbdiff$ falls as SaO_2 falls. The cerebral haemodynamic effects of suctioning are similar in conventional and high frequency ventilation,⁴³ and are significantly less during closed rather than open suction.⁴⁴

Surfactant

The introduction of surfactant brought with it concerns about potential effects on the neonatal brain.⁴⁵ Subsequently, NIRS was used to study these effects.^{46–48} Hb and HbO₂ altered as expected with changes in SaO₂. Changes in CBV were less consistent with studies reporting no change,⁴⁷ an increase,⁴⁸ or an increase or decrease,⁴⁶ with observed changes tending to be transient. Differences could reflect variations in surfactant guidelines.

Drugs

The vulnerability of the preterm cerebral circulation led researchers to use NIRS to study the effects of drug administration in neonates. Aminophylline was once widely used for the treatment of apnoea of prematurity but is associated with significant changes in CBV and CBF.⁴⁹ Caffeine, on the other hand, does not affect cerebral haemodynamics⁵⁰ and is now the preferred treatment.⁵¹ Indomethacin is used for the pharmacological closure of patent ductus arteriosus in preterm infants. A study using NIRS and Doppler ultrasonography suggested that intravenous indomethacin bolus administration is associated with a significant fall in CBV and CBF, persisting for at least 60 minutes.⁵² Ibuprofen is being trialled as an alternative to indomethacin and NIRS has been used to compare the cerebral haemodynamic effects. Unlike indomethacin, ibuprofen has little effect on CBV, CBF, or cerebral oxygen delivery.⁵³

Birth asphyxia

Perinatal asphyxia is a significant cause of neonatal hypoxic-ischaemic brain injury. Early assessment of severity is important for treatment and prognosis, but can be difficult as signs may develop late. Using NIRS, a raised mean CBV was found in neonates with brain injury.¹² This finding was confirmed in a more recent study using NIRS to measure cerebral haemodynamics during the first 24 hours following perinatal asphyxia.⁵⁴ Asphyxia was associated with an increase in CBV and CBF and a significant reduction in cerebrovascular reactivity (CBVR) compared with historical control data. CBVR can be calculated following induction of small changes in partial pressure of carbon dioxide (PaCO₂) by manipulation of ventilator settings.⁵⁵ CBVR was not predictive and tended to normalise after 24 hours. As a group, patients with poorer outcomes had much higher CBVs, but CBV alone did not reliably predict outcome.

Intraventricular haemorrhage

Intraventricular haemorrhage (IVH) and periventricular lesions remain a major cause of neurodevelopmental problems in VLBW infants.³ It was hoped that NIRS would enable identification of babies at risk of these complications. In extremely preterm infants, low CBF on the first day of life is a risk factor for severe IVH, leading to post-haemorrhagic dilatation and/or haemorrhagic parenchymal infarction.⁵⁶ This supports the hypothesis that cerebral ischaemia is an important predisposing factor in the development of such lesions. However, significant overlap occurred between results in babies without lesions and those with severe lesions.

Hypotension and anaemia

Cerebral FOE has been used to assess the impact of hypotension and anaemia in preterm infants.⁵⁷ Correcting moderate anaemia with a blood transfusion led to a reduction in FOE. Hypotension did not affect cerebral FOE and the researchers postulated that cerebral DO₂ might have been maintained by CBF autoregulation in these infants. Peripheral FOE was used to determine the need for blood transfusion in VLBW neonates, but 59% of transfusions given were clinically indicated despite “normal” FOE.⁵⁸

Tissue oxygenation index (TOI)

NIRS has been used to determine cerebral and splanchnic TOI in neonates with surgically proven splanchnic ischaemia and controls with apparently normal abdomens. The TOIs were expressed as a cerebro-splanchnic oxygenation ratio which was significantly lower in affected neonates.⁵⁹

Peripheral oxygen consumption

Early in circulatory compromise compensatory mechanisms maintain DO₂ to vital organs by redistributing blood away from the peripheries. Therefore, assessment of peripheral VO₂, by either venous⁶⁰ or arterial occlusion,⁶¹ may provide an early indication of circulatory compromise. A comparison of these methods in well neonates suggests that the arterial method is more repeatable. The mean value (SD) for VO₂ is 1.12 (0.25) for the arterial and 1.60 (0.48) mM/cm/min for the venous method. Peripheral VO₂ is sensitive to changes in global metabolic rate, limb temperature,^{62, 63} and blood pressure.⁶⁰ Further clinical evaluation is required to determine whether peripheral VO₂ assessment can improve outcome in the critical care setting.

CONCLUSIONS

NIRS has been used for perinatal applications since 1985. Initially NIRS equipment was scarce but this was overcome and hundreds of studies have since been performed. Used in a research context, NIRS has improved understanding of the cerebral circulation. Studies have been difficult to perform, but scientifically useful information has been obtained regarding the impact of a variety of clinical situations and interventions. The key question now is whether, after such extensive research, NIRS can be absorbed into the routine clinical care of the sick infant.

The promise of a fetal or neonatal “brain monitor” remains unfulfilled. Why has it been so difficult to produce such a monitor? CWNIRS initially struggled with various clinical groups evaluating their own preferred machines without any coordinated trials. The main reason suggested, however, is lack of quantification of brain oxygenation. Monitoring aims to keep parameters within set limits. Even with conventional monitoring, such as blood pressure, these can be difficult to define.³

Newer instruments are being developed with the capability of giving quantifiable results, and a small number of clinical studies have been undertaken. However, an evidence base to support the interpretation of the data obtained remains a long way off. At what level should CSvO₂ or CBV be maintained during intensive care? What variations can be allowed? Will maintaining these parameters within set limits improve neurological outcome? Will they provide prognostic information in cerebral compromise and assist in decisions around the use of neuroprotective agents?

It is our opinion, that perinatal NIRS is still very much a developmental technique and, as such, should be used only within clearly defined research programmes. Modern machines may hold considerable promise for the future, as quantification becomes more secure. Hopefully, these instruments will not find their way into routine clinical practice until proper large scale studies have been performed and real benefits shown. Continued international collaboration will be essential to achieve this aim.

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