Near-Infrared Spectroscopy

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Near-infrared spectroscopy (NIRS) is a relatively new technology that offers the enormous advantage of making measurements in vivo of changes in cerebral hemodynamics and oxygenation. Because NIRS is noninvasive and portable, it can provide real-time measurements of these changes at the bedside. Thus NIRS is ideally suited to the study of many physiological and pathological processes affecting the brain, particularly in the infant or young child in the intensive care unit or operating room. This review outlines the basic principles, advantages, and limitations of the current state of NIRS technology. An emphasis is placed on the animal and clinical studies that are relevant to the field of child neurology, with an eye to the future evolution and potential applications of this promising technique.

NEAR-INFRARED spectroscopy (NIRS) is based on the principle that near-infrared light is able to pass through tissue and is absorbed in an oxygen-dependent manner by hemoglobin and cytochrome oxidase aa_3.[1] Consequently, this technology has the important advantage of providing noninvasive and continuous measurements of changes in the oxygenation and hemodynamics of biological tissues. Moreover, the development of NIRS devices small enough to be brought to the bedside or operating room makes this technique particularly attractive for addressing a variety of critical clinical questions. NIRS is currently used as a research tool by neurologists, neurosurgeons, cardiac surgeons, and physiologists to study cerebral hemodynamics and oxygenation.

THEORY OF NIRS TECHNOLOGY

Light in the near-infrared range (700 to 1,000 nm) passes through skin, soft tissue, and bone with relative ease, particularly the very thin soft tissue and bone of the neonate or young infant. The light is then absorbed by two chromophores, namely, hemoglobin and cytochrome aa_3. The crucial principle of NIRS is that the absorption of near-infrared light by these chromophores changes as their oxygenation state changes. Thus, NIRS measures the absolute change in the tissue concentration of intravascular oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb), and from their summated change, that of total hemoglobin (THb). NIRS also measures changes in intracellular cytochrome aa_3, the terminal enzyme in the mitochondrial electron transport chain, and the final donor of electrons to molecular oxygen. Although the amount of cerebral cytochrome aa_3 does not change in the short term, its redox state does. NIRS measures the change in the concentration of oxidized cytochrome aa_3, which reflects the availability of oxygen to the mitochondrion, the delivery of reducing substances to the electron transport chain, and the rate of adenosine triphosphate (ATP) turnover.[2] Therefore, the significant advantage of NIRS is that it provides in vivo measurements of changes in both intravascular and intracellular oxygenation states and hemodynamics, rapidly and continuously.

Calculation of Chromophore Concentration From Absorbance

The relationship between the absorption of near-infrared (NIR) light by a chromophore and the chromophore's concentration in tissue is described by a modification of the Beer-Lambert law. The Beer-Lambert Law states that $A = \alpha BdC + G$, where A is the attenuation measured in units of optical density (OD), α is the specific absorption coefficient of the chromophore at a particular wavelength ($\mu molar^{-1}/cm^{-1}$), B is the differential pathlength factor (or DPF), d is the distance between the NIR optodes (cm), C is the concentration of the chromophore in the tissue ($\mu mol/L$), and G is an additive term representing the scattering losses. When the equation is solved to obtain the change in concentration of a chromophore, G cancels out, and we obtain $\Delta C = \Delta OD/(\alpha Bd)$. The extinction coefficients of each chromophore are known, the interoptode distance, d, is measured at the time of the study, and the differential pathlength factor (a measure of the increase in light pathlength due to tissue properties) has been determined for a

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number of different biological tissues (A further discussion of the DPF is found in the Limitations section.). The derivation of the concentration of several chromophores relies on the differences in their absorption spectra and the use of NIR light at wavelengths that correspond to the peak absorbances of the relevant chromophores.

Types of NIRS Devices

There are three different types of NIRS devices. The device used most commonly in animal and human studies to date is the continuous wave spectrometer. This type of device uses between 2 and 6 lasers to generate NIR light of different wavelengths. The NIR photons are transmitted into the brain via fiberoptic cable and an optode placed on the head. Within the brain, the NIR photons are absorbed and scattered, and the remaining light is transmitted back via a receiving optode to a photomultiplier tube (Fig 1). Absorbance for each chromophore at the selected wavelengths is converted into change in concentration by an algorithm specific to the wavelengths used. A second type of NIRS device uses the time-of-flight method, that is, a streak camera measures the time for the light to travel through the tissue. This approach has the advantage of measuring directly the pathlength of the light. However, time-resolved devices are very expensive and much larger, making bedside monitoring difficult. Finally, phase-resolved spectroscopy takes advantage of the phase shift that can be measured when the light is modulated at a known frequency. The usual NIRS signals as well as the pathlength can then be derived simultaneously and continuously. NIRS devices currently being developed for imaging purposes generally use either time-resolved or phase-resolved spectroscopy, with either an array of optodes or rotation of a few optodes around the object to be imaged.

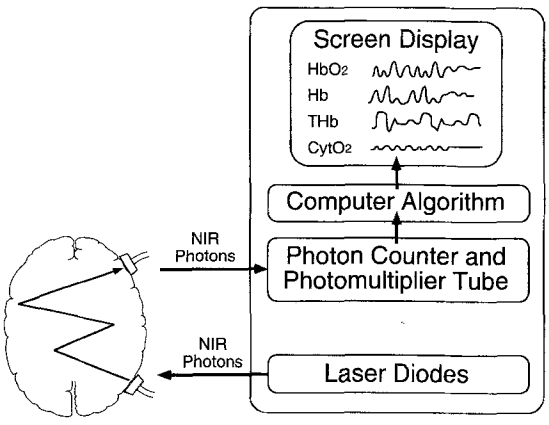

Fig 1. Diagram of a near-infrared spectroscopy system.

Measurement of Hemodynamic Variables of Interest

A particular advantage of NIRS is the ability to make noninvasive and repeated measurements of cerebral blood volume (CBV) and cerebral blood flow (CBF) at the bedside. For example, changes in cerebral blood volume (ΔCBV) can be calculated from changes in the total concentration of hemoglobin, THb, by a calculation that takes into account the concentration of hemoglobin and the cerebral-to-large vessel ratio. Second, the absolute CBV can be measured by inducing a very small change in the oxygen concentration, using the indicator dilution technique as described by Wyatt et al.[3] Finally, CBF can be measured by a modification of the Fick principle, which states that the amount of a substance taken up by an organ is equal to the difference between the rate of the tracer's arrival and the rate of the tracer departure from the organ.[4] If the measurements are made in less than the transit time of the tracer through the organ in question, the amount of tracer leaving the organ is zero and can be dropped from the equation. The calculation for flow then requires only measurement of the accumulation of the tracer in the organ and the arterial concentration of the tracer (ie, the amount of tracer introduced into the circulation). Tracers such as oxygen or indocyanine green (ICG) have been used, ICG being a dye that can be injected into the circulation and then rapidly cleared from the circulation by liver uptake and secretion into bile. When oxygen is used as a tracer, a very brief increase in the inspired oxygen is used to produce a "bolus" of oxygen in the systemic circulation that can be measured by a peripheral oximeter, and the HbO_2 signal provides the measurement of the cerebral oxygenation increase. The method using indocyanine green requires an intravenous injection of ICG and a separate device that measures ICG concentration in the systemic circulation. Both of these methods have been used and validated, as discussed later (see "Studies in Preterm and Term Newborns"). From these NIRS-derived measurements, one can also determine the rate of cerebral oxygen metabolism, cerebral oxygen delivery, CBV, and CBF vasoreactivity (eg, to

changes in P_{CO_2}). Thus NIRS has enormous potential as a technique for making bedside measurements of hemodynamic variables important to the understanding and management of various neuropathological processes.

CLINICAL APPLICATIONS OF NIRS

Antepartum Studies

The detection of impending fetal asphyxia before the development of a hypoxic-ischemic insult remains a significant clinical problem for obstetricians, largely because available monitoring techniques (eg, scalp pH, heart rate tracings) are either too insensitive or nonspecific to detect fetal cerebral hypoxia/ischemia. However, NIRS has been used to measure directly changes in cerebral hemodynamics in the fetal brain during labor by transvaginal placement of optodes on the fetus' head. A number of studies using NIRS during labor have demonstrated the ability of NIRS to detect important changes in fetal cerebral perfusion and oxygenation.[5-12] The first antepartum NIRS study demonstrated the decrease in oxyhemoglobin (HbO_2), deoxyhemoglobin (Hb), and the total hemoglobin (THb) accompanying most normal contractions, likely representing a fall in cerebral blood volume (of about 30%) due to compression of the fetal head.[5] These findings were subsequently confirmed by others.[6] Moreover, Peebles et al[5] showed that when contractions were accompanied by fetal heart rate (FHR) decelerations, NIRS detected an increase in the Hb signal with an accompanying fall in both HbO_2 and THb, suggesting cerebral oxygen desaturation. Further studies showed that contractions characterized by late FHR decelerations were associated with a prolonged decline in HbO_2 and increase in Hb following the contraction, compared with contractions not accompanied by FHR decelerations.[7,8] The HbO_2 and Hb signals returned to baseline after all contractions, and none of the babies was born with significant acidemia or clinical evidence of distress, confirming previous data that late decelerations are not well correlated with acidemia. However, more frequent uterine contractions (<2 minutes apart) were always accompanied by a rise in Hb and a fall in HbO_2, signifying a fall in mean cerebral hemoglobin saturation.[9] The authors in that study found a significant correlation between contraction interval and ΔHbO_2, with a similar but negative correlation between contraction interval and ΔHb. These intrapartum NIRS studies provided the first documentation of the changes in cerebral blood volume and oxygenation accompanying contractions with a variety of different FHR tracings.

The calculation of mean cerebral oxygen saturation ($SmcO_2$) was devised to provide an "absolute" measurement of cerebral oxygenation, rather than recording relative changes in hemoglobin saturation from an arbitrary baseline. In their first study, Peebles et al[5] calculated a $SmcO_2$ of 43% ± 10% for the eight fetuses studied, where $SmcO_2 = \Delta HbO_2/(\Delta HbO_2 + \Delta Hb) \times 100\%$. In one fetus whose $SmcO_2$ fell from 35% to 1%, the cord arterial oxygen tension was 1.2 kPa and the pH 7.17.[5] Their group subsequently showed a strong correlation between fetal $SmcO_2$ measured just before delivery and umbilical artery and vein pH measured immediately following delivery (in the range of umbilical arterial pH 7.09 to 7.43) in an intrapartum study of 33 fetuses.[10] The $SmcO_2$ also showed a strong negative correlation with P_{CO_2} and base deficit, but was less strongly correlated with P_{O_2}. This was the first study that showed a correlation between a measurement obtained by NIRS and a potentially clinically relevant variable that correlates with fetal distress, although none of the fetuses with a low pH developed neonatal encephalopathy. It remains to be determined whether NIRS has the capacity to detect cerebral hypoxia/ischemia in fetuses who are subsequently shown to have evidence of perinatal hypoxic-ischemic encephalopathy.

Unfortunately, there are a number of limitations regarding the use of NIRS in intrapartum monitoring. First, there is a significant amount of movement artifact during labor, along with difficulty obtaining an adequate baseline before a measurement period of interest. The above-mentioned studies reported that up to 30% to 40% of measurements could not be analyzed because of the poor quality of NIRS data. Second, the measurement of "absolute" $SmcO_2$ is limited by the requirement to obtain changes of Hb and HbO_2 that occur in the same direction, which does not occur in the initial period of declining cerebral oxygen saturation in the distressed fetus. Third, $SmcO_2$ represents a mixed arterial and venous sample that may also be influenced by changes in oxygen extraction. For example, the asphyxiated fetus monitored after the onset of a significant decrease in perfusion or oxygenation may not demonstrate a low $SmcO_2$ if

there is reduced oxygen extraction because of diffuse cellular injury. Finally, the NIRS data may be inadequate because of poor contact of the optodes with the fetal scalp, or excessive absorption of light by fetuses with darkly pigmented skin or hair. Whether this technology will lead to clinically relevant information in the intrapartum period that facilitates appropriate preventive interventions remains to be determined by further studies involving high-risk deliveries.

Studies in Preterm and Term Newborns

The preterm and term newborn have been the focus of much of the research using NIRS because of the spectrum of neurological injuries occurring in the newborn that involve disturbances of cerebral perfusion and oxygen delivery. Furthermore, the thin scalp and skull of the newborn is particularly transparent to NIR light and therefore well suited to the use of NIRS. Early studies concentrated on the measurement of hemodynamic variables of interest, such as CBV[3] and CO_2 vasoreactivity,[13] validating these measurements and establishing normative data in the preterm and term newborn. Using the oxyhemoglobin indicator dilution technique, mean CBV in the term newborn was found to be 2.22 ± 0.40 mL/100 g.[3] The CO_2 vasoreactivity (CVR-CO_2) was measured in 17 neonates by altering the $Paco_2$ by inducing a small change in the ventilator rate. The CVR-CO_2 was found to increase with gestational age from 0.07 mL/100 g/kPa at 26 weeks gestation to 0.51 mL/100 g/kPa of change in CO_2 at term.[13] Measurements of CBF using the oxygen method in newborns of gestational ages 25 to 44 weeks gave values of CBF ranging from about 5 to 30 mL/100 g/min in four studies.[4,14-16] Two of those studies used the ^{133}Xenon method to validate the NIRS-derived CBF measurements, showing a good correlation between CBF values measured by the two techniques ($r = 0.8$ and $r = 0.84$).[14,15] Patel et al[16] compared the oxygen and indocyanine green methods of measuring CBF in 6 newborns, and demonstrated a strong correlation between the CBF values determined by the two techniques ($r = 0.93$). It should be noted that there was intrasubject variation of CBF measurements ranging from 15% to 40% in these studies, with the ICG method giving the least intrasubject variation. Furthermore, because these measurements were all made in ventilated newborns (some of whom had cerebrovascular lesions), they do not represent true "normal" newborn values of CBF.

Changes in cerebral oxygenation and hemodynamics that occur during suctioning or spontaneous apneic events are easily measured by NIRS and may help the clinician adapt management of these events. For example, Shah et al[17] found a significant decrease in both peripheral and cerebral hemoglobin saturation, and an increase in CBV during endotracheal suctioning in 12 preterm infants. Moreover, they showed that this decrease in oxygenation could be prevented by preoxygenation achieved with a peripheral saturation of 100% before suctioning. Conversely, a more recent study found a clinically insignificant decrease in CBV during suctioning, and failed to show a significant difference between the decline in cerebral or peripheral oxygen saturation when comparing open versus closed endotracheal suctioning.[18] A number of causes for these changes in CBV might be postulated, from hypoxemia and increased intrathoracic pressure, both resulting in an increase in CBV, or bradycardia producing a fall in cardiac output and therefore a decrease in CBV.

A study of the changes in oxygenation and CBV accompanying spontaneous apneic events in 17 preterm infants also yielded a variety of responses in CBV.[19] Their NIRS recordings of 130 apneic episodes (either central, obstructive, or mixed apnea) showed a decrease in CBV in most infants, which was significantly greater with episodes of obstructive apnea than the other two types. However, about 12% of babies showed no change in CBV, and 28% showed an increase in CBV. They also found no correlation between the change in CBV and the lowest SaO_2 recorded, suggesting that the change in CBV was not simply a result of oxygenation changes. It should be noted that changes in Pco_2, which were not recorded in this study, may have a significant effect on changes in CBV with either suctioning or apnea. In another study of spontaneous apneic events in preterms, the episodes of hypoxia alone showed an increase or no change in THb, whereas all events associated with bradycardia showed a decline in THb.[20] These findings suggest that the fall in cardiac output overwhelmed the capacity of the preterm brain to vasodilate in the face of hypoxia. These studies emphasize the need to measure simultaneously many physiological variables when performing NIRS studies to be able to understand the contribu-

tions of these variables to the resultant complex changes in cerebral hemodynamics and oxygenation.

Understanding cerebral pressure autoregulation in the preterm infant is of particular importance because it has been postulated that disturbances of autoregulation may contribute to the development of cerebrovascular lesions, such as periventricular leukomalacia.[21] NIRS has been applied to the measurement of changes in cerebral hemodynamics and oxygenation to address the question of normal and abnormal autoregulation in preterm infants. Tyszczuk et al[22] compared CBF in two groups of preterm infants with a mean arterial blood pressure (MAP) below versus above 30 mm Hg. They used the NIRS oxygen method to make 2 to 6 measurements of CBF over a 2- to 3-hour period and calculated the mean MAP measured at the time of each CBF measurement. They found no correlation between the mean MAP and the mean CBF in individual infants, and no difference in the mean CBF between the two groups. The authors concluded that MAP was not correlated with CBF, suggesting intact cerebral pressure autoregulation. Instead they noted that CBF was positively correlated with transcutaneous P_{CO_2}. However, this study compared averaged measurements of MAP and CBF, which may not reflect the dynamic process of cerebral autoregulation occurring over a much shorter time period. Interestingly, Tsuji et al[23] defined a subset of premature infants in whom there was a strong correlation between dynamic online measurements of changes in MAP and changes in HbD (where HbD = HbO_2 − Hb, a measure of cerebral intravascular oxygenation) (Fig 2). All 9 of the 35 critically ill preterms with this pattern subsequently developed cerebrovascular lesions as demonstrated by cranial ultrasound (M.K. Tsuji, personal communication, February 1999). Moreover, changes in HbD have been shown to correlate with changes in CBF (as measured by radioactively labeled microspheres) in two animal studies, where changes in cerebral perfusion were produced by systemic hypotension in one study,[24] and by increased intracranial pressure during progressive acute hydrocephalus in the second study.[25] Therefore, if changes in HbD reflect changes in CBF in the human newborn, then the NIRS study by Tsuji et al[23] suggests that a subset of preterm infants may indeed have a pressure passive circulation and that these infants are at higher risk of subsequent neurological injury. Finally, this study demonstrates the capability of NIRS to analyze beat-to-beat changes in physiological variables, giving insight into dynamic processes, such as cerebral autoregulation.

NIRS has also been applied to the study of various interventions in neonatal critical care with the potential of affecting cerebral perfusion or oxygenation. Indomethacin has been shown to cause a significant decline in CBV, CBF, cerebral oxygen delivery, and CBV-CO_2 vasoreactivity.[26-28]

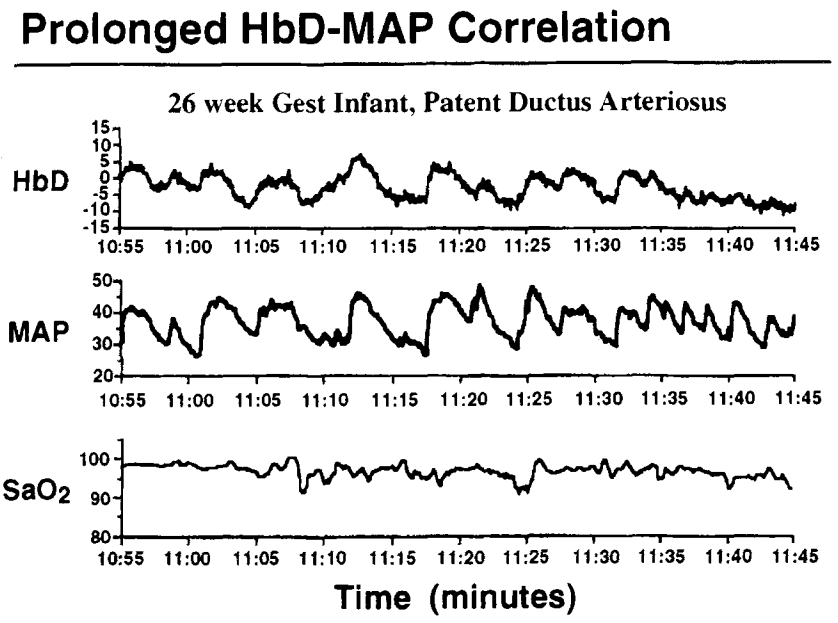

Fig 2. Data from a 1-hour study of a 26-week-gestation infant showing fluctuating mean arterial pressure (MAP) with parallel changes in HbD, suggestive of a pressure passive circulation. Note that conventional monitoring by pulse oximetry (Sao_2) gives no indication of these changes in cerebral oxygenation.

Moreover, Liem et al[27] found that indomethacin caused a substantial decline in oxidized cytochrome aa_3, which did not recover to baseline over the first 60 minutes following its administration, suggesting cellular hypoxia. NIRS has also been used to address the question of whether there is a secondary cerebrovascular injury with the development of posthemorrhagic hydrocephalus that might be prevented by removal of cerebrospinal fluid (CSF).[29,30] Studies using NIRS during CSF removal from infants with hydrocephalus have shown pronounced increases in CBV, oxyhemoglobin, and oxidized cytochrome aa_3, which did not simply correlate with the initial CSF pressure.[29,30] As in many early NIRS studies, the number of patients examined was small and thus larger studies will be needed to confirm these findings.

As potential therapies for the treatment of the asphyxiated newborn emerge, NIRS may prove to be an important tool to study the effects of both asphyxia and subsequent interventions. Several studies have shown the ability of NIRS to make measurements of important cerebral parameters that may guide future management of the asphyxiated infant. van Bel et al[31] found significant declines in CBV, oxyhemoglobin, and cytochrome aa_3 within the first 12 hours of life in severely asphyxiated term newborns when compared with normal controls or infants with moderate asphyxia (without subsequent neurological abnormalities in the newborn period or at 1 year of follow-up). The same group recently used NIRS to assess the effect of high-dose allopurinol in severely asphyxiated newborns and found a smaller CBV decrease in treated than untreated controls.[32] Although controversy persists about the validity of the cytochrome aa_3 signal, a piglet study of graded hypoxia showed that decreases of phosphocreatine (PC) and nucleoside triphosphate (both measured by ^{31}P magnetic resonance spectroscopy) correlated closely with decreases in oxidized cytochrome aa_3, but not with changes in HbO_2 or Hb (Fig 3).[33] This finding was subsequently corroborated by NIRS and ^{31}P MRS studies in rats, which showed a strong correlation between the percent cytochrome aa_3 reduction and percent PC or ATP.[34] These data support the notion that measurements of cytochrome aa_3 oxidation by NIRS reflect changes in cerebral high-energy phosphate metabolism. Conversely, the lack of correlation between intravascular oxygenation and high-energy phosphates cautions against the use of clinical neurodiagnostic devices measuring hemoglobin oxygenation alone. In a recent elegant animal study, Cooper et al[35] showed that changes in oxidized cytochrome aa_3 can be reliably measured by NIRS even in the presence of large changes in

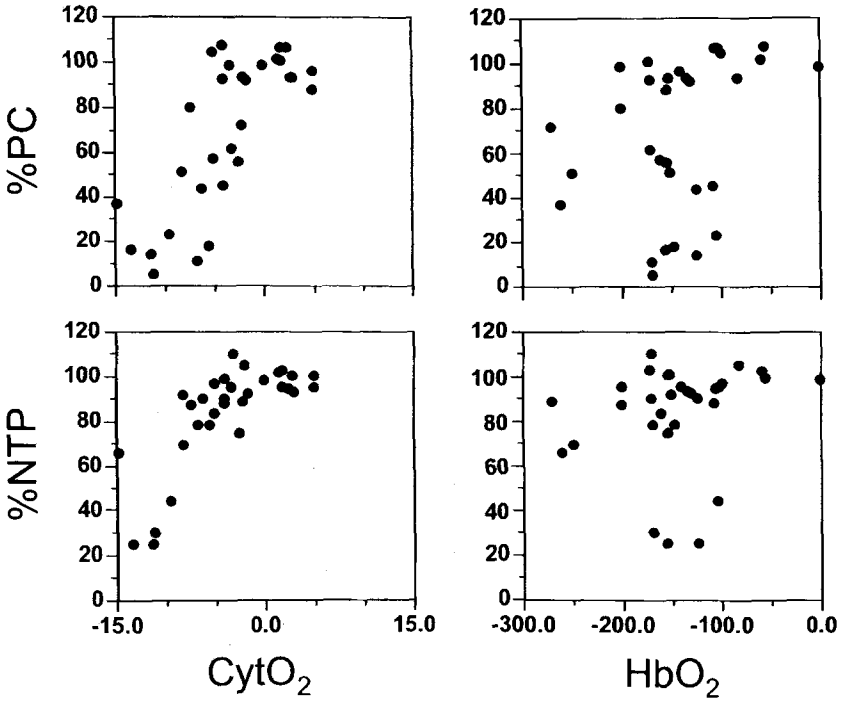

Fig 3. Combined ^{31}P-magnetic resonance spectroscopy and near-infrared spectroscopy study of cerebral high-energy phosphates (nucleoside triphosphate [NTP] and phosphocreatine [PC]), oxyhemoglobin (HbO_2), and oxidized cytochrome aa_3 ($CytO_2$) in a piglet model of graded hypoxia. Note the poor correlation between HbO_2 and NTP. On the other hand, the correlation between PC and $CytO_2$ ($r = 0.79$, $P < .001$) and between NTP and $CytO_2$ ($r = 0.77$, $P < .001$) was highly significant. (Adapted and reprinted with permission.[33])

HbO_2 and Hb. However, further studies to validate the cytochrome aa_3 signal and understand the enzyme's normal function and concentration in the human newborn brain are needed before this measurement can be used with confidence in the clinical management of infants.

Studies During and Following Cardiac Surgery

NIRS is ideally suited to the study of the infant undergoing cardiac bypass surgery because of its portability and its ability to make measurements in the electrically hostile environment of the operating room. The complex changes in cerebral hemodynamics and oxygenation that occur during cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA) are best studied by a device that provides continuous measurements of these changes. Because up to 25% of children undergoing CPB surgery may have postoperative neurological dysfunction,[36] studies with NIRS may provide the insights into the disturbances of cerebral perfusion and oxidative metabolism that likely underlie the development of brain injury in this setting. Early studies during CPB and cardiac surgery showed an initial decrease in THb at the onset of CPB, presumably due to hemodilution used during CPB.[37,38] During this decrease in THb, there was an accompanying increase in HbO_2 and decrease in Hb.[37,38-40] In a subsequent study, Kurth et al[39] studied 26 children undergoing cardiac surgery with DHCA and found that 3 children who had an abnormal postoperative neurological outcome had a smaller increase in cerebral hemoglobin oxygen saturation (ScO_2) and a shorter duration of CPB before DHCA compared with the neurologically normal children. These authors speculated that the increase in ScO_2 during cooling may be related to cerebral protection because there was no difference in temperature or baseline ScO_2 between the two groups. It is important to note that cerebral hemoglobin oxygenation measured by NIRS has been shown to correlate significantly with jugular bulb venous saturation,[41] which provides an estimate of cerebral oxygen extraction since arterial blood is fully saturated with oxygen during CPB.

Despite the increase in HbO_2 described during the cooling phase of these procedures, a simultaneous decrease in oxidized cytochrome aa_3 developed, suggesting a paradoxical uncoupling of cerebral intravascular and mitochondrial oxygenation.[38,40] This decrease in cytochrome aa_3 oxidation continued throughout CPB and DHCA and showed a delayed recovery during rewarming despite a brisk hyperemic reperfusion with a recovery of HbO_2 to greater than baseline levels after DHCA. The observation that the decline in oxidized cytochrome aa_3 continued after the minimum core temperature was achieved indicated that the fall in oxidized cytochrome aa_3 was not due to the effect of hypothermia alone. Rather, the results suggested that an intrinsic mitochondrial dysfunction or a failure of oxygen delivery to the mitochondrion, disturbances that may underlie a failure in cellular energy metabolism and hence play a role in the development of neuronal injury. In this study, older infants (ie, those >14 days old) developed a significantly greater decrease in cytochrome aa_3 during CPB/DHCA and a slower and lesser recovery of cytochrome aa_3 during rewarming compared with infants ≤14 days of age. This suggested either a maturational vulnerability of the mitochondrion to hypoxic-ischemic stress, possibly secondary to increased cerebral metabolic demand with age, or other maturational factors, such as an increase in excitatory amino acid receptors and accompanying increased susceptibility to excitotoxic injury.

Evidence of a metabolic impairment during the rewarming period comes from a recent study of cerebral fractional oxygen extraction (FOE) obtained by NIRS monitoring of infants and children undergoing either DHCA or continuous flow bypass.[42] This study used a brief period of jugular vein compression to obtain a NIRS measurement of central venous saturation (SvO_2). From this they derived the FOE, where $FOE = (SaO_2 - SvO_2)/SaO_2$. The patients who had undergone DHCA showed a decrease in FOE during rewarming that was significantly different from the rise in FOE observed in children who had continuous flow rather than DHCA. This finding may relate to an impairment in the cerebral metabolic rate of oxygen consumption after DHCA demonstrated in earlier studies.[43]

Finally, studies in the postoperative period following cardiac bypass surgery may also provide insight into cerebral perfusion and metabolic disturbances and help guide the complex management of these critically ill infants. Significant impairment of $CBV\text{-}CO_2$ vasoreactivity has been demonstrated for up to 48 hours in 38 infants following CPB/

DHCA.[44] The value of CBV-CO_2 vasoreactivity in the early postoperative period was similar to that found by Fallon et al[45] during hypothermic CPB in 13 infants but was markedly lower than that found in ventilated term infants.[13] Over the first 48 postoperative hours there was a trend towards recovery (ie, increase) of the CO_2 vasoreactivity.[44] Interestingly, a similar increase in oxygen vasoreactivity was seen over this time period.[46] These findings suggest an ongoing disturbance in cerebral vasoreactivity during the early postoperative period, when these infants are at risk for hemodynamic instability. This combination of systemic instability and impaired cerebral vasoregulation exposes the infant to risk for neurological injury. Therefore, NIRS may prove to be an important technique for the postoperative management of these patients.

Imaging Studies

An ideal goal of the NIRS technology is the generation of functional imaging of regional oxygenation changes in the brain in vivo. Over the past decade there have been important developments in this field; however, formidable challenges persist.[47] Specifically, although NIRS has excellent temporal resolution, its spatial resolution falls below that of other functional and structural imaging techniques. Functional NIRS studies are based largely on activation of focal brain regions, requiring the execution of very specific motor, visual, or cognitive tasks. Consequently, data are confined largely to adult volunteers. Recently, Watanabe et al[48] used 24-channel NIRS to demonstrate that NIRS could reliably determine the laterality of language dominance in healthy volunteers and epilepsy patients, with confirmation of their findings in the epilepsy patients by WADA testing. In a study of infants, Meek et al[49] used NIRS to measure local hemodynamic changes in the occipital cortex accompanying visual stimulation. The authors found an increase in both HbO_2 and Hb over the occipital region of infants shown a checkerboard pattern compared with the frontal region in the same infants or the occipital region in control infants.

Optical imaging with NIR has also been used for structural imaging, such as the imaging of hemorrhage in infants.[50,51] Using a circumferential optode array and a time-of-flight NIRS device, Van Houten et al[50] were able to generate images of intraventricular and subependymal hemorrhages from neonatal autopsied brain sections using a time-of-flight NIRS device. Both the autopsy study and the group's recent study in live infants[51] showed fairly good sensitivity but poor spatial resolution of the hemorrhages. These preliminary studies show promise for the clinical application of NIRS imaging to study focal cerebral changes, both physiological and pathological. Although the spatial resolution of NIR optical imaging is significantly less than that of CT or MRI, NIRS offers the advantage of noninvasive continuous data acquisition that can be collected at the bedside for prolonged monitoring.

CURRENT LIMITATIONS

Pathlength Measurements

The measurement of pathlength continues to be the issue that dominates the debate concerning the validity of NIRS data and the ability to obtain absolute measurements of chromophore concentration. Recent advances have seen increasing use of time-of-flight and intensity modulated devices with the ability to measure the pathlength for each wavelength used during the acquisition of data.[52] The importance of measuring pathlength at each study was demonstrated recently where the differential pathlength factor (DPF) was measured in 283 subjects ranging in age from 1 day to 50 years of age (recall that pathlength = interoptode distance × DPF).[53] Using phase-resolved spectroscopy, the DPF was smaller at higher wavelengths of light and increased with age (likely due to a number of factors including increasing head diameter, CBV, and myelin content with age). However, even within a particular age range there was a significant variability of DPF. Furthermore, certain pathological processes (eg, birth asphyxia) also appeared to affect the DPF compared with healthy children of the same age. Together, these findings emphasize the importance of developing devices capable of continuous measurement of DPF during each NIRS study yet small enough to still permit bedside monitoring, one of the primary advantages of NIR technology.

Movement and Light Artifact

The measurement of NIRS signals requires blockage of ambient light from the optodes to prevent contamination of the signals being measured. This is usually achieved quite easily with opaque cloth or aluminum foil shielding the optodes. However, optode movement will change the interoptode

distance, producing artifactual signals. This is a significant problem in certain settings, such as the measurement of fetal cerebral hemodynamics during labor and delivery. Movement artifact is one of the common reasons for excluding NIRS data from analysis, particularly during measurements of small changes, such as the small increase in oxygen induced for the measurement of CBF, or the measurement of changes in cytochrome aa_3 oxidation.

FUTURE DIRECTIONS

The distinct advantage of NIRS over other techniques of making noninvasive measurements of cerebral hemodynamics and oxygenation at the bedside has generated a growing body of previously inaccessible in vivo data. However, despite these features, NIRS has yet to enter widespread clinical use as a monitoring device. Several prerequisites will need to be met before this is likely to occur. First, it will be critical to further validate the reliability of the signals by simultaneous measurement of pathlength. Furthermore, large-scale studies are needed to validate the clinical significance of NIRS measurements before NIRS has an impact on the management of children with neurological disorders.

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