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NEONATAL INTENSIVE CARE: OBVIOUS YET DIFFICULT AREA FOR CEREBRAL NEAR INFRARED SPECTROSCOPY

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ABSTRACT

The first clinical application of near-infrared spectroscopy (NIRS) 11 years ago was on the head of newborn infants under intensive care. Since then much credible and some important data have been accumulated in this area of research. The best data have been obtained using manipulation of arterial oxygen saturation to obtain single or repeated estimates of cerebral blood flow or cerebral blood volume, or interference with cerebral venous return to obtain measures of venous oxygen saturation. It has been more difficult to take advantage of the continuous and noninvasive nature of NIRS. In particular, the value of the cytochrome signal can still be doubted. A role has not yet developed for NIRS in clinical neonatology. *© 1997 Society of Photo-Optical Instrumentation Engineers.*

Keywords near infrared spectroscopy; clinical neonatology; cerebral blood flow; brain; newborn.

1 INTRODUCTION

Improvements in peri- and neonatal care during recent years have increased the number of surviving newborn infants. Among the survivors of neonatal intensive care, 5 to 15% exhibit major neurodevelopmental handicaps. The major causes seem to be cerebral hypoxia and ischemia. The fundamental mechanism therefore is insufficient cerebral oxygen delivery, and the provision of sufficient oxygen to the brain is a major goal for neonatologists.

Transillumination of the head of small animals is possible using near infrared spectroscopy (NIRS).[1] The first clinical research use of NIRS in 1985 was in newborns.[2] Quantitative spectroscopy was subsequently performed in 1986.[3] Over the 9 years since then, many papers on NIRS in newborns have been published, but the precise technical details have not always been made clear. The purpose of this paper is to review the literature in the light of the current understanding of the limitations of NIRS.

2 NIRS METHODOLOGY

2.1 GEOMETRY

The newborn infant's head is ideally suited for NIRS. The overlying tissues are relatively thin, which ensures that the signal is dominated by brain tissue, probably white as well as gray matter. It also means that the results should be interpreted as ''global'' or possibly ''regional'' values. The NIRS recordings can be performed with the light being applied to one side of the head and received on the other side (transmission mode) in low-birth-weight infants with biparietal diameters from 6 to 9 cm, whereas larger babies can only be investigated with the emitting and receiving fibers in an angular arrangement (reflection mode), possibly with both on the same side of the head. The importance of the geometrical arrangement has not been investigated systematically, apart from its influence on path length.[4]

2.2 ALGORITHMS

Several different types of NIRS instruments have been used. The number of wavelengths used varies from 2 to 6.[1,5–9] The specific wavelengths used, and therefore the mathematical algorithms used to separate the signals of oxyhemoglobin (O_2Hb), deoxyhemoglobin (HHb), and the cytochrome aa_3 oxidase difference signal (Cyt.ox), have differed.[10] It is therefore not trivial to ensure that differences in results are not simply due to differences in NIRS methodology, particularly in the earlier papers. Furthermore, the light cycling frequency and the data sampling frequency vary.

2.3 PATH LENGTH

The path length of light traversing the tissue must be known to calculate concentrations. The path length in tissue exceeds the geometrical distance between the optodes by a factor of 3 to 6 (the differential path length factor, DPF). Estimation of path length is one of the basic problems in NIRS. A number of experimental techniques have been used

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to determine DPF. These are based on measurements of absorption of light by tissue water,[11] time of flight of photons,[12–14] or the phase shift of intensity-modulated light.[15]

Time-of-flight measurements in the brain of postmortem infants gave a DPF value of 4.39±0.28.[14] In living infants, the two other methods have yielded values for the head of 3.5 to 6, with interindividual differences of about 15%.[4,23] The source of the variation between reports and between methodologies has not been well analyzed. Intraindividual differences over regions or over time have not been well studied. Another issue is that the differential path length factor is not constant across wavelengths.[15] Light is scattered more at shorter wavelengths and less in more absorbing tissues. Approximate solutions to this problem have been proposed for the newborn brain.[16] Prototype equipment allows on-line measurement of path length at several wavelengths during spectroscopy. This should theoretically solve the problems of inter- as well as intraindividual variability of DPF. However, no data are yet available to prove that on-line measurement is indeed a significant improvement.

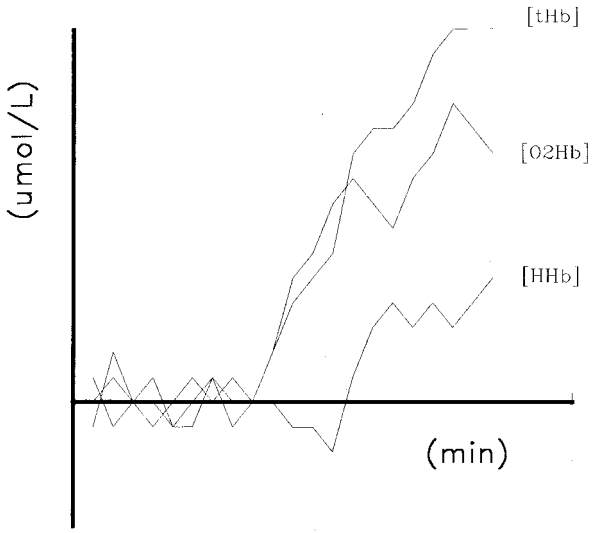

Fig. 1 A hypothetical result of monitoring cerebral oxyhemoglobin [O_2Hb] and deoxyhemoglobin [HHb] concentrations for some minutes, and their sum [tHb] in a newborn infant. A rise in all three signals is seen from an arbitrary baseline. What does it signify? It could be an increase in blood in the cerebral veins due to some relative obstruction of the veins on the neck or to the venous return to the heart. It could be an increase in cerebral blood volume and blood flow due to increased blood pressure, increased pCO_2 or increased metabolic needs, e.g., seizure. Is the oxygenation of the brain improved? It is not possible to give an answer outside a context in which the other physiological variables are monitored. This context-dependency of NIRS monitoring is its most important limitation.

3 MEASUREMENTS IN INFANTS

3.1 TREND MONITORING OF HEMOGLOBIN SIGNALS

Near infrared spectroscopy is a perfect candidate for a clinical monitor of the tiny, sick preterm neonate. It is noninvasive, gives real-time information, does not interfere with intensive care, does not affect the underlying skin, and does not remove the infants from the nursery (Figure 1).

In principle, NIRS allows on-line trending of changes in O_2Hb and HHb, and hence of tHb (the sum of [O_2Hb] and [HHb]), which is proportional to changes in cerebral blood volume (CBV), which in its turn can be used as a surrogate measure of cerebral blood flow (CBF). The appropriateness of this, however, has only been established for reactions to changes in arterial carbon dioxide tension.[8] Furthermore, a constant optode distance is crucial; if the head circumference changes by even a few millimeters as a result of a change in brain blood or brain water content, the trends may be significantly influenced. Minor changes in optode–skin contact induce large transients in the signal and/or baseline shifts.

The difference between [O_2Hb] and [HHb] (sometimes called Hbdiff, sometimes called oxygenation index, OI) is an indicator of the mean oxygen saturation of the hemoglobin in the blood vessels in the tissue. This quantity has been shown to change appropriately in many experimental and clinical studies, but has important limitations. First, in terms of interpretation, it is not known how much of the signal comes from blood in arteries, capillaries, and veins, respectively. Recent observations in piglets suggest that the arterial-to-venous ratio is about 1:2.[17] Second, the signal is confounded when there are concomitant changes in tHb, depending on which of the arterial, capillary, or venous compartments are changed. Finally, the lack of a fixed zero point makes it impossible to specify a threshold for intervention or even an alarm level for clinical use. In animal experimentation, the dynamic range of Hbdiff has been determined by inhalation of 95% O_2+5% CO_2 at the beginning of the experiment and by anoxic death at the end.

3.2 CEREBRAL BLOOD VOLUME REACTIVITY

Fluctuations in P_{aCO_2} (partial pressure in arterial blood) are common in infants undergoing intensive care. The correlation between cerebral blood flow and P_{aCO_2} has been confirmed in adults[18] and newborn infants.[19] It is a sign of active vascular control and hence a sign of health. In one study comparing the effects of P_{aCO_2} changes on CBV in mechanically ventilated preterm infants using NIRS measurements and the effects on CBF using ^{133}Xe measurements, the relation between CBV and CBF was found to be highly significant.[8] From the average interoptode spacing of 6 cm and an assumed differential path length factor of 4, the mean CBV reactivity was 0.08 ml/100 g/kP_a of P_{aCO_2}. In another

study, an increase in cerebrovascular reactivity from 0.07 ml/100 g/kP$_a$ at 26 weeks to 0.51 at 40 weeks was observed.[20] In a third study, CBV reactivity in preterm infants was 0.22 ml/100 g/kP$_a$.[21] The normal value of CBF reactivity in preterm infants is 30%/kP$_a$.[19] It is, however, known that the reactivity of CBV to CO_2 is less than that of CBF.[22] The reactivity of CBV to mean arterial blood pressure changes has not been systematically studied. We do not know if such CBV reactivity can be used as a surrogate for CBV–blood pressure autoregulation.

3.3 QUANTITATION OF HHB

Second-derivative spectroscopy, using a full spectrum of optical densities, allows a direct comparison between the HHb signal at 755 nm and water at 830 nm. Since the absolute concentration of water can be taken as known and constant over time, the absolute concentration of HHb can be estimated.[23]

3.4 QUANTITATION OF CEREBRAL BLOOD VOLUME

The effect of a small induced change in arterial oxygen saturation (S_{aO_2}) on [O_2Hb] may be used to quantify CBV[24] based on the indicator dilution principle. It is assumed that a small change in arterial oxygen saturation within the normal range will not significantly influence cerebral blood volume, flow, or oxygen consumption. Using the oxygenation index [OI=(Δ[O_2Hb]–Δ[HHb])/2] instead of Δ[O_2Hb] improves the signal-to-noise ratio and reduces the bias if there is a concomitant change in [tHb].[25] The total amount of cerebral hemoglobin available for saturation is then

$$[\mathrm{tHb}]=100\times(\Delta[\mathrm{O_2HB}]-\Delta[\mathrm{HHb}])/(2\times\Delta S_{aO_2})$$

(in micromoles/liter)

if S_{aO_2} is expressed in percent. The total cerebral hemoglobin is directly proportional to the cerebral blood volume:

$$\mathrm{CBV}=k\times[\mathrm{tHb}]\ \text{(in milliliters/100 g)},$$

where k=100/(Hb$\times R\times$1.05), Hb is the blood hemoglobin content in millimoles/liter (tetraheme), R is the cerebral-to-large vessel hematocrit ratio, usually taken as 0.69,[26] and the factor 1.05 g/ml is the brain density.

Values for CBV obtained by NIRS of 2.22±0.40,[14] 3.4 (range 0.9 to 6.7),[25] and 3.7±1.1 ml/100 g[21] are lower than the mean of 4.8 ml/100 g reported in adults.[27] It is not known whether the differences are due to differences in the instrumental techniques or reflect physiological differences. One explanation could be the lower cerebral blood flow in newborn infants compared with adults.[28] The only other technique used to estimate absolute values of CBV in newborns is ^{11}CO-labeled erythrocytes, which gave significantly higher values, possibly because all five infants in that study were small for their age, severely hypoglycemic, or asphyxiated.[29] Changes in CBV induced by bilateral jugular venous occlusion for 5 s, as estimated by NIRS using tHb, correlated well with strain gauge plethysmography.[30] This result remains one of the few external quantitative validations of NIRS in the neonatal brain.

The reactivity of CBV to P_{aCO_2} appears to be less using an estimate of [tHb] than using CBV calculated according to the oxygen tracer method.[21] The discrepancy is unexplained but may be due to the heterogeneity of the optical system (skin, scalp, skull, cerebrospinal fluid, gray and white matter), which is very different from the assumption of a medium with uniform absorption and scattering.

3.5 QUANTITATION OF CEREBRAL BLOOD FLOW

Measurement of blood flow by NIRS is based on Fick's principle[31] and uses a rapid change in arterial oxyhemoglobin as an intravascular tracer. By using the change in OI observed after a small sudden change in arterial concentration of oxygen, CBF can be calculated as follows:

$$\mathrm{CBF}=\Delta\mathrm{OI}\Big/\left(k\times\int S_{aO_2}\times dt\right)$$

(in milliliters/100 g/min),

where OI is measured in units of micromoles/liter, k=Hb$\times$1.05$\times$100, Hb is blood hemoglobin in millimoles/liter (tetraheme), S_{aO_2} is in percent, and t is time in minutes.

The method of measuring CBF rests on several assumptions. First, during the measurement, CBF, CBV, and oxygen extraction must be constant. Studies in animals and adult human subjects have shown that CBF and oxygen extraction are constant within the range of arterial tension between 6 and 13 kP$_a$,[18,32] whereas Livera et al.[33] have shown an increase in total hemoglobin with even mild hypoxia. Errors may be reduced by omitting the recordings with relatively large changes in the [tHb] signal.[34] Second, the period of measurement must be less than the cerebral transit time, and finally, this method of CBF measurement has practical limitations: In infants with severe lung disease, the S_{aO_2} may be fixed at a low level despite administration of oxygen, whereas in infants with normal lungs, S_{aO_2} is near 100%, even in room air. Elwell et al.[35] overcame this problem in healthy adults by giving them an air–nitrogen mixture with an FiO_2 of 0.15 to breathe and then switching to an FiO_2 of 0.21.

Measurements of blood flow with NIRS have been compared with ^{133}Xe clearance in sick newborn infants (Figure 2). These comparisons consti-

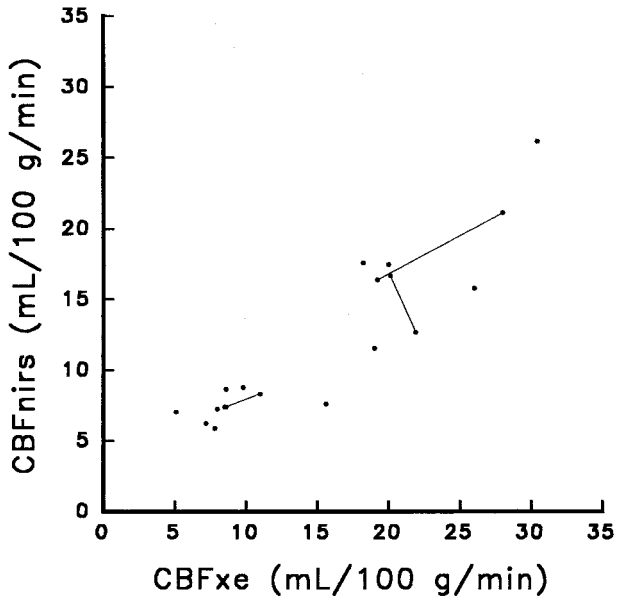

Fig. 2 The correlation between 19 measurements of cerebral blood flow in newborn infants obtained simultaneously with ^{133}Xe clearance and NIRS using the oxygen method. In each of three infants, two sets of measurements were obtained, as indicated by lines. The two methods agree well, indicating that the differential path length factor used (4.4) represents cranial tissues that are perfused with capillaries reasonably well, since ^{133}Xe is a diffusible tracer. The NIRS values are lower than the xenon values, indicating that the cerebral transit time of oxyhemoglobin, which is used by NIRS as a tracer, may be too short for correct measurements (a 7.5-s integration period was used). (Redrawn from Ref. 36).

tute important direct external validation of NIRS in the brain of human neonates. The agreement between the two methods is acceptable in terms of mean values. Both are based on the Fick principle, but xenon is a diffusible tracer with a mean transit time of several minutes, whereas oxyhemoglobin is nondiffusible, with transit times of less than 10 s. The values for CBF ranged from 5 to 30 ml/100 g/min; the higher values were underestimated by NIRS in comparison with the xenon values.[36,37] Studies comparing NIRS with venous occlusion plethysmography have shown good agreement between the blood flow measurements obtained in adult forearms.[38] Recently another method measuring CBF using NIRS and indocyanine green by venous injection has been introduced. In six children, values of CBF from 6 to 19 ml/100 g/min were found,[39] with good agreement between the oxygen and the indocyanine green method (limits of agreement +6.3 to 6.8 ml/100 g/min).

3.6 QUANTITATION OF CEREBROVENOUS OXYGEN SATURATION

Cerebral venous hemoglobin saturation reflects the balance between O_2 delivery and O_2 consumption. A normal cerebral venous oxygen saturation demonstrates an intact coupling between CBF and metabolic needs. During restricted blood flow, enhanced oxygen extraction is expected to occur and to result in a drop of cerebrovenous saturation. Cerebral venous oxygen content may be estimated by near-infrared spectrophotometry.[3] When venous outflow from the brain is impeded by tilting the head down[40] or by jugular venous occlusion,[41] [tHb] increases. Assuming that this is due exclusively to pooling of blood venules and veins, cerebral SvO_2 (venous oxygen saturation) can be measured using the formula:

$$cSvO_2 = 100 \times \Delta[O_2Hb]/(\Delta[O_2Hb] + \Delta[HHb]) \quad (\text{in}\%).$$

Tilting the head down is not always effective. Venous occlusion appears more effective, but has not yet been used in neonates. The noninvasive method of measuring $cSvO_2$ with partial jugular venous occlusion was validated with an invasive measurement of SvO_2 from co-oximetry of jugular bulb blood obtained during cardiac catherization and gave similar values.

3.7 CYTOCHROME AA_3 OXIDASE

Reduction of cytochrome may be a specific indicator of inadequate cellular O_2 availability.[42,43] We do not know at present, however, with any precision, the relation between tissue pO_2, cytochrome oxidation state, and neuronal function. Furthermore, the measurement of cytochrome oxidase with optical techniques is by no means as easy as that of hemoglobin. First, the cytochrome signal is at most one tenth of the hemoglobin signal in amplitude.[44] Second, the *in vivo* spectrum is determined by animal experimentation, which in the first attempts was complicated by residual hemoglobin signals and by agonal swelling of cells and subcellular elements, which influences scattering.[45] Third, there is no reference method. Finally, comparison of reported data is difficult because of differences in instrumentation and because the algorithms used have sometimes not been specified. In the first report, repeated episodes of hypoxia in preterm infants led to hemoglobin deoxygenation and a progressive drop in the Cyt.ox.[2] Subsequently, alterations in P_{aCO_2} were found correlated with changes in Cyt.ox, whereas a change in S_{aO_2} was found insufficient by themselves to change Cyt.ox.[46] Similarly, indomethacin administrated i.v. to preterm infants with persistence of the arterial duct resulted in a decrease in the Cyt.ox signal, a fall that paralleled a fall in CBV.[47] This was explained as a result of an alteration in intracellular oxygen availability, although there was no simple relation between cerebral oxygen delivery and Cyt.ox.

The consistency of near infrared spectrophotometric data was examined during introduction of cardiopulmonary bypass in young children undergoing open heart surgery.[48] Surprisingly, the cytochrome oxidase signal decreased while the $[O_2Hb]$ increased in the cyanotic children in the minutes

following switch-on, with a rise in S_{aO_2} from below 80 to 100%. The magnitude of the fall in Cyt.ox was closely associated with the magnitude of the fall in [tHb]. It is difficult to explain why cytochrome oxidase should be reduced in proportion to total cerebral hemoglobin concentration while at the same time the oxygenation index increases. The close association of Cyt.ox with [tHb] points to the Cyt.ox response being at least in part an artifact. A new NIRS algorithm, taking into account the wavelength-specific optical path lengths, produced smaller estimates of Cyt.ox changes which were unrelated to [tHb] changes. The new algorithm, however, did not reduce the error of fit of the algorithm (using four wavelengths for estimation of three chromophores). Another report on Cyt.ox during low-flow cardiopulmonary bypass in young children, which did not specify the algorithm, indicates a gradual decrease in Cyt.ox during bypass also in spite of increased [O_2Hb].[49] A theoretical quantitative comparison of the temperature dependence of the hemoglobin-oxygen dissociation curve and of the cerebral metabolic rate has suggested that increased venous oxygen saturation may indeed coexist with cellular hypoxia (and therefore presumably cytochrome oxidase reduction).[50]

In piglets, no cross-talk between Cyt.ox and cerebral Hb oxygenation or blood volume was found.[51] A decrease in Cyt.ox paralleled depletion of phosphocreatine and nucleotide triphosphates in the most severe episodes of hypoxia. Also in piglets, we have recently found a paradoxical (artifactual?) increase in Cyt.ox early in hypoxia, whereas reduction of Cyt.ox occurs late, in parallel with loss of EEG power and a rise in extracellular hypoxanthine concentration.[52] Until more basic work has been done, reports on changes in the redox state of cytochrome aa_3 in newborn infants must be viewed with caution.

4 CLINICAL RESEARCH QUESTIONS IN NEWBORNS ADDRESSED BY NIRS

Many of the studies using NIRS in newborns have involved small numbers of infants and require verification.

4.1 CEREBRAL OXYGEN CONSUMPTION

In a recently published study, cerebral venous saturation was measured by NIRS and compared with CBF simultaneously measured by the ^{133}Xe method.[40] The cerebral metabolic rate ($CMRO_2$) found in that study was 1.0 ml/O_2/min (SD 0.4) in the preterm infants, whereas it was 1.4 ml/O_2/min (SD 0.8) in the term asphyxiated infants. These values should be compared with 3 ml/100 g/min in healthy human adults. In another study using positron emission tomography (PET), similarly low values of $CMRO_2$ were reported in preterm infants with normal neurological outcome.[53]

4.2 ASPHYXIA

Abnormally high CBV in infants after perinatal asphyxia and reduced reactivity to changes in P_{aCO_2} has been demonstrated by NIRS during the first 48 h.[54] These CBV abnormalities very closely parallel the abnormalities of CBF and CBF regulation.[55]

4.3 HYPOGLYCEMIA

Hypoglycemia is relatively common in preterm infants. CBV was examined in 18 hypoglycemic preterm infants before, during, and following bolus treatment with glucose.[56] CBV decreased and a steady state was obtained after approximately 3 min. The magnitude of CBV reduction was inversely related to the pretreatment blood glucose level. The critical level of glucose at which CBV just responded was calculated to be 2.1 mmol/liter.

4.4 APNEA

Recurrent apnea, with or without bradycardia and a fall in arterial oxygen saturation, is a frequent problem in preterm infants. NIRS is suitable for determining if there are (short-lived) effects on the brain.[33] Arterial desaturation caused parallel drops in [Hbdiff], whereas [tHb] dropped only with associated bradycardia. Since newborn infants can increase cardiac stroke volume only moderately, it is suggested that bradycardia is associated with a fall in CBF.

4.5 ENDOTRACHEAL SUCTIONING

The effect of endotracheal suctioning on cerebral hemodynamics was investigated with dual-wavelength NIRS.[8] Increasing the inspired oxygen fraction before the procedure reduced the consequent fluctuations in [tHb]. In another study, however, preoxygenation only reduced the drop in [O_2Hb] and arterial oxygen saturation, whereas there was no effect on [tHb].[57]

4.6 AMINOPHYLLINE ADMINISTRATION

The influence of aminophylline on cerebral blood flow was examined in 10 preterm infants using NIRS. The reduction in CBF was larger than expected from the modest change in P_{aCO_2},[58] indicating that aminophylline had a direct effect on CBF. This is in agreement with studies using Doppler ultrasound or ^{133}Xe clearance.

4.7 INDOMETHACIN ADMINISTRATION

Indomethacin is regularly used to close the patent ductus in sick, preterm infants. The reduction of blood flow to many organs is a concern. One study on the effect of indomethacin showed that all parameters fell sharply, i.e., CBF, CBV, oxygen delivery, and the reactivity of blood volume, as a result of changes in arterial carbon dioxide tension.[59] The CBV reduction has been confirmed.[60] It is concluded that cerebral oxygen delivery should be op-

timized before administration of the drug, so that the risk of a critical reduction in oxygen supply is minimized.

4.8 EXOGENOUS SURFACTANT ADMINISTRATION

Endotracheal instillation of surfactant is a new and very effective treatment for respiratory distress syndrome. Side effects due to rapid changes in lung and/or heart function are possible. A transient but definite reduction in EEG activity has been demonstrated concurrently with a fall in mean arterial blood pressure in preterm babies after administration of a surfactant. Cerebral ischemia therefore must be excluded.[61] Using NIRS, a rise in cerebral blood volume[62,63] as well as a small transient decrease in CBV[64] has been reported. Unchanged CBFs have been demonstrated both with ^{133}Xe clearance[65] and with NIRS.[53] Therefore, it is unlikely that the EEG depression observed after surfactant instillation is caused by cerebral ischemia.

5 CONCLUSION AND FUTURE POSSIBILITIES

This review has covered areas where NIRS has provided credible and sometimes important information. However, for the simplest and potentially most practically useful parameter, the oxygenation index, a number of factors may confound the results. New technology, providing absolute quantitative tissue hemoglobin-oxygen saturation is available but has not yet been evaluated. If this technology proves reliable, small-scale trials will be needed to put this new monitoring parameter in a clinical context. Then, large-scale clinical trials, not yet designed, will have to demonstrate a benefit in terms of improved chances for the intact survival of sick newborn infants.

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