Regional Cerebrovascular Oxygen Saturation Measured by Optical Spectroscopy in Humans

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Regional cerebrovascular oxygen saturation, a quantitative measure of hemoglobin saturation in the combined arterial, venous, and microcirculatory compartments of the brain, can be measured noninvasively with near infrared spectroscopy. We assessed the sensitivity of this aggregate saturation to cerebral hypoxia during transient cerebral hypoxic hypoxia in seven human subjects. Regional cerebrovascular oxygen saturation measured over the middle frontal gyrus and analog electroencephalogram were recorded. We compared the time to achieve two end points: the earliest paroxysmal burst of theta–delta background slowing and a cerebrovascular oxygen saturation of <55%. Saturation fell below 55% prior to the electroencephalographic change (p<0.05). In a related effort, we also compared spectroscopically measured regional cerebrovascular oxygen saturation with an estimate of this value calculated from arterial and cerebral mixed venous saturation in nine patients. A positive linear relation (n=68, R^2=0.55, s=4.2) was noted. (Stroke 1991;22:596–602)

Organometallic molecules such as hemoglobin have characteristic infrared absorption spectra that shift with oxygenation and thereby permit the identification of oxygenated and deoxygenated molecules with spectroscopy.1 Near infrared light (650–1,100 nm) can penetrate the human head several centimeters, and the human brain contains 600–1,000 mg hemoglobin/100 g tissue. The brain is, therefore, an excellent organ for in vivo infrared spectroscopic measurements of hemoglobin and oxyhemoglobin.2–4 These measurements may allow the direct evaluation of oxygen transport and delivery to the brain, as initially recognized by Jobsis in 1977.4

In vivo optical spectroscopy can measure mixed oxyhemoglobin/hemoglobin transmission spectra from the exposed and unexposed brain of animals and neonates.5–14 These spectra can be reduced to a qualitative measure of cerebral oxygen content by referencing transmission intensity at select wavelengths to baseline intensity. Such paradigms are intended to track alterations in cerebral oxyhemoglobin concentration over time.

A quantitative measure of intracerebral, intravascular oxyhemoglobin content is of possible clinical significance, but the derivation of oxyhemoglobin content from transmission spectra requires knowing the distance that photons travel in the tissue (photon tissue path length).2 Photon tissue path length has been estimated from theoretical calculations or the attenuation of wavelengths sensitive to water, but these estimates have not been applied clinically with success.3,15 Time-resolved spectroscopy has also been suggested as a method for measuring photon tissue path length in situ to allow a quantitative measure of cerebral oxyhemoglobin content.2,16 However, the complex hardware involved in this technique is not yet suitable for clinical application.

Hoffman and Lübbers17 have described the feasibility of quantitative infrared spectroscopic measurements based on content ratios. The variable path length drops from the calculation. When applied to intravascular hemoglobin and oxyhemoglobin, this approach generates a quantitative, clinically meaningful parameter—hemoglobin oxygen saturation.

Cranial hemoglobin spectra reflect an aggregate of hemoglobin and oxyhemoglobin regardless of compartmentalization (i.e., arterial, venous, and capillary). Failure to consider compartmental influences on observed cranial transmission spectra has made the clinical application and interpretation of human qualitative and quantitative optical spectroscopic measurements difficult.9,10,12,13 No in vivo paradigm of infrared hemoglobin spectroscopy, qualitative or quantitative, has been demonstrated to correlate with a reference measurement of cerebral hemoglobin oxygen saturation in humans, nor has the sensitivity of any paradigm
been compared with an established measurement such as analog electroencephalogram (EEG).

We describe the correlation between an infrared spectroscopic measurement of aggregate cerebrovascular oxygen saturation (arterial, venous, and capillary) and a reference measurement in adult humans. The responsiveness of this spectroscopic measurement was compared with analog EEG activity during cerebral hypoxia.

Subjects and Methods

Cerebral infrared optical spectroscopy was performed by generating narrow (10–20 nm) bands of infrared light at five wavelengths: 672, 726, 750, 803, and 840 nm (INVOS 2910, Somanetics, Troy, Mich.). The intensity of each band was characterized by appropriate photodiodes. The light was passed through fiber-optic light guides to a patient-interface probe.

The patient-interface probe was an opaque hard plastic base affixed to the scalp with standard adhesives. The probe was designed to hold incident light bundles orthogonal to the skull. The incident light bundle created a 0.5-mm-diameter point source. A short receiving fiber-optic bundle affixed 27 mm from the source fed directly to the photodiode array to measure transmission intensity. Signal noise was monitored continuously, with data flagging at a signal-to-noise ratio of <30:1.

Computer modeling has demonstrated that infrared photons, diffusely transmitted from a point source on the scalp to receivers at various distances, travel along variable high-probability photon paths.2–16 These models fit with observed time-resolved photon kinetics.19,20 As the source-to-receiver distance increases, the photon path length increases and photons that spend more time deep in the tissue tend to emerge farther from the source.18 These photons spend a relatively longer time in cerebral (deep) than in scalp (superficial) tissue. This characteristic allows the selection of a source–receiver configuration that is spatially "focused" to emphasize absorption events in cerebral tissue. The 27 mm source-to-receiver distance used here describes cortical penetration of approximately 12 mm.21

The transmission intensity and incident intensity at each wavelength are processed through an algorithm based on the Beer-Lambert law

\[-\ln \frac{I_w}{I_{w_0}} = \Sigma \chi_j \beta_{w_j} \frac{C_j}{s}\]

where \(I_w\) is the intensity of transmitted light at wavelength \(w\), \(I_{w_0}\) is the intensity of the incident light at wavelength \(w\), \(\alpha\) is the molar extinction coefficient of oxyhemoglobin or hemoglobin, \(C\) is the concentration of this molecule in the tissue, and \(s\) is the photon path length in the tissue.

If absorption at a second wavelength, \(w\), is subtracted from the absorption at \(w\), the following expression is derived:

\[-\ln \frac{I_w}{I_{w_0}} + \ln \frac{I_{w}}{I_{w_0}} = \Sigma \chi_j \beta_{w_j} \left(\alpha_{w_j} - \alpha_{w}\right) C_j \frac{s}{s}\]

This expression is solved by making enough \((N+1)\) measurements to solve for \(C_j\) for oxyhemoglobin and \(C_S\) for deoxyhemoglobin. These values do not represent the actual chromophore concentrations but are proportional to them. Although a function of hemoglobin concentration, \(s\) is considered invariant for wavelengths over the 600–1,000 nm range.22 Thus, the effects of an unknown photon path length and the variable total hemoglobin concentration can be removed by expressing the solutions of Equation 2 as the ratio:

\[C_S/C_S\frac{C_S}{C_I} = H_r\]

where \(H_r\) is the ratio of the deoxyhemoglobin concentration \([Hb]\) to the oxyhemoglobin concentration \([HbO_2]\), which is converted to percentage hemoglobin oxygen saturation as

\[100/(1+H_r) = 100 \times [HbO_2]/([Hb]+[HbO_2]) = \%\ saturation\]

The two experimental protocols used to evaluate this approach were reviewed and approved by the Henry Ford Hospital Human Rights in Experimentation Committee.

Under the first protocol, nine critically ill patients in the neurologic intensive care unit with presumed abnormal cerebral oxygen delivery and an abnormal or fluctuating level of consciousness were studied. Such patients are routinely treated with indwelling arterial catheters and percutaneous jugular bulb cannulation on our service.23 The validity of jugular bulb cannulation as a source of mixed cerebral venous blood has been established.23,24 In all patients the jugular bulb catheter position was confirmed by radiography.

Each patient underwent several noninvasive spectroscopic measurements over the middle frontal gyrus during their stay in the intensive care unit. Samples of arterial and cerebral mixed venous blood were slowly drawn (1.0 ml over 45 seconds) while spectroscopic measurements were made. Blood samples were immediately placed on ice and analyzed for hemoglobin oxygen saturation on an IL 282 CO-Oximeter (Instrumentation Laboratories Inc., Lexington, Mass.) ≤5 minutes after being drawn.

A total of 68 spectroscopic measurements were made on the nine patients. Because the instantaneous arterial and venous blood volume of the middle frontal gyrus was unknown, published data on relative regional arterial and venous cerebral blood volume were used to estimate regional cerebrovascular oxygen saturation25,26 as

\[\text{Estimated saturation} = x(SaO_2) + (1-x)(SvO_2)\]

where \(x\) is the percentage of regional cerebral blood volume that is arterial, \(SaO_2\) is the systemic arterial oxygen saturation, and \(SvO_2\) is the mixed cerebral venous oxygen saturation.
The spectroscopically measured and the estimated cerebrovascular oxygen saturation were correlated with linear regression analysis.

In a second protocol, seven subjects <40 years of age with normal health histories were recruited. Standard scalp electrodes were placed for recording EEG data using a 19-channel referential montage (Bio-Logic Brain Atlas, Mundelein, Ill.). All electrodes were placed and data collected by a certified EEG technologist. A peripheral intravenous and an arterial line were started. The infrared patient-interface probe was placed 5.0 cm anterior to the coronal suture and 3.0 cm from the midline on the left. Lead I electrocardiogram, cuff blood pressure (2120 NIBP, Ohmeda, Boulder, Colo.), peripheral pulse oximetry (3710 pulse oximeter, Ohmeda), and end-tidal CO2 (Novametrix Medical Systems, Wallingford, Conn.) were monitored.

A soft plastic face mask was placed over the subject’s nose and mouth, and the subject respired room air for several minutes. Then, with warning, the system was switched to a 7% O2 mixture using helium as a carrier gas. An inflow bleeder-valve system was used to deliver low flow rates of CO2 to keep end-tidal CO2 at baseline (usually 35–40 torr). During hypoxia the subject was given simple neurologic checks to assess level of consciousness and motor function.

The hypoxic gas mixture was respired until one of the following end points was reached: cardiac arrhythmia, sinus tachycardia of >125 beats/min, mean arterial blood pressure change of ±20%, peripheral oxygen saturation of <50%, altered neurologic status (failure to perform task or respond to verbal stimulus), subject discomfort, or 15 minutes. In all subjects the end point reached was peripheral oxygen saturation of <50%. At this point, the respired gas was changed to 100% O2.

The data were analyzed to compare the time to abnormal EEG and the time to abnormal spectroscopy and to record individual cerebrovascular oxygen saturation responses to progressive hypoxia. The end points for EEG and SvO2 were chosen to be within the established abnormal ranges.

The EEG data were interpreted by an electroencephalographer blinded to the time course of hypoxia and its resolution. The EEG pattern considered abnormal was the onset of progressive theta-delta activity. Once such activity was noted in the record, the earliest associated burst was taken to represent the time that EEG demonstrated hypoxia.

An abnormal spectroscopically measured cerebrovascular oxygen saturation was defined as 55%. This corresponds to an SaO2 of 90% and a mixed cerebral SvO2 of <50% (Equation 5) at either extreme of cerebral venous blood volume percentage (0.72 and 0.82). A cerebral SvO2 of ≤50% is clearly below the range of normal.

Results

None of the data collected in these studies was flagged for a signal-to-noise ratio of <30:1.
using the two extremes of cerebral venous blood volume percentage (0.72 and 0.82) (Equation 5). The standard errors (s) using these two models are 3.5 and 4.2, suggesting that the assumptions of blood volume weighting do not importantly alter the relation of spectroscopically measured cerebrovascular oxygen saturation in these patients.

The induction and progression of cerebral hypoxia in the human model varies as a function of the subject’s pulmonary effort and physiologic response to hypoxia and the ventilator circuit (Table 1). No evidence of physiologic instability was observed during the human hypoxia trials. Serial measurements of cerebrovascular oxygen saturation for 5 minutes (24 measurements/min) were completed on room air prior to initiating hypoxia. The mean±SD cerebrovascular oxygen saturation on room air was 64±3.4%. Serial measurements taken at the same rate for 30 seconds prior to minimum saturation during hypoxia demonstrated a mean±SD drop in saturation to 35±9.6%. This desaturation took an average of 224 seconds.

The onset of hypoxia was defined as the time when SaO₂ dropped to 90%. Spectroscopically measured cerebrovascular oxygen saturation fell by 3 SDs from baseline (room air) values within 22±12 seconds after the onset of hypoxia, which was 113±59 seconds prior to the EEG change (Figure 3).

The response times (i.e., time from onset of hypoxia to an abnormal measurement) for spectroscopically measured cerebrovascular oxygen saturation and analog EEG were documented for each subject (Table 2). The mean response time is estimated to be 10 seconds less for spectroscopically measured cerebrovascular oxygen saturation than for analog EEG at a 95% confidence level.

The end-tidal PCO₂ data demonstrate that PCO₂ was well controlled in these subjects, with a mean±SD difference between baseline and minimum PCO₂ of 4.7±0.8 torr, eliminating the simultaneous effects of hyperventilation on EEG.

### Discussion

The use of infrared optical spectroscopy to quantify a clinically significant measure of cerebral oxygen delivery and/or consumption is conceptually elegant but technically demanding. Transcranial or transillumination-mode spectroscopy, in which infrared light is delivered to one hemi-cranium and collected over the opposite, has not been suitable for adult humans. Clinical application of this configuration is limited by a low signal intensity, an exceedingly long photon path length, numerous optical boundaries, and an excessive sample volume. Cranial time-resolved spectroscopy has shown the feasibility of collecting diffuse infrared transmission spectra ipsilateral to the light source, and the ipsilateral configuration has emerged as the preferred one to measure adult intracerebral hemoglobin absorption.

Knowledge of photon behavior in tissue is improving. Recent work with lattice models simulating a photon “random walk” through tissue predicts the photon kinetics observed in human tissue and tissue models. When two tissue layers of varying chromophore content are modeled, it is apparent that the distance between the photon source and the receiver is critical. As distance increases, the highest-probability path of a photon in the superficial layer shortens while that in the deeper layer lengthens. The deeper layer thus contributes more spectroscopic information than the superficial layer. The goal in collecting diffuse cerebral transmission spectra is to use a source-to-receiver distance that minimizes absorption in tissue superficial to the brain yet maintains adequate signal strength.

A separation of 27–30 mm is adequate based on time-of-flight data from the human head. At this separation, infrared dyes such as indocyanine green (Becton Dickinson Co., Baltimore, Md.) are readily detected when selectively placed in the intracranial circulation during carotid artery surgery (unpublished data). This separation distance generates an intracranial penetration of 8–12 mm, which defines a hemi-elliptical volume of approximately 1.0–1.5 ml. This volume varies depending on the degree of reflection at the gray matter–white matter junction, which is notable in postmortem brain. The effect of such reflection is to weight the measurement toward gray matter.

Chance et al have shown that a quantitative measure of oxyhemoglobin concentration in a diffuse transmission field requires that the photon path length be measured directly or by time-of-flight. In an inhomogeneous, highly scattering tissue medium, direct measurement is not possible and routine time-of-flight measurement is clinically impractical because of hardware considerations. One solution is to solve for the content

### TABLE 1: Subject Response to Induced Cerebral Hypoxia

<table>
<thead>
<tr>
<th>Subject</th>
<th>Last measure of cerebrovascular oxygen saturation (%)</th>
<th>Elapsed time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before hypoxia</td>
<td>After hypoxia</td>
</tr>
<tr>
<td>1</td>
<td>64.44</td>
<td>14.65</td>
</tr>
<tr>
<td>2</td>
<td>64.74</td>
<td>38.84</td>
</tr>
<tr>
<td>3</td>
<td>58.97</td>
<td>29.33</td>
</tr>
<tr>
<td>4</td>
<td>59.35</td>
<td>43.09</td>
</tr>
<tr>
<td>5</td>
<td>63.43</td>
<td>45.40</td>
</tr>
<tr>
<td>6</td>
<td>68.97</td>
<td>37.70</td>
</tr>
<tr>
<td>7</td>
<td>67.16</td>
<td>37.70</td>
</tr>
</tbody>
</table>

Mean±SD 63.86±3.43 25.24±9.63 28.62±10.21 224.3±66.41

### TABLE 2: Response Time From Onset of Hypoxia to Abnormal Measurement End Point

<table>
<thead>
<tr>
<th>Measurement</th>
<th>n</th>
<th>Elapsed time (mean±SD sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular oxygen saturation</td>
<td>7</td>
<td>75±58</td>
</tr>
<tr>
<td>Analog electroencephalogram</td>
<td>7</td>
<td>135±65</td>
</tr>
<tr>
<td>Difference</td>
<td>7</td>
<td>60±68</td>
</tr>
</tbody>
</table>
ratio of hemoglobin to oxyhemoglobin, which is quantitative and easily converted to hemoglobin oxygen saturation (Equation 4).

The mathematical reduction scheme described here makes the basic assumption that path length is not dependent on wavelength (i.e., remains constant) over a narrow band of the near infrared spectrum. There is experimental evidence to support this assumption. One advantage of using the concept of hemoglobin oxygen saturation is the preexisting clinical familiarity with this measure. There is, however, no readily available reference measurement to compare it with in patients, and this limits the section of this study dedicated to correlating this measure to a known reference. The estimate of cerebrovascular oxygen saturation used here has two major limitations.

First, the accuracy of the estimate is affected by inadequate knowledge of cerebral blood volume partitioning between the arterial, venous, and capillary compartments. In addition, volume may not be the only variable involved, and quite possibly the surface area of each compartment affects the likelihood of absorption events. However, the fact that the venous compartment is much larger (in both volume and surface area) than the arterial compartment should reduce the magnitude of the error in estimating blood volume distribution.

Second, the spectroscopic measurement (cerebrovascular oxygen saturation) is regional while the reference measurement (SvO2) is global. An inhomogeneous distribution of blood and metabolic activity would reduce the correlation of the two.

The regression data based on observations in the nine patients suggest that both the regional spectroscopic measurement and its estimate measure the same phenomenon (Figures 1 and 2). However, the correlations are not strong enough to suggest that the two are identical. This is expected because the complexity of an aggregate measure of hemoglobin in a regional cranial volume precludes a reference measure (or estimate) accurate enough for such a result. Furthermore, the variability of the regression data also demonstrates the limitations of the current algorithm and, to some degree, the technology. Additional investigation of signal modification by attenuation outside the cerebrovascular compartment and nonattenuating boundary events should lead to algorithms that reduce measurement variability. However, even with the present limitations in measurement accuracy, the usefulness of spectroscopic cerebrovascular oxygen saturation as a sensitive clinical parameter of adequate cerebral oxygen delivery was demonstrated in a human hypoxia model.

The sensitivity of spectroscopic cerebrovascular oxygen saturation to induced cerebral hypoxia was compared with analog EEG tracings. The end points chosen are conservative and favor the EEG. The EEG was interpreted retrospectively, and sustained short bursts of theta activity were identified as an end point, even though this interpretation could not be used prospectively for clinical monitoring. Analog EEG data increased the measurement sensitivity because of their high sensitivity to transient EEG changes.

The human hypoxia data reported here demonstrate that spectroscopy is at least as responsive to progressive human cerebral hypoxia as EEG. This sensitivity is expected because oxygen saturation is a direct measure of tissue oxygen delivery. In laboratory animals, the responsiveness of optical spectroscopy has been compared with nuclear magnetic resonance spectroscopy during cerebral hypoxia with similar results.

Diffuse optical transmission spectra are reducible to a quantitative measure of cerebrovascular oxygen saturation that correlates with an estimate of this parameter. Ours is the first quantitative optical spectroscopic measurement of cerebrovascular saturation to be systematically compared with a reference measurement in humans. The data demonstrate that optical spectroscopy is as sensitive as analog EEG to progressive human cerebral hypoxia. Spectroscopically measured cerebrovascular oxygen saturation may serve as a clinical tool for the early recognition of cerebral hypoxia or ischemia and the titration of therapy for these events.

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References


FIGURE 3. Time profile of each of seven subjects tested, showing responsiveness of cerebrovascular oxygen saturation (rSHbO2) to hypoxia (solid line) and time to occurrence of first theta-delta burst on analog electroencephalogram (arrow).

Baseline measurement of rSHbO2 prior to hypoxia and nadir saturation during hypoxia for each subject are given in Table 1.

KEY WORDS • anoxia • electroencephalography • hemoglobin
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