Near-infrared Measurement of Cerebral Oxygenation

Correlation with Electroencephalographic Ischemia during Ventricular Fibrillation

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Background: The application of phase-modulated near-infrared techniques for measurement of the oxygen saturation of cerebral tissue requires both validation by conventional measures of cerebral oxygenation and determination of normal and abnormal values. This study was undertaken to validate phase-modulated near-infrared measurements of cerebral oxygen saturation by comparing them with electroencephalographic evidence of cerebral ischemia during implantation of cardioverting defibrillators. This comparison also yields an estimate of the ischemic threshold as measured with near-infrared techniques.

Methods: Electroencephalograms and near-infrared measurements were performed during 85 episodes of ventricular fibrillation in ten patients. Light at 754, 785, and 816 nm was modulated at 200 MHz, transmitted through the skull, and the path lengths of the reflected light were determined by measuring the phase shifts. The electroencephalogram was inspected for changes during the hypotension associated with the arrhythmia and the oxygen saturation was calculated from the near-infrared path lengths. Changes in oxygen saturation were then compared with electroencephalographic evidence of cerebral ischemia.

Results: The mean saturation before fibrillation was 56.5% ± 1.2 (SEM). In 40 (47%) of the events, electroencephalographic evidence of ischemia was observed. Such changes were related to the minimum saturation observed during ventricular fibrillation (44% ± 2.5 vs. 56% ± 1.9 in the absence of electroencephalographic changes; P < 0.001). The ischemic threshold was estimated to be 47% saturation. The sensitivity of this technique was estimated to be 0.6, the specificity 0.84, and the predictive accuracy 0.73.

Conclusions: Near-infrared measurements reflect changes in cerebral oxygenation as indicated by electroencephalographic evidence of cerebral ischemia. (Key words: Brain; ischemia; Measurement techniques: electroencephalography; monitoring; near-infrared; oximetry.)

THE change in the near-infrared absorption spectrum of oxygenated hemoglobin as it undergoes desaturation is the physicochemical phenomenon underlying pulse oximetry. The development of similar techniques for the measurement of oxygen saturation in the microcirculation has been slowed by problems relating to the determination of the path length of light in highly scattering media. Measurements using very short (picosecond) bursts of light have validated the measurement of path length in tissue using continuous phase-modulated laser light,1,2 allowing the application of this less complex technique in the measurement of tissue oxygenation. Previous validation studies3 assumed that optical path lengths and hemoglobin concentration are constant during ischemic events, approximations that may not be accurate and may produce errors in the calculation of saturation. Validation of the algorithm by which the saturation is calculated from the optical signals is also necessary and problematic. Simulations and animal studies contain simplifications and differences in geometry that may influence tissue scattering and optical path. In humans, sampling of an intact in situ microvasculature bed is not possible, especially from the microvasculature of an important, highly metabolic organ like the brain. One way of circumventing the difficulty with direct tissue sampling is to compare a physiologic response to tissue desaturation with measurements made using the new optical technology. The electroencephalogram (EEG) provides such an independent physiologic signal in the cerebral cortex. Comparing electroencephalographic evidence of the cerebral ischemia (EEG) was undertaken with the following:

1. To validate the phase changes during ventricular fibrillation calculated from optical measurements of cerebral oxygenation documented during ventricular fibrillation.
2. To determine the level of oxygen saturation at which a change is expected to appear in the electroencephalogram.

Materials and Methods

Ten patients undergoing emergency cardioversion for the basis of ventricular fibrillation were enrolled. After obtaining informed consent, each patient received two intravenous doses of 0.5 mg/kg of lidocaine followed by 0.15 mg/kg of atropine. Anesthesia was induced with propofol, if necessary, and maintained with nitrous oxide and oxygen. Anesthesia was not considered deep, and laryngoscopy was not performed. No patient required negative pressure ventilation. After intubation, patients were ventilated with 100% oxygen. Ventricular fibrillation was induced by electrical stimulation. After each episode, the electroencephalogram was recorded for 3 min. In all patients, the duration of ventricular fibrillation averaged 6.5 ± 1.2 min. Four of the patients were premedicated with phenobarbital and atropine. The mean age of the patients was 61.5 ± 14.5 years. The mean body mass index (BMI) was 27.9 ± 3.5, and the mean systolic blood pressure was 128 ± 20 mm Hg. The mean heart rate at the time of fibrillation was 130 ± 20 beats/min. All patients were monitored with electroencephalography, oxygen saturation, and noninvasive arterial pressure. The electroencephalograms were recorded with a commercial machine (Neuropen N-1000, Neuropen Systems, Inc., Natick, MA). EEG data were recorded continuously at a frequency of 512 Hz and converted to the frequency domain with a 20-Hz filter using a custom-developed program in Systat software (Systat Inc., Evanston, IL). The presence of ventricular fibrillation was confirmed with the electrocardiogram. The duration of ventricular fibrillation was 6.5 ± 1.2 min.
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Fig. 1. Block diagram of near-infrared measurement system. Optical path length was measured using the frequency-encoded phase-modulation system shown above. Laser diodes at each wavelength are driven by separate oscillators and illuminate the subject by light guides. Optical pickup is carried by light guide to a photomultiplier for amplification and subsequent decoding. Individual phase detectors then measure the shift between input and output signals. (Courtesy of NIM, Inc., Philadelphia, PA)

such an independent physiologic response to desaturation in the cerebral cortex. Therefore, this study comparing electroencephalographic and optical assessment of the cerebral tissue oxygen saturation ($S_{O_2}$) was undertaken with the following two objectives:

1. To validate the phase-modulated technology by demonstrating a correlation between saturation calculated from optical measurements and cerebral ischemia documented by electroencephalography during ventricular fibrillation.
2. To determine the level of tissue saturation that represents the ischemic threshold of cerebral tissue.

Materials and Methods

Ten patients undergoing implantation and testing of internal cardioverting defibrillators were recruited on the basis of willingness, as well as availability of equipment and personnel. All but one of the patients were male, with a mean age of 68 yr. All had cardiac disease, with six having undergone recent (3) or distant (3) bypass grafting. Informed consent was obtained and the protocol was approved by the Institutional Review Board. Clinical monitoring included intraarterial pressure, end-tidal CO$_2$, pulse oximetry, electrocardiogram, central venous pressure, pulmonary artery pressure if clinically indicated, and nasopharyngeal temperature. Electroencephalograms were recorded from a 4-channel bipolar montage: F$_{p1}$-C$_3$, C$_1$-O$_1$, F$_p$-C$_4$, C$_2$-O$_2$. Anesthesia was not controlled by protocol, but all patients received isoflurane, with or without nitrous oxide and muscle relaxants. Anesthetic induction agents included thiopental (6), etomidate (3), and propofol (1). One patient received no opioids, eight received less than 3 µg/kg of fentanyl, and one subject received 6 µg/kg of fentanyl. The probes were placed over the left side of the forehead at the hairline and separated by 3.5–4 cm depending on anatomic considerations and the adequacy of the optical signal. In all cases, a line connecting the probes intersected a line connecting the F$_p$-C$_4$, EEG electrodes.

Path length measurements were made at 754, 785, and 816 nm using an experimental phase-modulated spectrophotometer, shown schematically in figure 1. This unit generates light whose amplitude oscillates at 200 MHz. After it is conducted fiberoptically to the patient, the light enters the tissues, where it scatters repeatedly. Eventually, some of the light scatters to the receiver optode where it is conducted back to the spectrophotometer. Throughout the scattering process, the light maintains its phasic amplitude oscillation so

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that the light being received has a phasic oscillation. After amplification, the phase of the returning signal can be compared with that of the initial signal. Because the speed of light in tissue is known (about $2.3 \times 10^{10}$ cm/sec), each cycle (360°) is 115 cm in length and thus, the light travels about 3.2 mm for every degree of phase delay. By measuring the phase shift of the returning light, the length of the average optical path can be determined. Because the spectrophotometer gain can vary from study to study, the quantitative relationship between phase-shift and path length was calibrated at the completion of each study using an adjustable optical bench.

Electroencephalograms, optical measurements, and all clinical monitors except venous and pulmonary arterial pressure were digitized at 128 Hz and stored for subsequent analysis on a Hewlett-Packard model 382 work station. The EEG was examined both in raw and power spectral forms (color-enhanced density spectral array, DSA) to determine the occurrence of change during ventricular fibrillation. Because of electrical artifact from the defibrillator discharge, only EEG change before the defibrillation could be evaluated reliably. As we have done previously, determination of change was done by visual inspection of EEG by a single skilled observer with reference to the EEG and blood pressure but without reference to the optical signals. If either the analog or DSA display demonstrated a change in the EEG, the event was considered ischemic. Because of the brief duration of the fibrillatory events, neither statistical confirmation of EEG change nor quantitation of the magnitude of change was possible.

Digital filtering was performed to minimize noise. Hemoglobin saturation is related to the path length of 754, 785, and 816 nm light ($L_754$, $L_785$, $L_816$, respectively) by the equation:

\[ S = \frac{182L_{785} - 268L_{754} - 134L_{816}}{268L_{785} - 87L_{754} - 181L_{816}} \]

which is derived in the Appendix. Unless otherwise specified, intergroup comparisons were performed using a t test and correlations were assessed by linear regression.

**Results**

Data were obtained during 85 episodes of ventricular fibrillation. The number of episodes per patient varied from 5 to 15, depending on the testing required to ensure function of the internal cardioverting defibrillator. Electroencephalographic changes suggestive of cerebral ischemia ("ischemic events") were identified in 40 (47%) of the 85 episodes of ventricular fibrillation. Two subjects showed EEG changes with every event, two showed no EEG changes with any event, and the remaining 6 showed EEG changes with some, but not all, events. Part of a typical study is shown in figure 2. This figure shows data obtained during three hypotensive episodes, the first of which shows less desaturation than the subsequent ones, due in large part to the continued pulsatile flow that resulted from the failure to induce ventricular fibrillation. This episode would not be considered as an event, ischemic or otherwise, because ventricular fibrillation was not induced. The other two hypotensive episodes contained fibrillatory events, the first of which terminated spontaneously whereas the second required defibrillation. Panel B shows an expanded display of the middle hypotensive episode and exemplifies the analog EEG changes (slowing and increased amplitude) as well as the measurement noise (variability) in the optical path lengths typically seen during these studies.

Ischemic events were different from nonischemic events in a number of ways. Although the mean baseline saturation for all events was 56.5% ± 1.2% (SEM), those events that subsequently became ischemic began at statistically lower values (53% vs 60%, $P < 0.005$). Greater changes in saturation occurred (8.6% vs 3.9%, $P < 0.001$), and consequently, the mean minimum saturation measured during the ischemic events was 44% ± 2.5%, compared with 56% ± 1.9% during nonischemic events ($P < 0.001$). Ischemic events were also of longer duration, 18.75 ± 1.7, compared to 12.38 ± 1.2 ($P < 0.005$) and demonstrated a more rapid desaturation, 0.6%/sec ± 0.09, compared with 0.4%/sec ± 0.06 ($P < 0.005$). Because the events were shorter than those reported in previous studies,3 reperfusion hyperoxia was not observed. The incidence of ischemic events was correlated with decreasing calculated tissue saturation ($P < 0.001$ by chi-squared analysis), as shown in figure 3. Neither ventilation nor ETCO$_2$ were controlled by protocol, however, a weak association was observed between the baseline saturation before an arrest and the pCO$_2$, ($r = 0.266$, $P < 0.02$).

Discriminant analysis based on the lowest measured saturation yielded a threshold value of 47% saturation. Using this value, it is possible to compare the detection of ischemia by near-infrared measurement to its detection by the EEG (table 1). The sensitivity is estimated

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Fig. 2. Typical Event. (A) A trended display of three hypotensive events during a study. The electroencephalogram (EEG) is recorded from Fp1-C3 and displayed in a density-modulated spectral array with 2-s epochs and 0.5 Hz resolution. Blood pressure is shown as the highest/lowest value occurring in a 2-s epoch. Tissue saturation is calculated from the three path lengths using the algorithm described in the text. The minor EEG changes associated with the first event are not diagnostic of ischemia, although those associated with the next two events are. The EEG in the final event shows a defibrillation artifact occurring at the end of the period of hypotension. Tissue saturation changes are minimal during the first event and more prominent during the next two. (B) An expanded representation of the middle hypotensive episode from (A). Electroencephalogram and blood pressure are now shown in analog form, and ECG has been added. Measurement noise (variation in path length) is more clearly evident and saturation changes are harder to appreciate than in the more trended display.

Discussion

Near-infrared Technology

There are three different technologies that use near-infrared light to estimate the hemoglobin saturation in the cerebral vasculature. All share certain properties, e.g., type of blood vessel from which the signal is derived, but differ markedly in a number of other ways, including fundamental assumptions about light propagation in tissues and measurement techniques. These differences must be understood to interpret differences between this work and others.

The simplest approach to the measurement of tissue oxygen saturation uses incoherent (nonlaser) light at two or more wavelengths. The number of wavelengths varies from 2 to 6, depending on the type of device, the number and nature of the assumptions used in calculating the saturation, and the use of empiric or “first-principle” equations. Pulse oximetry exemplifies the calculation of oxygen saturation using only two wavelengths and equations derived empirically. If first-principle equations are used, two wavelengths are insufficient to allow calculation of saturation, only relative change in saturation from a baseline may be computed. This approach has been used by Kurth et al.5 and by us,3 and has been accepted as a reflection of cerebral oxygenation under specific, rather limited conditions. To overcome some of these limitations, our previous work3 used two dual-wavelength devices and compared the patterns of desaturation to demonstrate that brain desaturation was observed by this technique. Quantitative...
cur as a result of changes in either scattering or absorption, making it impossible to separate these two effects with incoherent technologies. This, and other technical problems with these approaches, limits their usefulness and has stimulated work in coherent (laser) techniques, which permit separation of the effects of scattering and absorber.

Laser near-infrared technologies fall into one of two approaches, pulsed or phase-modulated. The pulsed approach uses very short bursts of light whose transmission is sensed by sensitive detectors. With repetitive pulses (up to a million per s) the average light transmission curve may be computed, a process known as time-resolved spectroscopy. The technical difficulties of applying this approach in an overly bright operating room appeared to be a major drawback, so we have emphasized the use of phase-modulation techniques. These possess less sensitivity to ambient light because the desired signal is easily identified by its radio frequency oscillations. Phase-modulation has been shown to be mathematically equivalent to pulsed laser light.

Source of the Signal
Considerable effort has been expended to demonstrate the location of the hemoglobin that is absorbing the light being measured with near-infrared techniques. Both physical and anatomic factors play important roles. Physical factors include questions of depth of penetration of the light, influence of overlying bone or other types of tissue differences, and the effect of probe positioning and separation. Anatomic factors relate to the size and type of blood vessels contributing to the signal.

Physical issues have been investigated by both theoretical and experimental techniques. Simulation of photon scattering in homogeneous media demonstrate that most photons reaching the receiver traverse a back

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**Table 1. Ischemia Detection: NIR Versus EEG**

<table>
<thead>
<tr>
<th>EEG Ischemia</th>
<th>Present</th>
<th>Absent</th>
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<tbody>
<tr>
<td>Present</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Absent</td>
<td>7</td>
<td>38</td>
</tr>
</tbody>
</table>

NIR = near-infrared, EEG = electroencephalogram.

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The depth of penetration below the skin is related to the curvature of the structure (model or skull) and the separation of the probes. Some aspects of the simulation have been validated by in vivo and in vitro models. Gopinath et al. 12 have shown that subarachnoid blood can be detected as asymmetrical optical absorbance. Harris et al. 15 examined the relative magnitude of an optical signal due to indocyanine green injections into the internal or external carotid artery and demonstrated deeper penetration of the skull as optode separation increased. Nevertheless, the optimum placement of optodes has not been determined.

Determining the size and type of blood vessels contributing to the optical signal is even more difficult, because physical or mathematical models of the microcirculation are, of necessity, simplifications. Morphometric analysis of the cerebral vasculature suggests that capillaries make up about 1.5% of the volume of the cerebral cortex, 14 which has a blood volume of 4.3%. Thus, at least one third of the signal should be derived from capillaries. The contribution of venous blood predominates in the remainder of the signal because the small veins are both more numerous and more voluminous than the arterioles. Unlike arteries and veins, capillaries do not contain hemoglobin at uniform oxygen saturation. As a result of oxygen extraction by the tissues, there is an oxygen gradient, with higher oxygen saturation at one end of the capillary than the other. Hematocrit also changes from macrovasculature to microvasculature. The optical signal is a weighted average of the hemoglobin saturation and concentration in all of the vessels illuminated, precluding identification of an equivalent sampling site from which reference values may be obtained. Previous work 9 has used a weighted average of arterial and venous saturations as an estimate of the capillary saturation but data validating this relationship are unpublished. Thus, unlike pulse or venous oximetry that can use empiric relationships, algorithms for computation of tissue oxygen saturation from near-infrared measurements must be developed from first principles and tested using in vivo preparations.

Experimental Model

The experimental model is that of acute global ischemia induced by cardiac arrhythmias. Previous work has demonstrated that the EEG changes observed with this technique occur in a time course similar to that seen with complete vascular occlusion. The time to EEG change with this model is also similar to that seen in potassium chloride-arrested rats. Examination of blood flow velocity during the induction of ventricular fibrillation (unpublished data) suggests that cerebral blood flow velocity decreases linearly with blood pressure reaching negligible values after about 5 s. The simultaneous measurement of transcranial Doppler flow velocity was not technically feasible in the patients in this study who were already monitored with EEG, optical, and invasive technologies.

The fibrillatory model includes several advantages over alternative hypoxic or ischemic models. When EEG change is induced by hypoxemia, the saturation in the overlying bone and soft tissue also declines. As a result, the demonstration of a change in saturation by near-infrared is not proof that the optical signal is derived from neurologic structures. Only if the bone and soft tissues were maintained in a normoxic state could one infer that a reduction in near-infrared-derived saturation reflects the underlying cerebral hypoxia. We have not measured the oxygen saturation in the overlying tissues, but believe the desaturation to be limited because of the short duration of ischemia and the slower desaturation demonstrated by similar types of tissues in the forearm during tourniquet ischemia. Thus, the fibrillatory model provides the benefit of normoxia of the overlying tissues in a simpler, clinically available paradigm.

Vascular interruption, e.g., carotid occlusion, provides an alternative clinical scenario in which the overlying tissues are maintained in the normoxic state. This model suffers from the variability of the ischemia induced by the vascular occlusion. Only 15–25% of subjects show EEG change with test occlusion of the carotid artery, and in these, both the area of EEG abnormality and the magnitude of the changes differ among patients. This regional and interpatient variability makes it difficult to ensure that the near-infrared light is passing through uniformly ischemic tissue. Thus, the measured saturation during carotid occlusion

<table>
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<th>NIR Ischemia</th>
<th>Absent</th>
<th>16</th>
<th>30</th>
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<td>Anesthesiology, V 83, No 4, Oct 1995</td>
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might be less representative of the ischemic threshold than that obtained with the fibrillatory model.

One potential disadvantage of the fibrillatory model is uncertainty about the role of oxygen diffusion rates. There is a continuous oxygen gradient from the capillary wall (about 50 mmHg at the arterial end) to the mitochondria (about 1 mmHg) and a finite period must elapse for the diffusion of the oxygen from blood into the tissues. Measurement of diffusion transients yields values of sufficient length (2–20 s) compared to the duration of fibrillatory events that changes in tissue oxygen tension may not be reflected in the capillary saturation. Such a situation would erroneously elevate the value determined to be the ischemic threshold and might reduce the predictive accuracy of the results.

Anesthetic technique was not standardized because of the variation of the severity of cardiac disease. This lack of anesthetic standardization is unlikely to modify the results because most of the subjects received similar agents, and supplemental medications were given in small doses. The EEG effect of the induction drugs would be minimal after the 30–40 min delay between induction and defibrillation. Also, in rats, the time to electrical silence during potassium chloride-induced arrest is not affected by the use of halothane or isoflu- rane, suggesting that the more modest differences in technique among these subjects did not influence the results. Nor are regional differences in the time to EEG change (if any exist) an issue, because the EEG analyzed was always recorded in proximity to the optical probes.

Saturation and Validation

The algorithm used in this study was developed from the work of Sevick, which showed that the saturation may be calculated from the ratio of the absorptive shortening of the path lengths (see Appendix equations A5 and A7). This solution requires an independent estimate of the path length in the absence of any absorber, but work by Smith et al. has shown that tissue scattering, which is the primary determinant of the absorber-free path length varies from individual to individual. The simplest theoretical solution is to measure three wavelengths of light and solve two equations simultaneously (see Appendix for details).

The average baseline saturation of 56.5% was slightly lower than the value of 60% that is quoted as the normal jugular bulb saturation, and significantly lower than the 73% we have published for normal awake persons. Part of this discrepancy may arise from the hyperventilation of these patients, which would be expected to decrease cerebral blood flow and increase oxygen extraction. It is also possible that these patients, all of whom had significant cardiac disease may have had lower than normal cerebral blood flows as a compensatory response to their chronic reduction in cardiac output. Alternatively, the cerebral vasculature of this population of patients aged 60–80 yr may differ somewhat from that of the healthy young adults who typically make up study populations.

The ischemic threshold of 47% compares well with the cerebral blood flow data of Cohen et al., in which 2 of 7 volunteers showed EEG changes during hypoxemia that reduced S_O2 to 63% and P_O2 to 44%. In patients undergoing carotid endarterectomy, venous saturations less than 50% have been associated with transient neurologic defects, further supporting the reasonableness of the observed threshold value. Others have reported somewhat lower threshold values.

It is also interesting to compare the rate of desaturation we observed with the rate measured by Kurth et al. in children undergoing hypothermic circulatory arrest. During the first 20 min of hypothermic circulatory arrest, absorbance changes were linear and corresponded to a change in saturation of about 0.05%/sec. Cerebral metabolic demands at 37°C are about ten times those at 18°C, so applying these data to normothermic adults would suggest desaturation should be observed at a rate of about 0.5%/sec. This value is strikingly similar to the rate of desaturation for the study population (0.48%/sec).

The observation that a statistically significant relationship existed between end-tidal CO2 and measured saturation is not surprising, and further supports a cerebral origin for the signal. Cerebral blood flow is reduced about 1 mL 100 g^-1·min^-1 for a 1 mmHg reduction in P_CO2, and this would be expected to produce a reduction of 0.7–1.0% saturation in jugular venous blood. The reduction in near-infrared saturation is likely to be nearly as great. The average reduction in our population, 0.99% saturation per mmHg is larger than might be expected; however, the cardiovascular effects of hyperventilation may have played a role as well. More careful studies using a strict anesthetic protocol and measuring arterial CO2 are indicated to validate this observation.

Ideally, a monitor provides early warning, high sensitivity, and specificity. Pulse oximetry is a good example of early warning, because even after the saturation begins to decrease, harmful levels are not reached immediately. By comparison, the baseline tissue saturation was much lower.
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...and increase oxygen cost of these patients, all of whom have hypoxic disease may have had blood flow as a consequence of the cerebral vascular resistance in cerebral vasculature of the mesencephalon-80 yr may differ somewhat from young adults who typi-

...of the EEG as a standard. Certainly all patients with an active EEG will show changes if profound ischemia is present for a sufficiently long time. However, the very transient nature of the events studied produced less profound ischemia and possibly less uniform ischemia, both of which may affect the accuracy of the EEG in detecting ischemia. The need to restrict EEG analysis to segments before discharge of the defibrillator may also reduce the accuracy of ischemia detection by EEG; and, as has been shown previously, any error in the reference technique (i.e., EEG) increases the error attributed to the experimental technique. Although some loss of accuracy may be attributable to EEG errors, a larger source is related to measurement error and the computational algorithm. The equipment used in this study is capable of measuring optical pathlength to less than 1% error (5 mm in a 50 cm optical path). Unfortunately, the equation for saturation involves the ratio of differences, a formula that amplifies the effect of measurement error. Improvements in equipment design offer substantial potential to reduce this error and increase the basic accuracy of the measurement. Based on the mean baseline and ischemic saturations, an accuracy of ±5% in saturation measurement seems mandatory. Although this is the accuracy quoted for current pulse oximetry equipment, further development is needed for the measurement of tissue saturation so accurately. Further development is also needed to provide integral calibration. The use of an optical bench for calibration after the completion of all measurements is incompatible with real-time monitoring.

In summary, we have demonstrated that the optical signal recorded over the forehead using phase-modulated near-infrared laser light is strongly influenced by the state of cerebral oxygenation. Tissue hemoglobin saturation, as determined by these path length measurements, correlates well with evidence of cerebral ischemia by EEG.

References


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Appendix

The absorption coefficient ($\mu_4$) of the Beer-Lambert relationship for hemoglobin may be written:

$$\mu_4 = \epsilon_{\text{Hb}}(\text{Hb}) + \epsilon_{\text{O2Hb}}(\text{HbO}_2).$$  \hspace{1cm} (A1)

where $\epsilon$ is the extinction coefficient for the reduced (Hb) and oxygenated (HbO$_2$) forms, and the square brackets signify the concentration of the enclosed species. Because the saturation, $S$, is given by the relationship

$$S = \frac{[\text{HbO}_2]}{[\text{Hb}]+[\text{HbO}_2]},$$  \hspace{1cm} (A2)

equation A1 may be rewritten

$$\mu_4 = \epsilon_{\text{Hb}}\text{e} \mu_{\text{Hb}} + \epsilon_{\text{O2Hb}}\text{e} \mu_{\text{HbO2}},$$  \hspace{1cm} (A3)

where $\epsilon_2$ is the difference between the extinction coefficients of the oxygenated and reduced forms. Equations of this form may be written for each wavelength ($\lambda$), and pairs of equations divided by to yield:

$$
\frac{\mu_{\lambda 1}}{\mu_{\lambda 2}} = \frac{\epsilon_{\lambda 1} + S\epsilon_{\lambda 2}}{\epsilon_{\lambda 2} + S\epsilon_{\lambda 1}}.
\hspace{1cm} (A4)
$$

Rearranging yields

$$S = \frac{\epsilon_{\lambda 2} - \epsilon_{\lambda 1}}{\mu_{\lambda 2} - \mu_{\lambda 1}}.$$

Similarly,

$$S = \frac{\epsilon_{\lambda 1} - \epsilon_{\lambda 2}}{\mu_{\lambda 1} - \mu_{\lambda 2}}.$$

Table A1. Molar Extinction Coefficients

<table>
<thead>
<tr>
<th>$\lambda$</th>
<th>$\epsilon_{\lambda 1}$</th>
<th>$\epsilon_{\lambda 2}$</th>
<th>$\mu_{\lambda 1}$</th>
<th>$\mu_{\lambda 2}$</th>
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<td>754</td>
<td>368</td>
<td>132</td>
<td>785</td>
<td>234</td>
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<tr>
<td>816</td>
<td>186</td>
<td>218</td>
<td>816</td>
<td>186</td>
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</table>

Because Sevick et al.\textsuperscript{2} has shown that

$$\frac{\mu_{\lambda 1}}{\mu_{\lambda 2}} = \frac{I_{\lambda 1}}{I_{\lambda 2} - I_{\lambda 2}} = \frac{\epsilon_{\lambda 1}}{\epsilon_{\lambda 2} - \epsilon_{\lambda 2}}.$$  \hspace{1cm} (A7)

where $I_0$ is the path length in the absence of absorption, equations A5, A6, and A7 may be combined as

$$\frac{\epsilon_{\lambda 1}}{\epsilon_{\lambda 2} - \epsilon_{\lambda 2}} = \frac{I_{\lambda 1}}{I_{\lambda 2} - I_{\lambda 2}}.$$  \hspace{1cm} (A8)

Rearranging yields an estimate of $I_0$ based on the three wavelengths $\lambda_1$, $\lambda_2$, and $\lambda_3$:

$$I_0 = \frac{\epsilon_{\lambda 1} \epsilon_{\lambda 2} + \epsilon_{\lambda 2} \epsilon_{\lambda 3} + \epsilon_{\lambda 3} \epsilon_{\lambda 1}}{\epsilon_{\lambda 1} + \epsilon_{\lambda 2} + \epsilon_{\lambda 3}}.$$  \hspace{1cm} (A9)

Note that the denominator is a constant, based only on the wavelengths of the light, as are each of the parenthesized terms of the numerator. In Table A1, the values for $\mu$ at 754, 785, and 816 nm wavelengths are given in units of $1 \cdot \text{mmol}^{-1} \cdot \text{cm}^{-1}$. Equation A9 reduces to

$$I_0 = 18.74 \mu_{\lambda 1} - 5.97 \mu_{\lambda 2} - 11.78 \mu_{\lambda 3}.$$  \hspace{1cm} (A10)

Saturation can then be derived by using equations A6 and A7. To compute saturation directly from the measured path lengths, equation A1 for all wavelengths are combined:

$$\frac{\mu_{\lambda 1} - \mu_{\lambda 2}}{\mu_{\lambda 2} - \mu_{\lambda 3}} = \frac{[\text{Hb}]\epsilon_{\lambda 1} - \epsilon_{\lambda 2} - S[\text{Hb}]\epsilon_{\lambda 2} + S[\text{HbO}_2]\epsilon_{\lambda 2}}{[\text{Hb}]\epsilon_{\lambda 2} - \epsilon_{\lambda 3} - S[\text{Hb}]\epsilon_{\lambda 3} + S[\text{HbO}_2]\epsilon_{\lambda 3}}.$$  \hspace{1cm} (A11)

Because Sevick et al.\textsuperscript{2} has shown that

$$\mu_4 = \frac{4\pi r_0^2}{c^2} \int_0^d \frac{I_0 - I_1}{I_0 - I_2}.$$  \hspace{1cm} (A12)

the left side of equation A11 reduces to wavelength-specific path lengths, and rearranging the right simplifies it, yielding

$$\ln \left( \frac{\lambda_1 - \lambda_2}{\lambda_2 - \lambda_3} \right)$$

$$\mu_{\lambda 1} - \mu_{\lambda 2} = \epsilon_{\lambda 1} - \epsilon_{\lambda 2} + S(\epsilon_{\lambda 2} - \epsilon_{\lambda 3}).$$  \hspace{1cm} (A13)

Rearranging for $S$ yields:

$$S = \frac{L(\epsilon_{\lambda 1} - \epsilon_{\lambda 2}) + L(\epsilon_{\lambda 2} - \epsilon_{\lambda 3}) + L(\epsilon_{\lambda 3} - \epsilon_{\lambda 1})}{L(\epsilon_{\lambda 2} - \epsilon_{\lambda 3})}.$$  \hspace{1cm} (A14)

Using the values in Table A1 this reduces to

$$S = 182L_{\lambda 1} + 48L_{\lambda 2} + 134L_{\lambda 3}.$$  \hspace{1cm} (A15)

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