

EMERGING TECHNOLOGIES

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Section Editor

Near-Infrared Spectroscopy: Theory and Applications

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NEAR-INFRARED spectroscopy (NIRS) theoretically offers a technique for continuous, noninvasive, bedside monitoring of cerebral metabolism. Like pulse oximetry and mixed venous oximeters, these instruments use principles of light transmission and absorption to noninvasively measure the concentrations of oxygenated (HbO₂) and deoxygenated (Hb) hemoglobin in tissue, most often cerebral tissue. The introduction of pulse oximetry in 1985 made it possible to continuously and noninvasively monitor the oxygenation of arterial blood. Although this monitoring modality dramatically improved the physician's ability to recognize and treat arterial hypoxemia, circumstances exist where tissue hypoxia, especially cerebral hypoxia, may develop in the presence of appropriate arterial and venous oxygen saturations. NIRS offers the possibility of monitoring the most important oxygenation end point, that of tissue oxygen utilization. Ninety percent of the oxygen that leaves the vascular space enters the mitochondria where it acts as the final electron acceptor in the electron transport chain. Transfer of electrons to oxygen occurs via the enzyme cytochrome aa₃ (Cytaa₃), also known as cytochrome C oxidase. Anoxia quickly results in complete reduction of this enzyme.¹ In 1977, Jobsis described a spectroscopic technique to determine the oxidation status of Cytaa₃ in intact cat brain and rat heart using light transmission through the tissue in a manner analogous to using oximetry for hemoglobin saturation.²

Continuous, noninvasive monitoring of cerebral oxygenation would provide information not currently available by any other modality. Such a monitor could be used during deep hypothermic circulatory arrest or during carotid endarterectomy to diagnose the onset of global or regional cerebral hypoxia. A continuous cerebral oxygenation monitor could have both research and clinical applications for patients recovering from cerebrovascular accidents (embolic or hemorrhagic). For nearly any disease state in which

cerebral oxygenation is compromised, such a monitor could provide valuable information about the pathophysiology of the disease as well as test the benefit of a given treatment, either in general or in a particular patient.

Currently available techniques can provide information regarding the metabolic state of cerebral tissue, including positron emission tomography scanning and nuclear magnetic resonance (NMR) spectroscopy (usually ³¹P or ¹H nuclei). Although these techniques offer much information about the metabolic state of the brain at the time of the scan, they are prohibitively expensive and time-consuming and require transport of the patient to the machine. None of these techniques provides continuous monitoring. Jobsis' report of a spectrophotometric technique to determine the state of tissue oxygenation, therefore, engendered much interest. However, translation of the principles that Jobsis described into clinically applicable instruments has proven to be extremely difficult.

This article reviews the technical and historical developments of these instruments, the problems that remain unresolved to date, and the available data on reliability and accuracy.

TECHNICAL DEVELOPMENT

All optical spectrometers consist of the same basic components (Fig 1): light sources (eg, light emitting diodes (LED) or laser diodes) to deliver light of a known intensity and wavelength to the tissues; a light detector (eg, a photodiode or photomultiplier tube) to measure the intensity of the light exiting the tissues; and a computer to translate changes in light intensity to clinically useful information (such as concentration of HbO₂, Hb, or oxidized Cytaa₃).³ Spectrometers may use light wavelengths in the visible range (optical spectrometers), or the near-infrared range (spectrometers). Although NIRS can be used in virtually any organ, cerebral oxygen delivery and utilization has been the chief area of interest. Despite nearly 2 decades of intense work, and considerable progress, the technical problems preventing application of NIRS to a clinical monitor have not been fully resolved. A discussion of the principles involved in spectroscopy is necessary in order to understand these problems.

Like all current oximetry monitors, NIRS is based on relatively simple physical principles. The first is that every substance in this world has a characteristic and unique absorbance spectrum. For example, oxygenated hemoglo-

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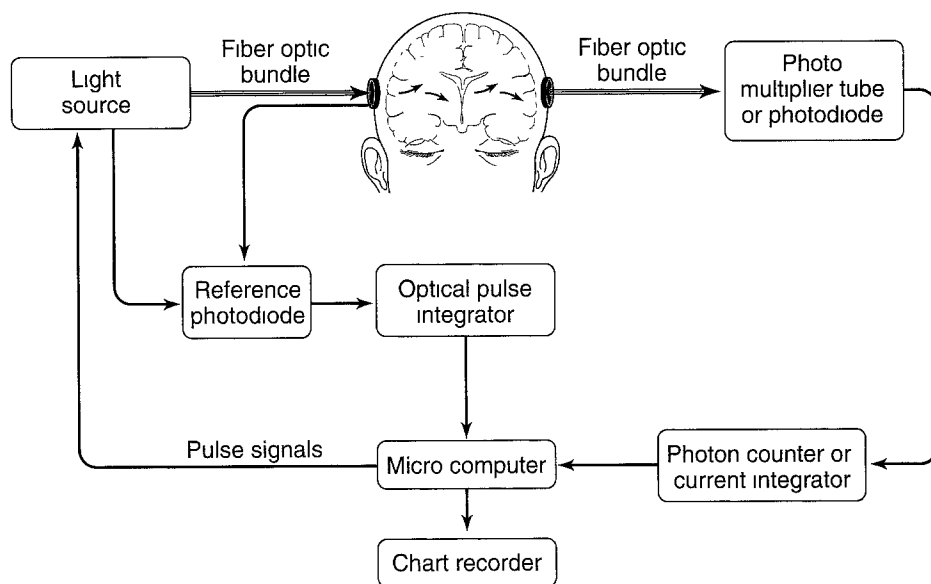


Fig 1 Schematic of the basic components of a NIRS system

bin absorbs less red light (600 to 750 nm) and more infrared light (850 to 1,000 nm) than does Hb (Fig 2).⁴ The second principle is that skin, water, and other biological tissues are relatively transparent to certain wavelengths of light (red and near infrared), allowing noninvasive and continuous measurement of certain light absorbing substances within the tissues (ie, HbO₂, Hb, and Cytaa₃).

The first demonstration that oxygenated blood could be differentiated from deoxygenated blood by their light absorbance characteristics occurred in 1864, when the German chemist Felix Hoppe-Seyler isolated the blood pigment responsible for carrying oxygen. He named this pigment hemoglobin and demonstrated that mixing air with hemoglobin altered its absorption of light.⁵

At about the same time, August Beer, working with the ideas of Heinrich Lambert, had described the Lambert-Beer law that states that the transmission of light through a solution is a logarithmic function of the density or concentration (C) of the absorbing molecules in the solution.⁶ The intensity of the transmitted light is also a function of the

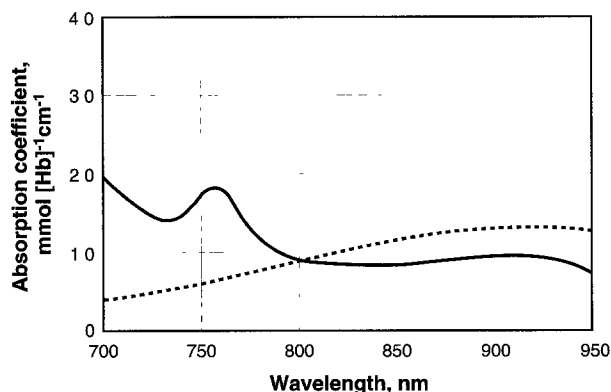


Fig 2 Light absorbance spectra of two hemoglobin species: oxyhemoglobin and deoxyhemoglobin. Deoxyhemoglobin is shown by the solid line; oxyhemoglobin is the dotted line. (Adapted with permission.³)

pathlength of light through the solution (D) and the specific extinction coefficient (ϵ) for the material at a given wavelength. This law may be written as the equation below:

$$I_{trans} = I_{in} e^{-D C \epsilon} \quad (1)$$

where I_{trans} = intensity of transmitted light; I_{in} = intensity of incident light; and e = natural log base (2.71828).

Thus, if a known substance is dissolved in a clear solvent in a cuvette of known dimensions, the solute concentration can be calculated if the incident and transmitted light intensities are measured. Using this principle, Drabkin and Austin were able to measure the saturation of hemoglobin in a cuvette.⁷ In addition, it is possible to measure the concentrations of multiple substances in the same solution by using a different wavelength for each substance, writing a separate Lambert-Beer equation for each, and solving the simultaneous equations through matrix inversion.

However, when making measurements in tissue, the situation is complicated by the effects of light scattering, which is caused by the refractive index variations between and within cells and the cell constituents. This scattering of light also leads to a loss of light intensity, the amount of which varies with tissue type, size, and the measurement geometry. Because only a fraction of the scattered light is detected, the total light loss is normally unknown, making absolute quantitation of the concentration of the absorbers in the tissue difficult. As a result, most tissue spectroscopy has been performed by setting the detected light intensities at the start of the measurements to zero and assuming that the "background" light attenuation caused by tissue scatter remains constant. Any changes in intensity are then assumed to arise only from the absorbers whose concentration can vary with time and/or oxygenation status (eg, hemoglobin and Cytaa₃). With these guidelines, the requirements for application of the Lambert-Beer equation to quantitative spectroscopic analysis of multiple substances in tissues are as follows: (1) a separate measurement wavelength for each absorbing substance; (2) a large

enough change in light intensity to be detected and quantified; and (3) an exact measurement of the length of the light path. The problems associated with meeting each of these requirements will be discussed in turn.

Absorbance Wavelengths

The first requirement proves to be a minor tissue. There are only a few chromophores that absorb light strongly in the 700- to 1,000-nm range. The most potent of these are the hemoglobins and the copper atoms of the Cytaa3 enzyme in the electron transport chain (Fig 3).⁸ Although there are other chromophores in tissue that alter their absorption of light depending on oxygenation state, they have virtually no absorbance in the near-infrared range.^{9,10} As described above, the absorbance spectra of Hb and HbO₂ have been known for more than 100 years. The cytochrome enzymes of the electron transport chain were originally described in 1925 by Keilin, who used spectroscopic techniques to demonstrate that Cytaa3 is completely reduced in the absence of oxygen.¹ Further development of sensitive spectrographic techniques by Chance in the 1950s permitted measurement of cytochrome absorption bands in intact cells.¹¹ These initial experiments used wavelengths of visible light, which do not penetrate tissues to a significant degree. Jobsis used near-infrared light and demonstrated the presence of a broad band of light absorption at 830 nm in well-oxygenated tissues that disappeared almost completely under anoxic condition.² Further work in isolated mitochondria and in rats perfused only with fluorocarbons (no hemoglobin present) confirmed that Cytaa3 could be identified with near-infrared technology.^{12,13} As can be seen from Figs 2 and 3, the wavelengths of light used for Cytaa3 monitoring lie in the same range as those used for hemoglobin measurement and their absorption spectra overlap. By using multiple wavelengths it is, in principle, possible to differentiate the absorbance caused by Cytaa3 from that of hemoglobin. However, extremely precise measurements are needed, because at typical tissue concentrations, the absorbance caused by hemoglobin is an order of magnitude greater than that of Cytaa3

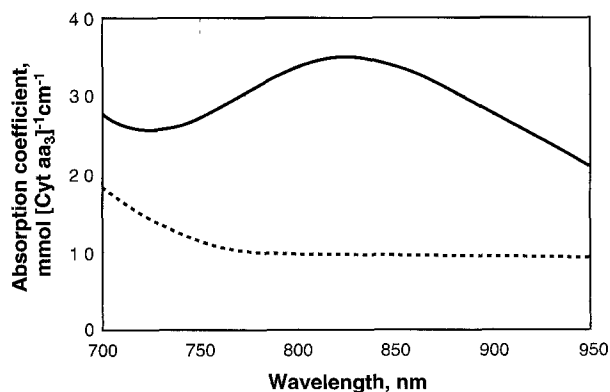


Fig 3. Absorbance spectra of purified cytochrome aa3 enzyme. Oxidized Cytaa3 is shown by the solid line, reduced Cytaa3 is shown by the dotted line (Adapted with permission⁸)

Measuring Change in Light Intensity

Measuring the loss of light intensity caused by absorption by a particular substance is a more significant issue. As previously mentioned, in addition to being absorbed, photons of light passing through tissue can be reflected or scattered. Loss of light intensity because of scattering and absorption is approximately one order of magnitude per centimeter of tissue traversed (one optical density, per cm).¹⁴ Because a full-term infant has a head diameter of about 10 cm, the loss of light intensity across that distance makes accurate measurement of small changes in intensity (eg, due to Cytaa3) very difficult. Use of pulsed high-power laser diodes such as transmitters and photo-multiplier tubes as receivers have improved the signal-to-noise ratio, enabling such measurements to be made with response times of a second or less. However, adult craniums are still too large for transmission spectroscopy. This limitation has been addressed by measuring changes in reflected light rather than transmitted light. Work on pathlength determination (see next) showed that the optical pathlength for reflected light is linearly related to the spacing between the transmission and receiving sites, and so many of the currently available NIRS instruments measure changes in reflected light intensity (not transmitted light intensity), placing the light source and detector several centimeters apart on the head. Although this spacing results in a measureable signal intensity, it affects the depth of penetration of the light signal, which carries implications both for the amount of tissue monitored and for the distribution of optical paths in the tissue.

Determination of Pathlength

One of the greatest obstacles to the application of the Lambert-Beer equation in a clinical near-infrared monitor of cerebral oxygen utilization has been, and to an extent still is, determination of pathlength. It is possible to ignore pathlength altogether, if actual concentrations are not sought. Instruments, such as pulse oximeters, which measure ratios of substances (HbO₂ to Hb), do not require determination of pathlength. Instruments that measure absolute concentrations of substances do require this determination. NIRS instruments may be divided into two distinct types: *concentration* monitors and *saturation* monitors. Concentration monitors may be further subdivided into those that only measure relative concentration changes, and those that attempt to measure absolute concentrations. As discussed next, relative concentration monitors do not require precise pathlength determination, whereas absolute concentration monitors do.

In Vivo Concentration Monitors

The reflection, scattering, and absorption of light photons result in a total optical pathlength that is many times that of the spacing between the light source and detector. In addition, exiting photons will not all have traversed the same path, and each will have traveled a slightly different distance.¹⁵ Pathlength is itself a function of the optical characteristics of the tissue, the concentration of absorber

in the tissue, and the measurement geometry.¹⁵ As the concentration of the absorbing substance increases, the optical pathlength shortens because photons with longer pathways have a greater likelihood of being absorbed.^{16,17} Over the years, the problem of pathlength determination has been dealt with in increasingly sophisticated ways. NIRS-derived data in the literature about cerebral oxygenation thus must be interpreted in the light of the method used to determine pathlength.

The initial, and least sophisticated, method for dealing with pathlength was to assume no change over time, and set it to unity in the equations. The first measured light intensity was set as the baseline, and changes from this baseline were assumed to be proportional to changes in the concentration of the absorbing substance. In laboratory animal studies, it was then possible to define a scale from 0 to 100 for the calculated concentrations of hemoglobin and cytochrome aa3, with values obtained at an $F_{I}O_2$ of 1.0 as 100, and values obtained at an $F_{I}O_2$ of 0.0, via 100% nitrogen, as 0. Because it is not feasible to ventilate human patients with 100% nitrogen, even for short periods of time, such a scale is not applicable to clinical monitors. The first NIRS cerebral oxygen monitors were thus trend monitors, reporting changes in arbitrary units from baseline.¹⁸

Alternatively, qualitative information was provided in relative units, denoted as variation in density (V/D). One V/D represents one order of magnitude change in the intensity of each wavelength as it traverses the tissue. Instruments reporting variations in density are also trend monitors. They detect changes from baseline but provide no information about whether the baseline value was normal, high, or low.¹⁹ In addition, information obtained in one patient cannot be applied to another because each patient serves as his or her own baseline. These instruments have been used for much of the laboratory work conducted in animals because each animal is treated similarly and can be expected to be "normal" at the beginning of the experiment. Useful information has been obtained about how cerebral hemoglobin concentration or tissue oxygen utilization, ie, Cytaa3 oxidation state, varies with changing conditions such as extreme anemia, hypoxia, or anoxia. However, these instruments provide no information about the absolute concentration or changes in the absolute concentration of the variables of interest.

The next level of sophistication in pathlength measurement involved the actual determination of the typical optical pathlength in a specific tissue and the observation that for a given tissue, this was equal to the source-detector spacing multiplied by a near-constant factor called the differential pathlength factor (DPF). The DPF is a function of how much scattering and absorption occurs and hence depends on the optical characteristics of the tissue.^{20,21} Wyatt et al determined the pathlength in the heads of postmortem infants by measuring the "time of flight" of photons traversing the head and demonstrated that the DPF for cerebral tissue was a near constant, 4.39 (no units), once the source-detector distance is greater than 25 mm.²² Subsequently, the same method was used to measure the DPF for adult head, arm, and leg, and these data were later

refined to determine the wavelength dependence of the DPF.^{23,24} More recently, data measured on a larger population using the phase measurement technique (see later) have shown both the statistical variation and age dependence of this parameter.^{25,26} Use of the DPF multiplied by the source-detector spacing in the modified Lambert-Beer equation results in quantification of the measured *changes* in absorber concentration, although absolute quantitation is still not possible because the light loss caused by background tissue scattering and the measurement geometry is still unknown. The term *differential* pathlength factor comes from the fact that it enables the *differences* in absorber concentration to be derived from the *differences* in attenuation.

However, other limitations remain. First, subject-to-subject variability exists in the DPF of approximately 10% to 15%, which creates a similar uncertainty in the calculated concentration changes.²⁵ Second, the light traversing the skull passes through different tissues, skin, bone, dura mater, and cerebral tissue, each of which has different optical characteristics and contributes differently to the total optical pathlength and hence to the DPF. If a change in hemoglobin concentration, therefore, occurs only in the cerebral tissues that occupy only a part of the optical path, the apparent concentration will be underestimated if the total optical pathlength is used in the NIRS calculation.²⁷ The extent of the contribution of each tissue to the total path is difficult to measure, but recent mathematical modeling of light transport in tissues has indicated that in the adult head, the cerebral tissues may only contribute 20% to 40% of the total pathlength.²⁸ The cerebral contribution in the newborn infant head may be much larger because of the thinner skin and muscle plus the lower scattering properties of the infant brain.²⁹ Finally, the DPF varies slightly in response to changes in tissue absorption (eg, increased blood volume). This relatively small change typically remains less than 5% for normal physiologic variations.^{15,30} These effects together represent a small deviation from the Lambert-Beer law used in the near-infrared instrument algorithms. Cope et al discuss the results of these effects and the method for correcting the algorithms.³¹ Instruments that use the DPF and source-detector spacing to estimate pathlength monitor trends only. Although they quantify *changes* in concentration, they provide no quantitative information about the *absolute* concentration of any of the chromophores of interest. Recent research has yielded techniques that permit quantitation of two hemodynamic parameters by comparing NIRS data and pulse oximeter data. The first parameter is absolute Hb concentration, and hence cerebral blood volume, and the second is cerebral blood flow.^{32,33}

The most sophisticated instruments measure actual pathlength as well as monitor changes in light intensity. These allow continuous measurement of pathlength in the individual patient and its incorporation into a modified Lambert-Beer equation. Again, these instruments cannot provide absolute values of chromophore concentrations but can more accurately determine changes in the measured chromophore concentrations. Three methods currently exist to

measure optical pathlengths. The first, the "time of flight" method, calculates pathlength from the mean transit time of picosecond light pulses.²⁰ The large and expensive instrumentation needed to make these measurements typically confines it to the specialist laboratory, although two portable "time of flight" instruments have been reported.^{34,35} The second method uses radio frequency-modulated light sources and measurement of the phase shift of detected light, which is directly related to the pathlength. This type of instrumentation is less expensive and more compact and can easily be built into a bedside instrument.^{36,37} The third method, involving conventional multiwavelength spectroscopy, uses the measurable absorption peak of water. Because water concentration in the brain is usually known to within 2% to 3%, the optical pathlength is obtained by dividing the apparent water concentration by the known concentration.^{38,39} The actual comparison is performed on the second derivative of the spectra, a technique that largely eliminates the effects of tissue scattering on the spectrum. Because Hb also has a measurable second derivative spectrum,⁴⁰ it is possible to calculate the ratio of the apparent hemoglobin concentration to the apparent water concentration and hence obtain an absolute measure of the Hb concentration.⁴¹

In Vivo Saturation Monitors

In vivo saturation spectrometers (such as the pulse oximeter) do not attempt to measure concentrations of HbO₂ and Hb in tissue but instead measure the ratio of the two and derive the hemoglobin oxygen saturation. By measuring a ratio, these instruments avoid the need to estimate optical pathlength because this factor appears in both the numerator and denominator of the ratio and hence cancels out. This assumption about pathlengths canceling is not absolutely correct but can under certain circumstances be correct to within a few percent. These instruments do not attempt to measure Cytaa3. Sevick first described a method using two modulation frequencies at two wavelengths to determine the ratio of the absorption coefficients.⁴² Haida and Chance, and more recently Liu et al, reported an improved method for obtaining the ratio of the absorption coefficients using phase modulation in vitro.^{43,44} Alternative methods that use a single frequency or conventional spectroscopy but measure phase or attenuation as a function of distance also exist.^{45,46} A further variant of this type of instrument (the INVOS; Somanetics, Troy, MI) attempts also to reduce the effects of surface tissues overlying the brain by measuring the absorption ratios at two different source-detector spacings and subtracting one from the other.⁴⁷

LIMITATIONS

As can be seen from the discussion so far, most of the requirements for a near-infrared cerebral oxygen monitor are in place. It is possible to deliver light of a known intensity and wavelength, using high-intensity laser diodes or LEDs of different wavelengths. It is likewise possible using sensitive photon detectors to measure changes in the attenuation of that light as it traverses the tissue of interest.

What remains to be finalized are techniques for simultaneously measuring the pathlength and improvements in the Lambert-Beer equation, which would take into account any small changes in the pathlength. However, even when the question of pathlength is resolved, there will remain some limitations to the applicability of these monitors. These limitations can be divided into technical and clinical issues. Technical issues include the effects of light source spectral bandwidth, dealing with motion artifact, and improvements in the algorithm for incorporating pathlength into the Lambert-Beer equation. Clinical issues include charting this unmapped territory by determining the range of normal values, accuracy, and response.

Technical Issues

As noted previously, the chromophores of interest (Cytaa3, HbO₂, and Hb) have absorbance spectra that overlap one another. Incomplete separation of the signals will cause Cytaa3 to follow the general trend in HbO₂. Any inaccuracies in the input wavelength can lead to an error, the effect being the greatest for wavelengths where the extinction slopes are the steepest, between 750 and 800 nm (Fig 2). The laser diodes used in near-infrared instruments have a narrow emission wavelength only a few nanometers wide, and the wavelength is slightly temperature dependent. Avoidance of wavelength errors involves either temperature control of the laser diodes or measurement of the temperature with software compensation for the wavelength shift. Instruments using LEDs as light sources, eg, pulse oximeters or the INVOS, are more prone to error because the broad emission bandwidth (30 to 40 nm) means that an average extinction over this range must be used in the calculation. The presence of any other wavelength-dependent absorber in the tissues (eg, melanin) can distort the received spectrum and hence lead to an error. The effect of this error on pulse oximeters has been reported.⁴⁸

Every spectrometer also must deal with the problem of motion artifact, which remains one of the chief problems with accuracy of pulse oximeters. Near-infrared instruments are sensitive to patient motion, including pressure on the sites where the transmitter or receiver are coupled to the skin. Position changes can be misinterpreted as changes in absorbance.¹⁹ To some extent, this problem can be minimized by careful design of the source and detector and their attachment to the tissues, and by careful choice of monitoring site. The newer pathlength measuring NIRS instruments should overcome this problem.

Even when determination of total pathlength is solved in general, the determination of the pathlength in the particular tissue of interest will remain a problem. This may only be resolved by careful clinical and animal studies in which known absorption changes are induced in specific organs. In the head, the contribution of cerebral tissue to the total optical pathlength may be a fixed ratio, and thus accounted for in the NIRS calculations, although the possible variation from source and detector position on the head would have to be tested, as would signal contamination by the overlying tissues such as dura, bone, and skin. Evidence to date indicates that to minimize contamination by overlying

tissue, the source-detector spacing should be as large as possible. Some of the recent near-infrared studies on cerebral-evoked responses indicate that the problem of signal contamination may have been overestimated.⁴⁹⁻⁵¹

Algorithm development yields continuing improvement. As the mathematical models of light transport in tissue improve, it becomes possible to predict with greater accuracy the effects of tissue inhomogeneity and geometry on the measured optical attenuation.⁵² Current algorithms have been developed using different assumptions, and have been tested on different animal models. A recent comparison of the four published algorithms using theoretically derived test spectra shows that each produces slightly different values for the derived concentrations, especially those for Cytaa3.⁵³ Proving which algorithm provides the correct values *in vivo* is currently impossible because there are no “gold standard” techniques for measuring tissue hemoglobin concentrations and Cytaa3 redox state *in vivo*.

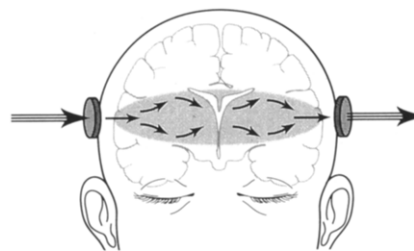
Clinical Issues

Clinical application of these monitors is further seriously hampered by the inability to compare accuracy and response of these monitors with “gold standards” as well as the difficulty of defining what is being measured and from where in the tissue. Theoretically, near-infrared spectroscopy offers measurement of the global tissue concentration of Hb, HbO₂, and oxidized Cytaa3. However, the information provided by current instruments fails to meet this ideal goal.

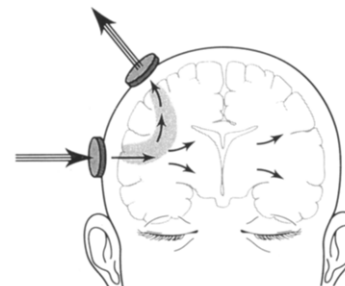
Global. As described previously, initial NIRS measurements involved transillumination of small heads (cats, rats, or infants) that enabled sampling of most of the brain. The attenuation of light across greater distances requires reflection rather than transmission measurements. As Fig 4 demonstrates, this reduces the section of the tissue monitored from the majority of the brain to a “banana”-shaped wedge of one hemisphere. The spacing of the source and detector also affects the depth of light penetration into the tissue. What spacing ensures penetration of the light into cerebral tissue? Ranges from 2 to 5 cm appear in the literature, evoked response studies demonstrate a cerebral signal at spacings of 2 to 3 cm.^{54,55} Inappropriate positioning of the source or detector over surface muscles, or use of too small a spacing, may account for some reports that extracranial blood flow strongly influences the measured cerebral hemoglobin concentration or saturation.^{54,56-58} Given their different algorithms, and different methods of dealing with surface tissue contamination, concentration measuring and saturation measuring NIRS systems (such as the INVOS [Somanetics, Troy, MI]) can be expected to provide different measurements of cerebral oxygenation. Variation in detector spacing between early (1 and 2.7 cm) and later (3 and 4 cm) models of the INVOS instrument further complicates interpretation of studies with this instrument.

Tissue. NIRS instruments determine changes in the concentrations of HbO₂ and Hb without differentiating in which vascular bed the hemoglobin is found (arterial, capillary, or venous). More than 70% of the hemoglobin in the brain at any given time is believed to be in the venous

A. Transillumination



B Reflectance



C Invos 3000

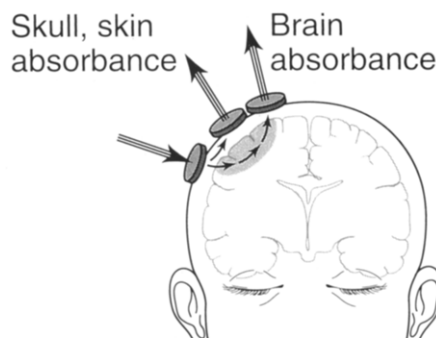


Fig 4. Light absorbance may be measured in (A) a transillumination mode or in (B, C) a reflectance mode. The mode of monitoring determines the portion of cerebral tissue that will contribute to the light absorbance signal. The (C) INVOS 3100 uses two light receivers in an attempt to differentiate between light absorbance owing to skull and overlying tissues and light absorbance caused by cerebral tissue.

compartment. Near-infrared-derived hemoglobin oxygenation thus reflects more a venous saturation than a tissue saturation. Decreases in cerebral hemoglobin saturation denote either a decrease in oxygen delivery as would occur with alterations in blood flow, hematocrit, or arterial saturation, or an increase in oxygen utilization. Relative changes in blood volume of the venous or arterial compartment, even without a change in saturation of either, can influence mean cerebral hemoglobin saturation. For instance, an increase in the portion of Hb may signal an increase in the amount of venous blood relative to arterial blood. A simple example of this is a change from the head-elevated Fowlers' position to the head-down Trendelenburg position. Obviously, placement of the source and

detector is crucial—if they are positioned so that the light is mainly transmitted through, or reflected from the sagittal vein, the hemoglobin monitored will be nearly all venous.⁴⁰ This may of course be a useful clinical signal in some circumstances.

Assuming the problems of accuracy are solved, and the instrument is able to report cerebral tissue saturation or concentration, these monitors by themselves provide no information on cause or cure. As with mixed venous oximeters, changes in cerebral oxygen saturation will indiscriminantly reflect changes in any of the parameters that determine either oxygen delivery such as hemoglobin concentration, cardiac output, and arterial saturation, or oxygen consumption, such as cerebral metabolic rate and temperature. The information these monitors provide, therefore, must be interpreted in conjunction with that from other clinical monitors, although NIRS instruments do have the distinct advantage of being noninvasive. It remains to be seen whether these monitors can aid clinical decision making and thus improve patient outcome.

Accuracy and precision. As noted earlier, there is no “gold standard” against which to judge the NIRS instruments. The closest clinical standard is jugular venous bulb saturation as determined by oximeter catheters in the internal jugular vein.^{57,59} In some circumstances, current NIRS cerebral saturation monitors may not track the jugular bulb saturation accurately, although whether this denotes inaccuracies in the instrument or a true difference between tissue versus jugular bulb saturation cannot be determined.⁵⁷ Although some preliminary comparisons have been made between NIRS monitoring and ³¹P NMR spectroscopy for assessment of birth-asphyxiated infants, differences in the type of information provided makes interpretation difficult.^{60,61} In the laboratory, indwelling or surface tissue optodes or Clark electrodes measuring tissue oxygen tension may provide some insights regarding accuracy. However, differences in the volumes of tissue sampled again make quantitative comparison difficult.⁶² It is premature to consider comprehensive clinical trials given the continual development of the current NIRS instruments. However, with resolution of the technical problems of absolute quantitation, a method to assess the accuracy and precision of these instruments will assume greater importance.

APPLICATION OF NIRS TECHNOLOGY

Table 1 lists some of the commercially available NIRS instruments, with information regarding type of instrument and availability. As noted earlier, there are no “gold standards” against which to measure any given instrument, and large-scale clinical trials have not been conducted comparing instruments to each other. Also, there have been no “outcome” trials to date.

Concentration Measuring Instruments

This report cannot present all the experimental data on cerebral function that have been derived using NIRS technology. Table 2 lists reports of cerebral physiology using NIRS technology in animal models and gives some

information about the instrument used in each instance.^{2,62-72} Table 3 does the same for human data.^{27,56,61,73-87} These tables are not meant to be exhaustive, but rather illustrative of the types of models that have been tested using NIRS technology. Most of the data were derived using prototype instruments not in commercial production, using a wide variety of algorithms, and reporting derived concentrations in different ways. For the data calculated using the path-length derived from the DPF and source-detector spacing, the previously mentioned standard deviation in the data must be considered. In addition, it is not possible to compare prototype instruments regarding accuracy, precision, bias, or drift, although some of the commercial instruments do provide such data.

Clearly, the chief proposed use of NIRS technology is as a real-time, noninvasive, on-line monitor of the concentration of cerebral HbO₂, Hb, and oxidized Cytaa3. Concentration monitors, which independently determine changes in the amount of HbO₂ and Hb, can sum the two and report changes in total hemoglobin volume, which should follow total cerebral blood volume. NIRS has been used as a monitor of HbO₂, Hb, Cytaa3, and cerebral blood volume in monitoring newborns, especially birth-asphyxiated infants, in fetuses during labor, and in adults.

Birth asphyxia occurs when the fetus suffers cerebral hypoxia during labor and delivery. Monitoring for this devastating complication has included fetal heart rate and sampling of fetal scalp blood for determination of acid-base status, both indirect monitors of cerebral oxygenation. Near-infrared monitoring of fetal cerebral oxygenation allows a direct assessment and offers the potential for rapid intervention if cerebral hypoxia occurs. Studies using NIRS monitoring during labor demonstrate a relationship between uterine contraction pattern and fetal cerebral deoxygenation, show an increase in fetal cerebral oxygen saturation during administration of supplemental oxygen to the mother, and predict infant acid-base status after delivery.⁸⁵⁻⁸⁷ Fetal hemoglobin has not been found to alter the measurement of cerebral oxygenation.⁸⁸

NIRS has also been used to assess the extent of brain injury in birth-asphyxiated infants after delivery.^{60,61,73,81} Normal infants show a characteristic response of cerebral blood volume, as determined by NIRS, to either a tilt or to changes in inspired O₂ or CO₂.^{60,79,81,89} Birth-asphyxiated infants show either no response, or a very different pattern of response to these physiologic interventions, even immediately after the event. In contrast, studies of asphyxiated, then resuscitated infants using ³¹P-NMR demonstrate that brain energy status is nearly normal the first day after resuscitation, with a significant decrease thereafter.^{60,61,89} NIRS technology thus may provide earlier information about the extent of injury in these infants.

The majority of NIRS-generated information concerning normal cerebral physiology comes from studies on normal infants. Studies in newborns show that cerebral oxygenation (Hb and HbO₂), cerebral oxygen utilization (redox state of Cytaa3), and total cerebral blood volume can be seen to change with alterations in respiratory pattern, with inspired O₂ or CO₂, with stimulation, during exchange

Table 1 Animal Studies Using Near-Infrared Instruments

Author	Date	Type	Wave-lengths	Variables	Units of Measure	Animal	Model	Findings
Jobsis ²	1977	Local	Many from 700 to 900	Hb, HbO ₂ , Cytaa3	Absorption coefficient, mmol/[Hb or Cytaa3]/cm	Cat brain, dog heart	Normoxia, anoxia	Oxygenation state of Cytaa3 and hemoglobin can be recorded effectively and continuously
Mook ⁶²	1984	Omni 4	3 770, 813, 905	Hb, HbO ₂ , PO ₂ (surface)	0-100 scale	Cats	Progressive hypoxia	Correlation of PO ₂ to % Cytaa3 reduction yield a correlation coefficient of -0.77 ($r^2 = 0.604$)
Caimes ⁶³	1986	Local	3 765, 800, 905	Hb, HbO ₂ , cytaa3, cerebral blood flow	0-100 scale	Cat	Increased intracranial pressure	Increased F _I O ₂ alone—no benefit, 50% O ₂ with 5% CO ₂ increases perfusion, cytaa3 oxidation, and decreased Hb.
Ferrari ⁴⁰	1989	Local	Many from 740-840	Sagittal sinus SvO ₂ (NIR) versus true SvO ₂ (bench top co-oximeter)	Log(1/Td)†	Dog	Graded hypoxia	NIR determined SvO ₂ regressed against sampled SvO ₂ yielded r value of 0.97
Ferrari ⁶⁴	1989	Omni 3	3 775, 815, 905	Hb, HbO ₂ , CBF, MTT	V/D	Dogs	Hemorrhagic hypotension	Autoregulation is preserved until cerebral perfusion pressure is 30-40 mmHg
Lubarsky ⁶⁵	1992	Local	4 775, 810, 870, 904	Hb, HbO ₂ , Cytaa3, SvO ₂ , VO ₂	0-100 scale	Rabbits	Normovolemic hemodilution	SvO ₂ decreases to <50% at hemodilution of 10 mL/kg, Cytaa3 is preserved at 95% until SvO ₂ decreases to 30%
Kakihana ⁶⁶	1992	Local	4 700, 730, 750, 805	Hb, HbO ₂ , Cytaa3, MbO ₂ Heart and brain	0-100 scale	Rats	Hypoxia, fluorocarbon exchange	Oxygenation states of cardiac muscle and brain behave similarly during progressive hypoxia
Ferrari ⁶⁷	1992	Omni 3	3 775, 815, 905	Hb, HbO ₂ , tHb, MTT CBF (dye and spheres)	V/D	Dogs	Hemorrhagic hypotension	CBF is autoregulated between 40-130 mmHg via increases in CBV. Below 30 mmHg, CBF decreases
Hirano ⁶⁸	1993	NIR-1000	6 780, 808, 830, 847, 867, 911	Hb, HbO ₂ , tHb	mmol/cm/Lt	Rabbits	Carotid ligation plus graded hypoxia (F _I O ₂ 0.18, 0.15, 0.10) and hypoxia plus CO ₂	Carotid ligation decreases HbO ₂ , tHb, increases Hb. Hypoxia + ligation cause more severe response than ligation alone but do not increase tHb very much
Hoshi ⁶⁹	1993	Local	4 700, 730, 750, 805	Hb, HbO ₂ , tHb, Cytaa3 EEG tracing	0-100 scale	Rats	Graded hypoxia, induced seizures (pentylentetrazol)	Describe in detail the alterations in Cytaa3 that occur preictal and postictal. Results support classic theory of cellular hypoxia during seizures
Schafer ⁷⁰	1993	Omni-3	3 775, 815, 905	Hb, HbO ₂ , tHb, Cytaa3	V/D	Rats	Endotoxin bolus	Endotoxin-induced reduction in CBF is associated with a decrease in Cytaa3 redox state, proportional to decrease in HbO ₂
Tamura ⁷¹	1993	Local	4 780, 790, 805, 830	Hb, HbO ₂ , tHb, Cytaa3	0-100 scale*	Rats	Fluocarbon exchange	Fluorocarbon with F _I O ₂ of 1.0 can maintain Cytaa3 oxidation until circulatory collapse intervenes
Kamer ⁷²	1994	NIR-1000	6 780, 808, 830, 847, 867, 911	Hb, HbO ₂ , tHb, Cytaa3	mmol/cm/Lt	Rabbits	Intracranial hemodynamics with hyperventilation during hypocarbia ± hyperoxia (100% O ₂)	Cytaa3 decreased during hyperventilation except during 100% O ₂

NOTES. Omni 3, 4, International Instrumentation Laboratories, Inc, Durham, NC, NIR0500, Hamamatsu Photonics KK, Japan; NIR-1000, Hamamatsu Photonics KK, Japan, Omni 4, International Instrumentation Laboratories, Inc, Durham, NC; UCL, Prototype NIR 1000 built at University College of London

Abbreviations. local, a prototype made in that laboratory; MbO₂, oxy-myoglobin, Hb, deoxyhemoglobin, HbO₂, oxyhemoglobin; Cytaa3, cytochrome aa3; CBF, cerebral blood flow (indocyanine green or microspheres), MTT, mean transit time (transit time of dye through cerebral circulation); tHb, total hemoglobin, SvO₂, venous oxygen saturation, V/D, variation in density (see text).

*Algorithm is provided in article

†All NIR0500 and 1000 instruments use same algorithm (see references 3, 4, 23-26)

‡Log (1/Td) obtained by subtracting log (1/Tdr), where Tdr is detected radiation, from log(1/Tdo); where Tdo was detected transmittance; plotted as a function of wavelength.

Table 2 Human Studies Using Near-Infrared Instruments

Author	Date	Type	Wave-lengths	Variables	Units	Subject	Model	Findings
Ferrari ⁷⁴	1986	Local	Not stated	Hb, HbO ₂ , tHb, -- Cyt _{aa} 3	Change from baseline	Healthy neo- nates	Monitor changes over time, tilt head down 15°	Changes can be detected
Wyatt ⁷³	1986	UCL	4 778, 813, 867, 904	Hb, HbO ₂ , tHb, Cyt _{aa} 3	μmol/100 g	11 neonates with various dis- ease states	Monitor over time, tilting	Report changes associated with patent ductus, brain edema, cystic encephalomalacia Changes in variables plotted against arterial HbO ₂
Hampson ⁷⁵	1990	Local	4. 775, 810, 870, 904	Hb, HbO ₂ , tHb, Cyt _{aa} 3	v/d, values obtained at 97% SpO ₂ were baseline	8 adult men	Progressive hypoxia in the presence of normo- capnia or graded hypo- capnia	Hypoxia results in steady decline in HbO ₂ and Cyt _{aa} 3, hypocapnic hypoxia causes greater decline than normocapnic hypoxia
Livera ⁷⁶	1990	Local	4 775, 805, 845, 904	Hb, HbO ₂ , tHb	mmol/L, change from base- line	Infants	Hypoxia 16 infants, 50 episodes Bradycardia 9 infants, 15 episodes	Decrease in arterial HbO ₂ corre- lates with decrease in brain HbO ₂ Bradycardia results in decrease in tHb
Edwards ⁷⁷	1991	NIR 1000	6 779, 802, 831, 848, 866, 907	Hb, HbO ₂ , tHb, Cyt _{aa} 3	μmol/L, reported as changes from base- line	8 preterm infants	Moderate changes in F _i O ₂ and carbon dioxide	Changes in SaO ₂ from 85%-99% do not cause changes in Cyt _{aa} 3 Changes in PaCO ₂ result in increases in Cyt _{aa} 3 and tHb
Liem ⁷⁸	1992	Radiometer	4 775, 805, 845, 904	Hb, HbO ₂ , tHb, Cyt _{aa} 3	μmol/100 g, change from base- line	5 infants	ECMO (extracorporeal membrane oxygenator)	HbO ₂ and Cyt _{aa} 3 increase with induction of ECMO, correlated with increases in SaO ₂ and tcPO ₂
Skov ⁷⁹	1992	Radiometer	4 775, 805, 845, 904	Hb, HbO ₂ , tHb, Cyt _{aa} 3	Change from baseline	10 asphyxiated neonates, 22 preterm with RDS	15° head down tilt	NIRS determined oxygenation cor- related with cerebral blood flow by xenon clearance in 19/33 infants
Faris ⁸⁰	1992	Local	4 775, 805, 845, 904	Hb, HbO ₂ , tHb, Cyt _{aa} 3	mmol/L, change from base- line	Preterm infants and fetal moni- toring during second stage of labor	Mild induced hypoxia, changes over time	Neonatal and fetal monitoring of cerebral oxygenation is possible with NIRS Changes in cerebral oxygenation correlate with changes in arterial oxygenation
van Bel ⁸¹	1993	Radiometer	4 775, 805, 845, 904	Hb, HbO ₂ , tHb, Cyt _{aa} 3	Change from baseline	8 healthy neo- nates, 15 asphyxiated neonates	Monitor over 24 hours	CBV, HbO ₂ , Cyt _{aa} 3 decreased in asphyxiated neonates, associ- ated with neurologic defects
Germon ⁵⁶	1994	Invos 3100	2 730, 810	rSO ₂	% saturation of Hb	Adult volunteers	Scalp ischemia, graded hypoxia, and frontalis muscle exercise	Invos can detect tissue hypoxia deep to scalp, but also is affected by changes in extracra- nial blood flow
Williams ⁸²	1994	Invos 3100	2 730, 810	rSO ₂	% saturation of Hb	Adults	Carotid endarterectomy	Changes in blood pressure are associated with changes in rSO ₂
Liem ⁸³	1994	Radiometer	3 904, 845, 775	Hb, HbO ₂ , tHb, Cyt _{aa} 3	μmol/100 g	Neonates	Indomethacin treatment for PDA	Indomethacin results in decrease in cerebral blood flow result- ing in decrease in cerebral tissue oxygenation
vandeBor ⁸⁴	1994	Radiometer	3 904, 845, 775	Hb, HbO ₂ , tHb, Cyt _{aa} 3	Change from baseline	Neonates	Exchange transfusion	Exchange transfusion results in change in cerebral blood volume
Aldrich ^{85, 86}	1994	NIRO 500	4 from 777-913	smcO ₂ , CBV	Change from baseline	Fetal (active labor)	1 Supplemental maternal oxygen 2 Compared with acid- base status	Maternal oxygen increases fetal smcO ₂ , fetal acid/base status correlates with smcO ₂ before birth
Peebles ⁸⁷	1994	NIRO 500, 1000	4-6 wave- lengths	smcO ₂ , CBV	Change from baseline	Fetal (active labor)	Contraction pattern	Rapid contractions (< 2.3 min) assoc with decrease in fetal cerebral oxygen saturation

NOTES. local, a prototype made in that laboratory, NIR-500, 1000, Hamamatsu Photonics KK, Japan; UCL, Prototype built at University College of London, Invos 3100, Somanetics, Troy, MI

Abbreviations MbO₂, oxy-myoglobin, Hb, deoxy-hemoglobin, HbO₂, oxyhemoglobin, CytA, cytochrome aa3, CBF, cerebral blood flow (indocyanine green or microspheres), CBV, cerebral blood volume, MTT, mean transit time (transit time of dye through cerebral circulation), rSO₂, intracerebral oxygen saturation (authors' abbreviation), smcO₂, mean cerebral oxygen saturation; SpO₂, pulse oximetry obtained arterial saturation; tHb, total hemoglobin, a measure of cerebral blood volume, RDS, respiratory distress, PDA, patent ductus

Table 3 Currently Available NIRS Instruments

Company	Instrument	Type	Parameters	Approval
INVOS 3100	Somanetics (Troy, MI)	Saturation	Hb saturation	Investigational use
NIRO500	Hamamatsu Corp (Bridgewater, NJ)	Concentration	Hb, HbO ₂ , Cytaa3, CBV	Investigational use
RedOx 2001	Critikon (UK) and Johnson & Johnson (Bridgewater, NJ)	Concentration	Hb, HbO ₂ , Cytaa3, CBV	Investigational use
Shimadzu OM-100A	Biorad Laboratories (Boston, MA)	Concentration	Hb, HbO ₂ , Cytaa3, CBV	Investigational use
Runman 2000	NIM Incorporated (Philadelphia, PA)	Concentration	Hb, HbO ₂ , CBV	Investigational use
Multiscan OS10	NIOS, GmbH (Wuppertal, Germany)	Concentration	Hb, HbO ₂ , Cytaa3, CBV	Investigational use

Abbreviations. Hb, deoxyhemoglobin, HbO₂, oxyhemoglobin; Cytaa3, oxidized cytochrome aa3; CBV, cerebral blood volume

transfusions, and during indomethacin treatment for patent ductus arteriosus.^{73,74,76-84} Reports exist of NIRS as a research tool in both adults and infants to study changes in cerebral oxygen utilization during periods of mental work,^{50,51,90} during transient hypoxia,⁷⁵ during cardiopulmonary bypass,^{91,92} and extracorporeal membrane oxygenation.⁷⁸

Tissue Saturation Instruments

The only saturation measuring instrument that is available commercially is the INVOS (Somanetics, Troy, MI). The modified Lambert-Beer equation that it uses is based on the assumption that "pathlength is not dependent on wavelength, ie, remains constant, over a narrow band of the near-infrared spectrum."⁹³ The original prototype instrument used five wavelengths of light delivered and detected two photodiodes originally placed 1 and 2.7 cm from the transmitter. In the commercial version of the instrument, the light source was replaced with two LEDs operating at 725 nm and 797 nm. By using two detectors, this instrument theoretically can differentiate signal changes caused by absorption in the scalp and skull, detected by the receiving diode at 1 cm, from absorption in the cerebral circulation, detected by the receiving diode at 2.7 cm.^{47,55} Early reports of interference from scalp blood flow led to an increase in the source-detector distances to 3 and 4 cm. However, Germon et al concluded from their data that, although the INVOS can detect cerebral hypoxia under controlled circumstances, changes in extracranial blood flow may still affect the reported cerebral saturation.⁵⁶

The INVOS matches predicted, theoretical decreases in cerebral saturation in volunteers breathing a hypoxic gas mixture.⁴⁷ Another study monitored the cerebral hemoglobin oxygen saturation during circulatory arrest at 18°C. The investigators found that the five patients in whom saturation remained above 35% had no demonstrable neurologic insult, whereas the one patient whose saturation decreased below 35% had evidence of a global hypoxic injury at postmortem examination.⁹⁴ Williams et al used the INVOS to monitor for cerebral oxygenation during carotid endarterectomy, reporting that "major changes in blood pressure are associated with significant changes in [cerebral oxygen

saturation]."⁸² However, Brown et al reported a poor correlation between INVOS-derived cerebral saturation and jugular bulb venous saturation in patients undergoing elective cardiac surgery.⁵⁷ Harris and Bailey report no change in INVOS-derived saturation despite a doubling of Doppler-determined middle cerebral artery velocity during hypercapnia.⁵⁸ These authors postulate that the larger source-detector separation used in the later model still does not guarantee sampling of only intracerebral saturation and that current monitors may be affected by external carotid blood flow to the scalp and skull.

Pollard et al studied the relationship between cerebral oxygenation as reported by the INVOS 3100 against that predicted by weighted averages of arterial saturation (pulse oximetry, arterial blood estimated to contribute 25% of the signal) and jugular venous saturation (jugular venous bulb samples, venous blood estimated to contribute 75% of the signal).⁹⁵ They found a decreased sensitivity but increased specificity with progressive hypoxia and also found that changes in patient position and PaCO₂ confound the relationship between reported cerebral saturation and estimated saturation.^{95,96} These authors conclude that because of the lack of a "gold standard" against which to validate this monitor, and because of the influence of position and PaCO₂, the INVOS at present serves best as a supplemental trend monitor.

SUMMARY

In conclusion, NIRS appears to offer both a new monitoring modality and new information about cerebral oxygenation. Technical problems in the application of this technology persist, most notably determination of pathlength and the volume of tissue interrogated. Those familiar with the history of pulse oximetry will recall that although Millikan developed an ear oximeter in 1947, it was not until Aoyagi combined recognition of the pulse signal with spectroscopy in the 1970s that oximetry was transformed into a clinically applicable monitor. In much the same way, NIRS may find the same tremendous usefulness as a noninvasive monitor of cerebral oxygen utilization, pending resolution of the remaining technical problems.

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