Noninvasive Determination of Brain Tissue Oxygenation during Sleep in Obstructive Sleep Apnea: A Near-Infrared Spectroscopic Approach

Christopher O. Olopade, MD, MPH1; Edward Mensah, PhD2; Rajarsi Gupta, PhD3; Dezheng Huo, PhD4; Daniel L. Picchietti, MD5; Enrico Gratton, PhD1; Antonios Michalos, MD6

1Department of Medicine, University of Illinois at Chicago, IL; 2School of Public Health, University of Illinois at Chicago, IL; 3Laboratory for Fluorescence Dynamics, Department of Physics, University of Illinois at Urbana-Champaign, IL; 4Department of Health Studies, University of Chicago, IL; 5University of Illinois and Carle Clinic Association, Urbana, IL; 6ISS, Inc., Urbana-Champaign, IL.

Study Objectives: Recurrent apneas and hypoxemia during sleep in obstructive sleep apnea (OSA) are associated with profound changes in cerebral blood flow to the extent that cerebral autoregulation may be insufficient to protect the brain. Since the brain is sensitive to hypoxia, the cerebrovascular morbidity seen in OSA could be due to chronic, cumulative effects of intermittent hypoxia. Near-infrared spectroscopy (NIRS) has the potential to noninvasively monitor brain tissue oxygen saturation (SO2), and changes in concentration of oxyhemoglobin [O2Hb], deoxyhemoglobin [HHb] and total hemoglobin [THb] with real-time resolution. We hypothesized that brain tissue oxygenation would be worse during sleep in OSA relative to controls and sought to determine the practical use of NIRS in the sleep laboratory.

Design: We evaluated changes in brain tissue oxygenation using NIRS during overnight polysonography.

Setting: Studies were conducted at University of Illinois, Chicago and Carle Hospital, Urbana, Illinois.

Patients: Nineteen subjects with OSA and 14 healthy controls underwent continuous NIRS monitoring during polysomnography.

Measurements and Results: We observed significantly lower indexes of brain tissue oxygenation (SO2: 57.1 ± 4.9 vs. 61.5 ± 6.1), [O2Hb]: 22.8 ± 7.7 vs. 31.5 ± 9.1, and [THb]: 38.6 ± 11.2 vs. 48.6 ±11.4 µmol/L) in OSA than controls (all P <0.05). However, multivariate analysis showed that the differences might be due to age disparity between the two groups.

Conclusions: NIRS is an effective tool to evaluate brain tissue oxygenation in OSA. It provides valuable data in OSA assessment and has the potential to bridge current knowledge gap in OSA.

Keywords: Obstructive sleep apnea, brain tissue oxygenation, near-infrared spectroscopy

Citation: Olopade CO; Mensah E; Gupta R; Huo D; Picchietti DL; Gratton E; Michalos A. Noninvasive determination of brain tissue oxygenation during sleep in obstructive sleep apnea: a near-infrared spectroscopic approach. SLEEP 2007;30(12):1747-1755.

INTRODUCTION

OBSTRUCTIVE SLEEP APNEA SYNDROME (OSA) IS ASSOCIATED WITH INCREASED RISK OF CARDIOVASCULAR AND CEREBROVASCULAR MORBIDITY AND MORTALITY.1-4 Repetitive episodes of complete or partial collapse of the upper airway leading to recurrent hypoxemia characterize OSA. Using transcranial Doppler to determine cerebral blood flow velocity, there is some evidence that apneas during sleep are associated with profound changes in cerebral blood flow to the extent that cerebral autoregulation may be insufficient to protect the brain.5-7 Apnea-induced hypoxemia combined with reduced cerebral perfusion may predispose to nocturnal cerebral ischemia in patients with OSA.

Since the brain is very sensitive to hypoxia, it has been suggested that the cerebrovascular morbidity seen in OSA results from chronic, cumulative effects of intermittent nocturnal hypoxia.8 Although computerized tomography and magnetic resonance imaging have failed to consistently demonstrate brain structural abnormalities in patients with OSA, impairment in cerebral metabolism, especially in the white matter, has been demonstrated using magnetic resonance spectroscopy in patients with moderate to severe OSA.9-11 The degree of metabolic impairment correlates with the severity of OSA, supporting the notion that the repetitive hypoxemia associated with OSA leads to anoxic injury and cerebral dysfunction. Consistent with this concept, a recent cross-sectional comparative study demonstrated that the pattern of cognitive impairment seen in severe untreated OSA is similar to the pattern of subcortical brain damage seen in patients with multiple infarct dementia.12

Although arterial blood oxygen saturation (SaO2) may decrease due to hypoventilation during an apnea, if cerebral blood flow increases simultaneously, it is possible that the increased flow can compensate for the reduced SaO2, thereby maintaining oxygen supply to the brain. Therefore, it is important to measure changes in cerebral tissue oxygenation during obstructive apnea events to ascertain whether repetitive hypoxia during sleep induces anoxic brain damage. Unfortunately, earlier methods of quantifying cerebral blood flow, cerebral blood volume (CBV), and metabolism during sleep such as Xenon-133 computerized tomography,13-15 transcranial Doppler ultrasonography,16-21 and magnetic resonance spectroscopy10 are cumbersome, not readily available, and technically difficult to use.

Brain activity is associated with changes in optical parameters, namely the absorption and scattering coefficients. These changes are coupled to changes in regional blood flow, blood oxygenation, and metabolism. Hemoglobin and cytochrome c oxidase are the only biological components of the brain that exhibits variable absorption of near infrared light in response to changes in oxygen variability.

Near infrared spectroscopy (NIRS) is a portable and noninvasive diagnostic tool that facilitates the direct monitoring of
oxygen saturation and changes in oxyhemoglobin \([O_2Hb]\), deoxyhemoglobin \([HHb]\) and total hemoglobin \([tHb]\) concentration in tissues such as the brain. Technical advances in time-resolved spectroscopy (TRS) [such as frequency domain (FD) and time domain techniques (TD)], which uses short-pulsed laser diodes as light sources, represents an improvement over earlier NIRS methods and now makes quantification of brain tissue oxygenation and cerebral blood flow possible with real-time resolution.

Frequency domain NIRS (FD-NIRS) determines hemoglobin concentration and saturation, allowing us to determine changes in tissue oxygenation and blood flow from detecting fluctuations in concentration of \([O_2Hb]\), \([HHb]\), and \([tHb]\). FD-NIRS offers unambiguous quantification (by separating absorption from scattering) of tissue oxygenation and provides accurate and immediate information on tissue ischemia.

Cerebral total hemoglobin concentration \([tHb]\) is analogous to cerebral blood volume (CBV), \([O_2Hb]\) is reflective of cerebral tissue oxygenation while cerebral oxygen saturation (SO\(_2\)) is determined by \([O_2Hb]/[tHb]\). Based on our initial observation that cerebral oxygenation and hemodynamics may be compromised in patients with OSA during voluntary breath-holding (at functional residual capacity) and diurnal napping while NIRS measurement was recorded, we embarked on a study to determine the feasibility of simultaneous all-night NIRS monitoring during PSG and to test the hypothesis that brain tissue oxygenation and hemodynamics are worse during sleep in patients with OSA than in healthy controls.

METHODS

Nineteen subjects with OSA and no significant other medical comorbidities (such as hypertension, diabetes mellitus, or stroke) and 14 healthy control subjects were enrolled into the study. Every subject underwent continuous concurrent NIRS monitoring during overnight PSG.

Study Procedures

Overnight Polysomnography (PSG)

All subjects were asked to report to the Clinical Research Center, UIC, and the Sleep Center at Carle Foundation Hospital at 20:00 on the study date. They were instructed to refrain from drinking caffeinated or alcoholic beverages during the afternoon and evening hours prior to the PSG. The subjects were instructed to come with clean hair and no hair spray or oil. Upon arrival, an explanation of the study procedure was given and the standard sleep questionnaire administered. Following completion of the questionnaire, the PSG was done using standard methodology. Digital data acquisition and analysis was performed using the Sleepscan II analysis software (Bio-logic Systems Corp, Mundelein, IL) and Sandman 7.2. Scoring of the PSG was done using the standard criteria.

**Determination of Brain Tissue Oxygenation and Hemodynamics: Near-Infrared Spectroscopy Monitoring (NIRS)**

**Instrumentation**

We employed frequency-domain NIRS for the optical measures. We used the first commercially available quantitative tissue oximeter (OxiplexTS, ISS Inc, Champaign, IL). The frequency domain tissue spectrometer operates at a modulation frequency \(f\) of 110 MHz, a cross-correlation frequency \(\delta\) of 5 KHz, and at two discrete wavelengths, 690 and 830 nm. The 16 light sources (8 laser diodes per wavelength) are turned ON and OFF in sequence by a multiplexer. The light penetrates the scalp and skull and diffuses through the entire head. The light we collect and analyze is localized to 2 cm from the surface of the head. The average intensity of the light we use images a volume of the cortical brain equal to 1-2 cm\(^3\).

Two wavelengths (690 nm and 830 nm) were chosen to maximize the absorption contribution of \([O_2Hb]\) and \([HHb]\) respectively. This allows simultaneously determination of the absorption and scattering at two different wavelengths, and hence, the absolute amount of \([O_2Hb]\) and \([HHb]\). NIRS determines changes in brain tissue oxygenation and blood flow from detecting fluctuations in concentration of oxyhemoglobin and deoxyhemoglobin.

**Measurement Protocol**

**Optical Probe Calibration:** The optical probe was calibrated using a phantom of known optical properties, comparable to the optical properties of brain tissue, prior to the measurements on study subjects. All subjects were studied in the supine position with the room dimly lit and comfortable ventilation and temperature.

**Optical Probe Placement:** The optical probe was positioned high on the forehead where the overlying tissue thickness is at a minimum, the skull is poorly perfused, and the sinuses are avoided. The probe was firmly attached to the forehead by means of a medical adhesive (Hollister #7730). Care was taken to ensure that the attached probe did not constrict the head and did not block scalp blood circulation.

**Protocol:** The measuring protocol was performed in 3 stages.

1. Following complete relaxation for 2 minutes, baseline measurements of \(SO_2\), \([O_2Hb]\), \([HHb]\), \([tHb]\), \(SaO_2\), heart rate, and respiratory rate were obtained for 3-5 min.
2. Subjects were asked to hold their breath at the end of expiration (at functional residual capacity). This exercise was repeated 3-4 times at 2-min intervals after resumption of breathing.
3. Patients were then asked to go to sleep; PSG and concurrent monitoring of brain tissue oxygenation indexes continued throughout the night.

**Data Acquisition**

The signals from each sensor were fed into the data acquisition card inserted in the computer. The card features 2 channels and 16-bit data acquisition on each channel with on-time sample-and-hold capability. Each sensor accesses one channel with the upper limit of the sampling determined by the cross correlation frequency. The 8 light sources of each channel are electronically multiplexed at a rate of 40 Hz, so that each light source is on for 25 msec. In addition, the signals are averaged over 4 full cycles for a total of independent measurement time of 0.8 sec, which facilitates measurement of absorption and scattering independently. Details of the instrumentation, light source, measurement, and data processing algorithms and methods have been published in detail elsewhere.

The complete instrument setup and sample
display of raw data as it is being collected and displayed on the monitor in this study are shown in Figures 1 and 2 respectively.

The Institutional Review Board on human and animal research at the University of Illinois at Chicago and the Carle Foundation Hospital, Urbana-Champaign approved the research protocol, and all subjects who participated in the study provided written informed consent.

Statistical Analysis

Demographic characteristics and polysomnographic measurements of the OSA and control groups were compared using Fisher’s exact tests for categorical variables and two-sample t-tests or Wilcoxon rank-sum tests, as appropriate, for continuous variables. A single average value for each of the NIRS variables was determined for the duration of the overnight recording. This value was based on over 20,000 data points during a typical 6-h overnight recording after excluding periods of study interruption to use the bathroom or adjust electrodes. Histogram display of the single average analysis method for brain tissue oxygen saturation index on both sides of the forehead is as shown in Figure 3. Other NIRS variables of interest were similarly determined.

We examined whether the brain tissue oxygenation indexes measured on left and right forehead were in agreement using Lin’s concordance correlation coefficients. Since the agreement between oxygenation indexes measured over the left and right forehead was good, we considered they were 2 repeated measures for the same underlying oxygenation indexes, and took the average for further analyses. Two-sample t-tests were used to examine whether brain tissue oxygenation indexes were different between the 2 study groups. Spearman nonparametric correlation coefficients were used to assess the relationship between brain tissue oxygenation indexes and apnea hypopnea index. Multiple linear regression models were used to assess the relationship between brain tissue oxygenation indexes and age, BMI, and polysomnographic variables.

RESULTS

We enrolled 33 subjects into the study as follows: 19 with OSA and 14 healthy controls as shown in Table 1. There was no significant difference in gender and ethnicity between OSA cases and healthy controls. The OSA group was significantly older (age, 47.4 ± 8.2 y; mean ± SD vs. 29.7 ± 10.9 y; P < 0.001), more obese (BMI, 35.1 ± 9.7 kg/m² vs. 27.2 ± 5.6; P < 0.01), and by design had moderate to severe OSA (AHI, median 55 vs. 0.45; P < 0.001). Seven subjects in the OSA group had mild OSA, 2 had moderate OSA, and 10 had severe OSA. Taking all subjects (n=33), there was no significant gender difference in AHI (P = 0.11); the median AHI (interquartile range) was 11 (1.2-73) in men and 5.2 (0-14.5) in women. Total sleep time was significantly shorter (two-sample t-test, P = 0.002) in OSA patients (246 ± 110 min) than in controls (347 ± 64 min). However, sleep efficiency index was not significantly different between OSA patients and controls. Peripheral oxygen saturation nadir was significantly lower (Wilcoxon rank-sum test, P = 0.03) in OSA patients (median = 83%) than in controls (median = 89%).
Are Brain Tissue Oxygenation Indexes Similar Between Left and Right Forehead?

All 4 NIRS indexes were consistent between left and right forehead with concordance coefficients greater than 0.7, suggesting that the agreement was very good. Because agreement between oxygenation indexes measured on the left and right forehead was very good, we considered they were 2 repeated measures for the same underlying oxygenation indexes. The values measured on the left and right were averaged for further analyses. The average results in OSA and controls are shown in Table 2.

Is Brain Tissue Oxygenation Worse in OSA Than Controls?

As detailed in Table 2, we observed significantly lower mean brain tissue oxygen saturation (SO$_2$), [O$_2$Hb], and [tHb] in pa-

---

**Table 2**—Brain Tissue Oxygenation Levels in OSA and Healthy Controls

<table>
<thead>
<tr>
<th></th>
<th>OSA (N=19)</th>
<th>Control (n=14)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain oxygen saturation (SO$_2$), (%)</td>
<td>57.1 ± 4.9</td>
<td>61.5 ± 6.1</td>
<td>0.028</td>
</tr>
<tr>
<td>Brain tissue oxyhemoglobin [O$_2$Hb], (µmol/L)</td>
<td>22.8 ± 7.7</td>
<td>31.5 ± 9.1</td>
<td>0.006</td>
</tr>
<tr>
<td>Brain tissue deoxyhemoglobin [HHb], (µmol/L)</td>
<td>16.2 ± 4.0</td>
<td>17.1 ± 3.6</td>
<td>0.53</td>
</tr>
<tr>
<td>Total brain tissue oxygenation [tHb], (µmol/L)</td>
<td>38.6 ± 11.2</td>
<td>48.6 ± 11.4</td>
<td>0.017</td>
</tr>
</tbody>
</table>

*P-values were calculated from t test. SD, standard deviation

---

**Table 3**—Linear Regression of NIRS

Simple linear model

<table>
<thead>
<tr>
<th>Brain oxygen saturation (SO$_2$), (%)</th>
<th>Reg. coef.</th>
<th>Corr. coef.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>-0.28</td>
<td>-0.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>-0.31</td>
<td>-0.48</td>
<td>0.004</td>
</tr>
<tr>
<td>Total sleep time (minute)</td>
<td>0.027</td>
<td>0.48</td>
<td>0.005</td>
</tr>
<tr>
<td>Sleep efficiency index</td>
<td>0.073</td>
<td>0.22</td>
<td>0.21</td>
</tr>
<tr>
<td>Peripheral nadir oxygen saturation (%)</td>
<td>0.028</td>
<td>0.04</td>
<td>0.82</td>
</tr>
<tr>
<td>% of time oxygen saturation &lt;90%</td>
<td>-0.13</td>
<td>-0.19</td>
<td>0.35</td>
</tr>
<tr>
<td>&lt;5% vs. 0% of time</td>
<td>-2.70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Multiple linear model

<table>
<thead>
<tr>
<th>Brain tissue oxyhemoglobin [O$_2$Hb], (µmol/L)</th>
<th>Reg. coef.</th>
<th>Partial corr. coef.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>-0.47</td>
<td>-0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>-0.39</td>
<td>-0.38</td>
<td>0.03</td>
</tr>
<tr>
<td>Total sleep time (minute)</td>
<td>0.046</td>
<td>0.51</td>
<td>0.002</td>
</tr>
<tr>
<td>Sleep efficiency index</td>
<td>0.201</td>
<td>0.39</td>
<td>0.03</td>
</tr>
<tr>
<td>Peripheral nadir oxygen saturation (%)</td>
<td>0.184</td>
<td>0.17</td>
<td>0.35</td>
</tr>
<tr>
<td>% of time oxygen saturation &lt;90%</td>
<td>-3.97</td>
<td>-3.70</td>
<td>0.49</td>
</tr>
<tr>
<td>&lt;5% vs. 0% of time</td>
<td>-6.82</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Brain tissue deoxyhemoglobin [HHb], (µmol/L)</th>
<th>Reg. coef.</th>
<th>Corr. coef.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>-0.08</td>
<td>-0.29</td>
<td>0.10</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>-0.07</td>
<td>-0.16</td>
<td>0.37</td>
</tr>
<tr>
<td>Total sleep time (minute)</td>
<td>0.015</td>
<td>0.41</td>
<td>0.02</td>
</tr>
<tr>
<td>Sleep efficiency index</td>
<td>0.089</td>
<td>0.43</td>
<td>0.01</td>
</tr>
<tr>
<td>Peripheral nadir oxygen saturation (%)</td>
<td>0.072</td>
<td>0.16</td>
<td>0.37</td>
</tr>
<tr>
<td>% of time oxygen saturation &lt;90%</td>
<td>-2.81</td>
<td>-2.61</td>
<td>0.18</td>
</tr>
<tr>
<td>&lt;5% vs. 0% of time</td>
<td>-1.21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total brain tissue oxygenation [tHb], (µmol/L)</th>
<th>Reg. coef.</th>
<th>Corr. coef.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>-0.57</td>
<td>-0.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>-0.45</td>
<td>-0.33</td>
<td>0.06</td>
</tr>
<tr>
<td>Total sleep time (minute)</td>
<td>0.060</td>
<td>0.52</td>
<td>0.002</td>
</tr>
<tr>
<td>Sleep efficiency index</td>
<td>0.288</td>
<td>0.43</td>
<td>0.01</td>
</tr>
<tr>
<td>Peripheral nadir oxygen saturation (%)</td>
<td>0.249</td>
<td>0.17</td>
<td>0.33</td>
</tr>
<tr>
<td>% of time oxygen saturation &lt;90%</td>
<td>-7.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5% vs. 0% of time</td>
<td>-8.19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---
tients with OSA than in controls (P < 0.05), but no significant differences were observed in [HHb] between the 2 study groups.

Is Brain Tissue Oxygenation Correlated With OSA Severity Measured as AHI?

Spearman nonparametric correlation coefficient was calculated to assess the relationship between AHI and brain tissue oxygenation levels in all 33 subjects. Brain tissue oxygen saturation and [O$_2$Hb] were significantly (P < 0.05) and inversely correlated with AHI (-0.37 and -0.36 respectively), while [HHb] and [tHb] were not statistically significantly correlated with AHI.

What Is the Effect of Age on NIRS values?

As shown in Table 3, age was negatively and strongly correlated with (SO$_2$), [O$_2$Hb], and [tHb] in the univariate analysis with correlation coefficients greater than 0.4 (P < 0.05). The partial correlation coefficients can be interpreted as effect due to aging. Age-related influence on brain tissue oxygenation indexes in OSA subjects and healthy controls are also shown in the scatter plots of age and the 4 NIRS variables, stratified by study group in Figure 4.

Is There Any Relationship between Polysomnographic and NIRS variables?

We then used simple linear regression model to examine the relationship between PSG variables (total sleep time (TST), sleep efficiency, O$_2$ saturation nadir, percentage time spent with saturation <90% and the NIRS variables. The results are shown in the left panel of Table 3. Total sleep time was positively correlated with all 4 NIRS variables with correlation coefficients ranging from 0.4 to 0.5; P < 0.05. Sleep efficiency index was also positively correlated with 3 NIRS variables, with correlation coefficients ranging from 0.39 to 0.43; P < 0.05. There was no significant correlation between peripherally determined oxygen saturation nadir and any of the NIRS variables. Because percentage time of oxygen saturation <90% was not symmetrically distributed, we grouped percentage time of oxygen saturation into 3 categories

**Figure 2**—Digital Display of Raw Data During NIRS Collection. Figure 2 shows real time raw data as displayed on the PC monitor during NIRS recording. The upper left corner shows instantaneous numerical readout of brain oxygen saturation (SO$_2$), total hemoglobin concentration (THC), oxyhemoglobin concentration (oxy), and deoxyhemoglobin (De-oxy) in the 2 wavelengths on the right (Rt) and left (Lt) forehead. The lower portion of the graph
(0%, <5%, >5% of time). Three, 8, and 8 OSA patients had 0%, <5%, and >5% of time oxygen saturation <90%, respectively. In contrast, the corresponding numbers for control group are 9, 5, and 0 (Fisher’s exact test, P = 0.002). There was no statistically significant correlation between percentage time of oxygen saturation <90% and the 4 NIRS variables.

Predictors of NIRS

Next, we assessed how much of the variations in NIRS variables can be predicted by commonly measured variables, including age, BMI, and polysomnographic variables. We used multiple linear regression models with a backward selection procedure to construct the final model (right panel of Table 3). As shown in Table 3, BMI was positively correlated with brain oxygen saturation, brain tissue oxyhemoglobin, and total brain tissue oxygenation in the univariate analysis, but it was no longer significant after adjusting for age. “R²” was calculated to indicate percentage of variation in NIRS variable explained by independent variables. Commonly measured variables can predict about 50% of variation in (SO₂), [O₂Hb], and [HHb], but only 18% variation in [HHb]. It should be noted that “independent” was used here simply to indicate whether a variable has additional discriminating value when other variables were included in the model. It does not imply causal relationship. For example, sleep efficiency may be determined by NIRS rather than cause of NIRS.

DISCUSSION

In this study, we show that brain tissue oxygenation, defined by the concentrations of [O₂Hb], [HHb], and [Hb], is reduced during sleep in OSA patients relative to healthy controls (although these changes may be attributed to age-related differences between the two groups). This observation using a non-invasive methodology provides a valuable tool for the objective determination of brain tissue oxygenation in OSA and has the potential to provide a better understanding of the role of impaired cerebral perfusion during sleep on neurobehavioral consequences of OSA. It may also prove to be a valuable tool in monitoring response or lack of response to therapy by comparing brain tissue oxygenation indexes at baseline to post-treatment values in selected patients.

NIRS has been used in sleep research to identify changes in brain oxygenation and circulation during sleep in healthy newborn infants. Cyclical desaturation and reoxygenation of cerebral blood during periodic breathing in association with periodic
apneas was first demonstrated with NIRS in 42% of apneas with a mean decrease in cerebral blood volume (CBV) of 0.32 µM/L in a group of 30 full-term infants. Obstructive apnea was observed to have the strongest impact on CBV in preterm infants.

The feasibility of continuous NIRS monitoring during overnight PSG for determination of changes in blood tissue oxygenation and CBV has been demonstrated. In a small number of patients with moderately severe OSA, Hayakawa showed decreases in [O$_2$Hb] levels and a simultaneous increase in [HHb] and [tHb] levels during apneas. There was a negative correlation between changes in [O$_2$Hb] and apnea duration, which was worse during REM sleep. Valipour and colleagues also performed NIRS measurements continuously during overnight PSG in 13 men with OSA. They showed that the drop in brain tissue oxygenation index ([O$_2$Hb]/([O$_2$Hb] + [HHb]) during obstructive apneas was negatively correlated to peripheral SpO$_2$. Longer apneas occurring during REM sleep resulted in even greater reductions in brain tissue oxygenation index. Cerebral oxygenation and cerebral blood volumes were continuously low in a small number patients with OSA; cerebral hemodynamic mechanisms did not increase cerebral oxygenation to normal values.

While these studies demonstrate that NIRS as a noninvasive tool can be used to quantify brain tissue oxygenation and hemodynamics, the number of enrolled patients were relatively small, there were few to no controls, patients were not well characterized, and only men were studied.

The frequency domain methodology used with the current NIRS instrumentation in this study has several advantages. The response time of the instrument is instantaneous with the oximeter capable of making hemodynamic measurements every 0.02 sec, although measurements were made every 0.80 sec in the current study. The ability to obtain real-time quantitative information on changes in brain tissue oxygenation and hemodynamics concurrent with pulse oximetry during overnight PSG as shown in Figure 2 also represents an improvement over previous NIRS instruments.

Consistent with earlier observations which showed that brain tissue oxygenation and hemodynamics are compromised at baseline and worsened during apneas, using NIRS, we observed significant differences in mean brain tissue oxygen saturation (SO$_2$) and concentration of [O$_2$Hb] and [tHb] between OSA and controls, while no significant differences were observed in [HHb]. However, the observed differences in the simple linear model were due to age disparities between the 2 study groups.

We also explored whether handedness was a factor in the observed small differences between the right and left NIRS values; but because we had only 2 left-handed and 31 right-handed subjects, we did not have enough power to explore whether the ob-

**Figure 4**—Scatter Plots of Four NIRS Outcomes and Age by OSA and Control Group. Scatter plots showing the effect of age on brain tissue oxygenation indexes in the OSA and healthy control groups. A= brain oxygen saturation; B= brain oxyhemoglobin concentration; C= brain deoxyhemoglobin concentration and D= brain total oxyhemoglobin concentration.
served left/right differences could be explained by handedness. However, with over 70% concordance between the right and left side NIRS values, we concluded that no major differences exist in brain tissue oxygenation between the 2 sides.

In our study, the OSA group was significantly older than controls, a limitation of the study. While our subjects had no underlying diabetes or uncontrolled hypertension and were younger than the cohort studied by Harmann and colleagues (which showed age-related decline in [O₂,Hb] in response to cognitive tasks), we also observed that (SO₂, [O₂,Hb], and [Hb]) were negatively correlated with age. Multiple linear regressions also demonstrated the importance of age as a major determinant of cerebral perfusion. Even though we evaluated brain tissue oxygenation changes during sleep, our findings are consistent with previous studies which showed age-dependent decline in brain activation during performance of cognitive tasks assessed by NIRS during wakefulness. Additional studies with better matching for age are needed to more accurately define the impact of OSA on cerebral perfusion.

Another limitation of our study is the lack of separation of brain tissue oxygenation indexes based on sleep stages (NREM versus REM), a factor that made it impossible for us to determine state related changes in brain tissue oxygenation during sleep. While details about sleep stage specific changes may be missing with the single average method used in this study, the average value for each of the NIRS variables during the overnight recording was determined based on over 20,000 data points during a typical 6-h overnight recording after excluding periods of study interruption as shown in Figure 3. This first-pass method provides important information on changes in brain tissue oxygenation and cerebral hemodynamics during sleep and is a prelude to incorporation of the NIRS signal directly into the PSG montage.

Despite these limitations, our observation that changes in brain tissue oxygenation can be easily and noninvasively measured by NIRS during sleep is important and is consistent with the only other study which used NIRS to evaluate brain tissue oxygenation changes during sleep in OSA; that study showed decreases in cerebral oxygenation during apneas and hypopneas but observed considerable inter-individual variability in response to a given arterial oxygenation change. Unfortunately, only 13 men with OSA and no control subjects were included in that study. The age range of the subjects 47.7 y ± 9.8 was comparable to that of our OSA subjects, but that study did not explore age-related influence on observed changes in brain tissue oxygenation during selected apnea events. With better matching between OSA and healthy controls, we will be in a better position to evaluate changes in cerebral perfusion during sleep.

In healthy subjects, the typical response of the brain to hypcapnia related to voluntary breath hold, sleep related apnea, or controlled CO₂ infusions is an increase in [O₂,Hb], a decrease in [HHb], and an increase in [Hb]. The increase in [Hb] during these hypoxic and hypercapnic episodes reflects an increase in cerebral blood volume. In contrast to peripheral tissues such as the skin or muscle, sustained hypcapnia for up to 1 hour has been demonstrated to lead to sustained elevation of cerebral blood flow instead of a transient increase in blood flow and return to baseline flow pattern seen in peripheral tissues. This reaction to hypcapnia (cerebrovascular autoregulation) is unique to the brain and may serve to protect the brain from anoxic injury. Since OSA is associated with cardiovascular and cerebrovascular disease, we suspect that the loss of brain vascular autoregulation and failure of the brain to protect itself from hypoxic injury is likely responsible for the inability of the brain to increase [O₂,Hb] and decrease [HHb] in response to apnea events in patients with moderate to severe OSA.

We posit that chronic repetitive hypoxemia in OSA leads to compromised vascular autoregulation and brain injury, which may be irreversible. This position is supported by studies that demonstrated that the pattern of cognitive deficits seen in OSA is similar to those observed in patients with multi-infarct dementia. This position is also supported by studies that relate OSA severity and degree of oxygen desaturation to persistent neurocognitive deficit even after effective CPAP therapy.

The disparity between restitution of physiologic function during sleep and persistent daytime symptoms represents a significant gap in our understanding of OSA. With improved instrumentation and the ability to obtain absolute values of changes in brain tissue oxygenation, FD-NIRS can be used to examine the effect of repetitive hypoxia during apneas on cerebral perfusion. Additionally, correlation of brain tissue oxygenation with cognitive performance before and after effective therapy is now possible. Finally, our long-term goal is to incorporate the FD-NIRS signal into the PSG montage, so that event-by-event changes in brain tissue oxygenation may be captured and state related changes better defined.

ACKNOWLEDGMENT

The authors are grateful to Nicholas Fossland for his dedication to the project and assistance with the overnight studies.

Supported by NIH-SBIR grant 2-R44 NS40597-03. This study was performed in the General Clinical Research Center at the University of Illinois Medical Center, which was funded by NIH grant MO1-RR-13987.

REFERENCES

9. Kamba M, Inoue Y, Higami S, Ogawa T, Chen W. Cerebral meta-


