UC Irvine
UC Irvine Previously Published Works

Title

Diminished cerebral circulatory autoregulation in obstructive sleep apnea investigated by near-infrared spectroscopy

Permalink

https://escholarship.org/uc/item/2hg3w5h0

Journal

Sleep Research Online, 5(4)

ISSN

1096-214X

Authors

Safonova, LP
Michalos, A
Wolf, U
et al.

Publication Date

2003-12-01

Copyright Information

Peer reviewed

Diminished Cerebral Circulatory Autoregulation in Obstructive Sleep Apnea Investigated by Near-infrared Spectroscopy

Larisa P. Safonova[1], Antonios Michalos[1,2], Ursula Wolf[1], Jee Hyun Choi[1], Martin Wolf[1], William W. Mantulin[1], Dennis M. Hueber[2], and Enrico Gratton[1]

[1]*Laboratory for Fluorescence Dynamics, Department of Physics, University of Illinois at Urbana-Champaign, Illinois, USA*
[2]*ISS, Inc. Champaign, Illinois, USA*

ABSTRACT

We applied near-infrared spectroscopy (NIRS) to assess cerebral tissue oxygenation and hemodynamics in obstructive sleep apnea (OSA) sufferers and control volunteers. We designed NIRS sensors and applied measurement schemes that included certain polysomnography parameters, such as arterial hemoglobin oxygen saturation (SaO_2), heart rate (HR), and respiratory signal (RS), together with NIRS parameters, such as oxy- ($[O_2Hb]$), deoxy- ($[HHb]$), total hemoglobin ($[tHb]$) concentrations, and tissue hemoglobin oxygen saturation (SO_2). Twenty-one volunteers (8 females, 13 males, age 22-74 years) participated in the study. Eight were OSA sufferers, while 13 constituted the control group. Measurements were conducted during breath holding exercises and 30-45 minute daytime naps. In comparing OSA subjects with controls during breath holding, a smaller increase or even a decrease in SO_2, $[O_2Hb]$, and $[tHb]$ and a simultaneous larger increase in $[HHb]$, confirmed insufficiency of the circulatory compensatory mechanism that prevents brain tissue hypoxia. Changes in cerebral oxygenation and hemodynamics due to hypoxia during breath holding showed statistically significant differences ($p<0.05$) between control and OSA subjects and between non-snorers and OSA subjects ($p<0.03$ for $\Delta[O_2Hb]$, $\Delta[HHb]$, $\Delta[tHb]$, and ΔSO_2). NIRS provides the clinician with important, direct insight on the cerebral tissue oxygenation and hemodynamics related to the chronic intermittent hypoxia in OSA for potential identification of individuals at risk for cerebrovascular morbidity.

CURRENT CLAIM:

We observed diminished cerebral hemodynamic response to hypoxia in subjects diagnosed with obstructive sleep apnea as compared with control subjects.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) has been increasingly recognized as a cause of associated disease. In the middleaged work force, 2% of women and 4% of men meet the minimal diagnostic criteria for sleep apnea syndrome (apnea/hypopnea score of 5 or higher and daytime hypersomnolence) (Young et al., 1993). OSAS is described as a potentially lethal disease because it leads to hypoxia and hypoxemia. Altered quality of life, daytime sleepiness, neuropsychological dysfunction and cognitive deficits have been associated with OSAS as well as cardiovascular disease, including systemic and pulmonary hypertension, arrhythmias and ischemic heart disease (Blankfield et al., 2000; Lavie et al., 2001; Marrone est al., 1998; Mitler et al., 1987; Peker et al., 2000; Redline and Strohl, 1998; Sharabi et al., 2003). OSAS is a disorder accompanied by a decrease in the arterial hemoglobin oxygen saturation and by temporary changes in brain tissue oxygenation and hemodynamics (Hayakawa et al., 1996; Michalos et al., 2000, 2002a, 2002b). Since the brain is very sensitive to hypoxia, it has been suggested that recurrent decrease of the arterial oxygen saturation (SaO_2) in sleep apnea leads to brain injury. Cerebrovascular accidents, ranging from transient ischemic attacks to fatal strokes, are closely associated with sleep apnea (Neau et al., 2002; Palomaki et al., 1992; Pressman et al., 1995).

Overnight polysomnography can detect sleep apneas and their degree of severity (Douglas and Thomas, 1992; Fry et al., 1998). However, current clinical methods do not provide direct information on brain tissue oxygenation and hemodynamics,

which could be important factors to consider, especially in subjects with concomitant anatomical or functional vascular pathology.

The ability of light to penetrate several centimeters into tissues and the differences in absorption spectra of [O₂Hb] and [HHb], in the wavelength range of 700-900 nm, constitute the basis for near-infrared spectroscopy (NIRS) tissue blood oxygenation measurements (Jöbsis, 1977). The applied theoretical model of near-infrared light propagation in highly scattering media, using the frequency-domain approach, has been described by several investigators (Fantini et al., 1994; Fishkin and Gratton, 1993). NIRS can non-invasively monitor tissue oxygenation (SO₂) and changes in oxy-hemoglobin concentration ([O₂Hb]), deoxy-hemoglobin concentration ([HHb]) and total hemoglobin concentration ([tHb]) (Hueber et al., 2001; Michalos et al., 2000, 2002a, 2002b; Toronov et al., 2000). As a result of this unique quantitative information content and a variety of technique features such as the compactness, the low cost, and the high-wearing comfort level, NIRS is a promising diagnostic method for carrying out non-invasive, real-time measurements of changes in cerebral hemodynamics and oxygenation (Elwell et al., 1994, 1996; Lichty et al., 2000; Madsen and Secher, 1999; Nielsen et al., 2001; Wolf et al., 2000).

It has been assumed that the optical penetration depth can be significantly affected by a layered structure such as the one present in the head (skin/scalp-shy-skull-cerebrospinal fluid (CSF)-cerebral tunics-brain). However, based on research progress in the field of NIRS (Franceschini et al., 1998; Okada and Delpy, 2000; Owen-Reece et al., 1996; Young et al., 2000), we deem that the contribution of the superficial layers of the head (scalp, skull, and CSF) to the NIRS output signal is negligible, due to much greater absorption and scattering changes in the deeper layers (gray matter) as compared to the superficial layers. Moreover, appropriate source-detector separation selection ultimately determines the depth of light penetration.

Hayakawa et al. (1996) first applied NIRS on adult OSAS patients. They found a consistent increase in [tHb] and a consistent decrease in [O₂Hb] in the cerebral tissue during the apneic episode. They used a NIR tissue oximeter (OM-100A; Shimadzu; Kyoto, Japan), which operates with three wavelengths (780, 805, and 830 nm) and only one source-detector distance (3.5 cm). The observed opposite direction of changes in [O₂Hb] and [HHb] due to sleep apnea episodes, obtained with their approach, most probably reflects hemodynamic changes in the skin. The multi-distance approach in NIRS tissue oximeters, such as the one we used in this study, allows the assessment of hemodynamic changes occurring in deeper layers of the head mostly independently of changes occurring at the skin level (Franceschini et al., 1998; Hueber et al., 2001).

The main objective of this study was to introduce frequency-domain, multi-distance NIRS to sleep medicine for the investigation of brain oxygenation and changes in hemodynamics during sleep apnea. We exploited the NIRS technique to evaluate the cerebrovascular effects of intermittent hypoxia and hypoxemia during sleep apnea. We investigated cerebral tissue oxygenation and hemodynamics under two hypoxic conditions: first, during voluntary breath holding exercises, and second, during brief apneic/hypopneic episodes in the course of diurnal napping. We compared the findings from the OSA subjects with the results from the control group.

Our hypothesis is that the observed changes in cerebral tissue oxygenation and hemoglobin concentrations are modulated by recurrent apneic episodes in OSA subjects during daytime napping. The observed changes in brain tissue oxygenation and hemodynamics depend on the arterial hemoglobin deoxygenation and on the efficiency of the protective cerebrovascular response, the so-called autoregulation of cerebral blood flow.

Lower levels of SaO₂ and intermittent hypoxia due to sleep apnea/hypopnea events might result in more profound cerebral deoxygenation during sleep. We propose that breath holding-induced hypoxia may be a consistent test for assessing efficiency of cerebral circulatory compensation (brain autoregulation) in OSA subjects compared to the controls for potential screening of individuals at risk for cerebrovascular consequences of OSAS.

METHODS

Instrumentation

We simultaneously measured SaO₂ and HR with a pulse oximeter (N-200, Nellcor Inc., Pleasanton, CA), breathing rate with a respiratory strain gauge (Resp-EZ, Sleepmate, New Life Technologies, Midlothian, VA), and SO₂, [O₂Hb], and [HHb] with a two-wavelength (690 nm and 830 nm) frequency-domain tissue oximeter (Oxiplex TS; ISS Isnc., Champaign, IL).

The Oxiplex TS, frequency-domain, dual-channel, tissue spectrometer operates at a modulation frequency of 110 MHz and a cross-correlation frequency of 5 kHz. The eight light sources of each channel (four laser diodes per wavelength of 690 nm and 830 nm) were electronically multiplexed at a rate of 40 Hz, so that each light source was on for 25 ms. The signals from

each detector were averaged over four cycles of the eight light sources, resulting in a total acquisition time of 800 ms per measurement. Each laser diode (light source) was coupled to an optical fiber of 400 μmm in core diameter leading to the measuring probe. Progress, achievements, and prospects with the ISS tissue oximeters in the field of NIRS have been repeatedly demonstrated by different investigators (Franceschini et al., 2001; Hueber et al., 2001; Michalos et al., 2000; Toronov et al., 2000; Zhang et al., 2000).

A near-infrared (NIR) dual-sensor probe, having a two-channel configuration, was specially designed for comfort during lengthy measurements. The optical source fibers were arranged in pairs, such that each pair contained one fiber connected to a source emitting at each wavelength. The optical signals detected at the tissue surface were guided to the photomultipliers (one per channel) of the oximeter by optical fiber bundles of 3 mm internal diameter each. The output ends of the paired light source fibers were arranged at increasing distances from the input ends of the detector fiber bundles. The four source-detector distances (SDD) ranged from 1.98 to 4.08 cm. The probe could be firmly attached on the forehead via a medical adhesive. Thus, it did not constrict the head, and it did not block the blood circulation of the scalp. Figure 1 shows the instrumental set-up as well as the sensor configuration and dual sensor probe design.

The probe was calibrated using a calibration block of known optical properties before the experiments were carried out.

Subjects
Twenty-one right-handed volunteers, eight females and 13 males, participated in the study. The mean age was 43 years, ranging from 22 to 74 years.

Eight subjects, two females and six males (age 49.4±16.4 years, range 29-74 years), had documented OSA by means of overnight polysomnography (apnea/hypopnea index (AHI) >20) in an accredited sleep laboratory affiliated with the University of Illinois College of Medicine. All OSA subjects were snorers. Two individuals, one of them previously treated surgically for OSAS, were candidates for nasal continuous positive airway pressure (CPAP) treatment. All the remainder OSA subjects were receiving CPAP treatment ranging from two months to 13 years of therapy. Two OSA subjects had a history of and received therapy for severe hypertension and asthma. One individual was diagnosed with mild hypertension that was not treated. No other OSA subject had any history of co-morbid conditions.

The remaining 13 individuals, six females and seven males (age 36.5±10.9 years, range 22-54 years) constituted the control group. One control subject had a family history of OSA. Six controls (four females, two males) were snorers, according to the bed partner's testimony, without documented OSAS. A young control snorer had borderline hypertension that was not requiring any treatment. The medical history of the control subjects was unremarkable.

Certain subjects were measured via NIRS twice or three times in a one-month period in order to check the reproducibility of the results. Ethical standards were used in the present study. The research protocols involving human subjects have received prior approval from the Institutional Review Boards of the University of Illinois at Urbana-Champaign (Case #01067) and ISS Inc, Champaign, IL. All subjects were asked to fillout a questionnaire regarding sex, age, height, weight, diagnosis and treatment of OSAS, and other relevant medical history in order to fulfill statistical requirements. Written informed consent had been obtained from all subjects before testing.

Measurement Technique
Subjects were measured in the supine position for more than one hour. The pulse oximeter sensor was attached to the index finger of the subject. A respiratory strain gauge was wrapped around the lower chest area. The NIR probe was positioned on the forehead, avoiding the sinuses, and as close as possible to the hairline.

We investigated brain oxygenation in the OSA subjects and in the healthy controls under two conditions: first, during voluntary breath holding exercises, and second, during the course of diurnal napping.

Experimental Set 1: Effects of Induced Hypoxia on Brain Hemodynamics and Oxygenation
To characterize the cerebral response to the reduction of oxygen supply in the brain, we induced hypoxia by voluntary breath holding for at least 10 seconds. We simulated sleep apnea by breath holding at functional residual capacity (at the end of a normal expiration). The reason we perform breath holding exercises is to evaluate vascular reactivity and cerebral hemodynamic responses to hypoxia and hypercapnia. Carbon dioxide is a vasodilator in the brain (O'Regan and Majcherczyk, 1982; Bayerle-Eder et al., 2000).

Subjects rested, lying down in a quiet room with appropriate ventilation and temperature and dim lighting.

    A. Following complete relaxation of several minutes, measurements of cerebral hemodynamics were obtained via the tissue oximeter. The arterial hemoglobin oxygen saturation, heart rate, and breathing rate, were simultaneously

recorded via the pulse oximeter and the respiratory strain gauge, respectively. The values obtained were averaged and considered as the baseline values.

B. Subjects were invited to hold their breath, at the end of a normal expiration, for as long as they were comfortable (approximately 10 to 30 seconds), and measurements were acquired. Following resumption of breathing and return of the SaO_2 to its baseline values, this procedure was repeated 3-5 times.

Experimental Set 2: Effects of Sleep Apnea on Brain Hemodynamics and Oxygenation During Diurnal Napping
Individuals suffering from OSA have apneic/hypopneic episodes even during brief daytime napping. The assessment and evaluation of the impact of sleep apnea on cerebral oxygenation during diurnal napping as performed. The control and OSA subjects rested, lying down in a quiet dim room with appropriate ventilation and temperature.

A. Following complete relaxation of several minutes, the baseline measurements of cerebral hemodynamics were obtained via the tissue oximeter. The SaO_2, HR, and RS were recorded by the pulse oximeter and the respiratory strain gauge, respectively. The baseline was so determined.
B. Subjects were invited to take a 30-minute nap. The parameters mentioned above were recorded continuously.

Data Analysis

Respiratory Signal
We processed the respiratory signal to estimate the frequency of the respiratory rhythm to assess normal breathing and also to detect and count sleep apnea/hypopnea episodes and apneas due to breath holding, as well as to determine their duration.

Arterial Hemoglobin Oxygen Saturation and Heart Rate
We analyzed changes in SaO_2 due to hypoxia during sleep apnea and during breath holding. We compared it with the corresponding changes in SO_2. The decrease in the average SaO_2 level, compared to the baseline, was used as an indicator that the subjects slept during the diurnal nap in addition to the subjects' confirmation. The baseline levels of SaO_2 and HR of OSA and control subjects were compared.

Oxy-, Deoxy-, and Total Hemoglobin Concentrations: Cerebral Tissue-Hemoglobin Oxygen Saturation
To calculate the absolute optical coefficients of the investigated tissue, we used the previously described multi-distance frequency-domain method (Fantini et al., 1994; Fishkin and Gratton, 1993; Hueber et al., 2001). Values of the absolute absorption (μ_a) and reduced scattering (μ_s') coefficients of the tissue were calculated using slopes (S_{AC} and S_φ) of the corresponding $\ln(r^2 AC)$ and F plots, as a function of the source detector distance (r), where AC is the amplitude of the light intensity, and F its phase (Hueber et al., 2001).

$$\mu_a = \frac{\pi F}{v}\left(\frac{S_\phi}{S_{AC}} - \frac{S_{AC}}{S_\phi}\right); \qquad \mu_s' = \frac{S^2_{AC} - S^2_\phi}{3\mu_a} - \mu_a,$$

where F=110 Mhz, is the modulation frequency; v is the speed of light in the medium (in cm/s).

Subsequently, the following well-known equations were used to calculate the tissue hemoglobin parameters (Rolfe, 2000; Zhang et al., 2000):

$$[O_2Hb] = \frac{\mu_a*(\lambda_1)\varepsilon_{Hb}(\lambda_2) - \mu_a*(\lambda_2)\varepsilon_{Hb}(\lambda_1)}{\varepsilon_{O_2Hb}(\lambda_1)\varepsilon_{Hb}(\lambda_2) - \varepsilon_{O_2Hb}(\lambda_2)\varepsilon_{Hb}(\lambda_1)};$$

$$[HHb] = \frac{\mu_a*(\lambda_2)\varepsilon_{O_2Hb}(\lambda_1) - \mu_a*(\lambda_1)\varepsilon_{O_2Hb}(\lambda_2)}{\varepsilon_{O_2Hb}(\lambda_1)\varepsilon_{Hb}(\lambda_2) - \varepsilon_{O_2Hb}(\lambda_2)\varepsilon_{Hb}(\lambda_1)};$$

$$[tHb] = [O_2Hb] + [HHb]; \quad SO_2 = 100*[O_2Hb]/[tHb],$$

where the brackets [ ] indicate the concentration of the chromophore; $\varepsilon_{Hb}(\lambda_1)$, $\varepsilon_{Hb}(\lambda_2)$, $\varepsilon_{O2Hb}(\lambda_1)$, $\varepsilon_{O2Hb}(\lambda_2)$ are the molar extinction coefficients of [HHb] and [O_2Hb] for the wavelength λ_1 and λ_2; μ_a* indicates absorption coefficients corrected for water content of the brain tissues; $\mu_a*(\lambda) = \mu_a(\lambda) - 0.7\mu_a^{H2O}(\lambda)$, where $\mu_a^{H2O}(\lambda)$ is the water absorption coefficient at the wavelength λ.

We compared quantitative and qualitative changes in [O$_2$Hb], [HHb], [tHb] (µmol/L), and SO$_2$ (%) observed in OSA subjects with those recorded from the control group during breath holding and diurnal napping.

RESULTS

The baseline levels of SaO$_2$ were 1-3% lower (p<0.03) in OSA subjects compared to the controls. The HR baselines in both groups were not significantly different. There was a correlation in brain hemodynamic responses between left and right frontal lobes due to regular breathing and apnea episodes (sleep apnea/hypopnea and breath holdings).

Repetitive measurements on seven OSA subjects, four snorers and four non-snorers, showed high reproducibility of the results.

A control subject with a family history of sleep apnea, but not clinically diagnosed with OSAS, showed patterns of repetitive apneic episodes during daytime napping and reduced cerebrovascular compensation (autoregulation) during breath holding in both trials he participated in. We eliminated these data from the control results used for the comparison with OSA data.

Arterial and Brain Tissue Hemoglobin Oxygen Saturation
To estimate the degree of the blood and cerebral tissue deoxygenation, we analyzed decreases in SaO$_2$ and SO$_2$, normalized (Δ_n) by the duration of the corresponding hypoxic period (Δ_nSaO$_2$ and Δ_nSO$_2$, respectively), during the breath holding exercise, and during daytime napping. Changes due to apneic episodes during sleep were calculated for OSA subjects only. Δ_nSaO$_2$=ΔSaO$_2$/t$_a$; Δ_nSO$_2$=ΔSO$_2$/t$_a$, where t$_a$ indicates the duration of the apnea event; ΔSaO$_2$ and ΔSO$_2$ indicate decreases in SaO$_2$ and SO$_2$ below baseline values during the breathing exercise or during nap. Normalized changes indicate arterial and brain tissue hemoglobin deoxygenation per unit of apnea (induced or in OSAS) duration. The normalized changes in SaO$_2$ and SO$_2$ are less dependent from the duration of the apneic episode, compared to the absolute changes in SaO$_2$ and SO$_2$ and more accurate for discrimination and screening.

Normalized individual changes in SaO$_2$ and SO$_2$ show a significant difference (Kruskal-Wallis H-test; $p \leq 0.02$ for Δ_nSaO$_2$ and $p \leq 0.025$ for Δ_nSO$_2$) between control and sleep apnea subjects (Figure 2). Table 1 presents control and OSA subject data about the mean values and standard deviations of the Δ_nSaO$_2$ and Δ_nSO$_2$. A higher rate of arterial anΔ brain tissue deoxygenation was observed for OSA individuals during sleep. For the sleep apnea group, Δ_nSaO$_2$ was larger during napping than during the breathing exercise ($p \leq 0.05$). A similar trend was observed in normalized differences in SO$_2$.

OSA subjects showed comparatively higher mean absolute values of SaO$_2$ (on 3-7%; $p \leq 0.01$, two-way ANOVA) and SO$_2$ (on 1-2%; $p \leq 0.01$) during breathing exercises compared to diurnal napping.

Oxy-, Deoxy-, and Total Hemoglobin Concentrations
Individual time traces of the respiratory signals, SO$_2$, and changes in [tHb], [O$_2$Hb], and [HHb] for control and OSA subjects during breath holding and diurnal napping are presented in Figures 3 and 4. Changes in [tHb], [O$_2$Hb], and [HHb] are relative to the corresponding baseline values described in the methodology we followed. Figures 3c and 3a show increased cerebral tissue deoxygenation in an OSA subject during breath holding compared to changes in SO$_2$ in a healthy control subject, respectively. Figures 3b and 3d show changes in the hemodynamics (Δ[O$_2$Hb] and Δ[HHb]) of these subjects during breath holding. In the control, those changes show typical cerebral autoregulatory response, that is, an increase in [O$_2$Hb] and a decrease in [HHb]. Figures 3c and 3d represent severe brain deoxygenation and seriously compromised brain autoregulation in the OSA subject with a decrease in [O$_2$Hb], and an increase in [HHb].

In the control subjects during daytime napping, we observed opposite direction of changes in [O$_2$Hb] and [HHb] due to periodic vasomotion (Figure 4b). In OSA subjects during daytime napping, changes in [O$_2$Hb] and [HHb] (Figure 4d), due to sleep apnea/hypopnea episodes, were not in opposite-phase correlation but had a different time shift. The amplitude of the changes of [tHb], due to apnea episodes during napping (Figure 4d), was twice as large as the amplitude of the changes of [tHb] observed in the control subject during diurnal napping (Figure 4b).

Figure 5 shows the dynamics of the autoregulatory changes in [O$_2$Hb] and [HHb] relative to the baselines in a healthy control subject (Figure 5a) and a chronic OSA subject who was also treated for hypertension and asthma (Figure 5b). Similar patterns of different amplitudes of Δ[O$_2$Hb] and Δ[HHb] and different breath holding duration were observed for all control and OSA subjects. In individuals with OSA and no other medical condition, we detected a protective cerebrovascular response to hypoxia and hypercapnia that is vasodilation and opening of the capillary bed consistent with an increase of cerebral blood flow, which is likely to prevent eventual brain injury during apnea. Specifically, we detected an

increase in $\Delta[O_2Hb]$ and an increase in $\Delta[tHb]$ that were significantly reduced compared to changes in the control non-snorers. In OSA subjects with preexistent cardiovascular pathology, this protective mechanism may be defective, as seen in Figure 5b.

We analyzed 19 recordings (71 breath holdings) of 11 control subjects (five snorers and six non-snorers), using the described breath holding protocol, and 17 recordings (58 breath holdings) of eight OSA subjects. Changes in cerebral oxygenation and hemodynamics due to hypoxia during breath holding showed statistically significant differences ($p<0.05$, except [tHb]) between control and OSA subjects (Figure 6) and between non-snorers and OSA subjects ($p<0.03$ for $\Delta[O_2Hb]$, $\Delta[HHb]$, $\Delta[tHb]$, and ΔSO_2).

Snorers of the control group had an inefficient hemodynamic response to hypoxia ($p<0.05$, Mann-Whitney test) compared to the control non-snorers. In 90% of breath holding events of the six non-snorers, the $[O_2Hb]$, [tHb], and SO_2 did not decrease below baseline values. In the OSA population, in 27% of breath holding events, we observed a significant decrease in $[O_2Hb]$, [tHb], and SO_2, and an increase in [HHb]. The duration of breath holdings was 1.75 times longer in the control subjects compared to the OSA subjects.

DISCUSSION

Elwell et al. (1994) have shown that physiological changes due to regular respiratory oscillations did not significantly affect cerebral blood volume (CBV) or cerebral blood flow (CBF) in healthy subjects under normal resting conditions. In accord with these findings, we did not observe significant variations in cerebral oxygenation and hemodynamics in the control subjects during nap or baseline measurements. However, hypoxic events caused significant changes in arterial and brain tissue hemoglobin oxygen saturation in OSA subjects during diurnal napping. Based on our observation, we suggest that recurrent changes in cerebral tissue oxygenation and hemodynamics due to chronic intermittent hypoxia in sleep apnea, recorded by NIRS, may be associated with an increased risk for cerebro/cardiovascular morbidity in OSA subjects.

According to Nielsen et al. (2001), even a small change in arterial CO_2 partial pressure was able to increase brain $\Delta[O_2Hb]$ in healthy volunteers during exercise. Cerebral oxygenation increased and decreased only when maximal exercise elicited a significant arterial deoxygenation during cycling ergometry with different levels of resistive breathing. Our results for control non-snorers correlate with these findings. We observed that the response to simple breath holding exercises, registered by NIRS, was significantly reduced in OSA subjects compared to the healthy control volunteers. In controls, the amplitude of the hemodynamic response to the hypoxia was significantly larger ($p<0.01$) than the amplitude of the baseline fluctuations and changes during nap. In contrast, in the OSA group, the amplitude of changes in cerebral tissue oxygenation and hemodynamics due to sleep apnea was comparable to the amplitude of corresponding changes due to breath holdings that is a risk for eventual brain injury.

We observed and quantitatively estimated changes in cerebral hemodynamics ($[O_2Hb]$, [HHb], and [tHb]) and tissue oxygenation during the measurements. These changes correlate with changes in CBV and CBF, and the protective cerebrovascular response (circulatory compensatory mechanism) to hypoxia can be estimated by these changes (De Blasi et al., 1997; Elwell et al., 1994; Nielsen et al., 2001; Owen-Reece et al., 1996; Vernieri et al., 1994; Wolf et al., 2000).

The observed changes in [tHb] caused by hypoxia during breath holding and during napping are directly proportional to the variation of the regional CBV (De Blasi et al., 1997; Vernieri et al., 1994). The simultaneous increase in $[O_2Hb]$ and a stable level or decreases in [HHb] indicate a rise in CBF (Elwell et al., 1994; Nielsen et al., 2001). These changes in brain tissue oxygenation and hemodynamics depend on the arterial hemoglobin deoxygenation and on the efficiency of the protective cerebrovascular response, the so-called autoregulation of CBF. Based on this study, we propose that the autoregulation of brain circulation can be characterized qualitatively and quantitatively by analysis of the optical data, shown in Figures 5 and 6. Quantitative estimation of changes in $[O_2Hb]$, [HHb], [tHb], and SO_2 induced by hypoxia may discriminate OSA subjects from healthy subjects and assess cerebral oxygenation dysfunction for different stages of the disease, as well as distinguish between snorers and non-snorers.

Conclusion
Our objective in this preliminary study of cerebrovascular responses to hypoxia was to apply NIRS, a non-invasive method, to monitor changes in brain oxygenation and hemodynamics in order to estimate effects of chronic intermittent hypoxia in obstructive sleep apnea syndrome.

A comfortable probe and appropriate measurement protocols have been developed and successfully implemented on human volunteers diagnosed with OSAS and on control subjects. Long traces of data have been collected and analyzed using new

algorithms we specifically developed. We assessed changes in cerebral tissue oxygenation and hemodynamics during diurnal napping-related apnea/hypopnea episodes and voluntary breath holding exercises. These hemodynamic responses characterized the efficiency of the cerebral autoregulation to prevent hypoxic brain morbidity. The frequency-domain, multi-distance approach, despite the methodological limitations, allowed us to validate significant differences in brain oxygenation and hemodynamic changes between control and OSA groups during breath holding exercises and diurnal napping.

We observed that hypoxic episodes during diurnal napping in OSA subjects induced recurrent cerebral tissue deoxygenation, which was larger than the SO_2 changes during the breath holding exercises, and also larger than cerebral tissue deoxygenation recorded in control subjects during breath holdings. From our measurements, we can assume that in healthy subjects there is a protective cerebrovascular response to hypoxia (increase in cerebral blood flow and cerebral blood volume), which is likely to prevent eventual brain injury. In OSA sufferers, the chronic vasomotor responses due to chronic, intermittent cerebral hypoxia produce alterations of the vascular wall. This may lead to structural and functional cerebral macro and microangiopathies, and the ability of the vessels to dilate in order to increase the blood flow to meet the oxygen demands of the brain is compromised. According to our results in the OSA group, depending upon the severity and chronicity of sleep apnea, this response may be diminished or absent.

In a second phase of our investigation, we intend to apply NIRS concomitantly to the overnight polysomnographic recordings in both OSA sufferers and healthy controls in order to validate our findings and correlate them to the information from other monitoring instrumentation, such as electroencephalography. We will also monitor cerebrovascular reactivity to hypoxia and hypercapnia in a more rigorously selected subject population in a properly controlled study.

NIRS has the capability to complement polysomnography with a new, powerful modality. NIRS may provide the clinician with an important direct insight of the cerebral tissue oxygenation and hemodynamic changes during the intermittent hypoxic episodes in obstructive sleep apnea. It may also be used as a stand-alone technique for the detection of brain vascular hemodynamic abnormalities in the obstructive sleep apnea sufferers, and for screening OSA suffers at risk for brain vascular injuries in order to prevent cerebrovascular morbidity and mortality.

REFERENCES

1. Bayerle-Eder M, Wolzt M, Polska E, Langenberger H, Pleiner J, Teherani D, Rainer G, Polak K, Eichler HG, Schmetterer L. Hypercapnia-induced cerebral and ocular vasodilation is not altered by glibenclamide in humans. Am J Physiol Regul Integr Comp Physiol 2000; 278(6): 1667-73.

2. Blankfield RP, Hudgel DW, Tapolyai AA, Zyzanski SJ. Bilateral leg edema, obesity, pulmonary hypertension, and obstructive sleep apnea. Arch Intern Med 2000; 160(15): 2357-62.

3. De Blasi RA, Almenrader N, Ferrari M. Brain oxygenation monitoring during cardiopulmonary bypass by near infrared spectroscopy. Adv Exp Med Biol 1997; 413: 97-104.

4. Douglas NJ, Thomas JMA. Clinical value of polysomnography. Lancet 1992; 339(8789): 347-50.

5. Elwell CE, Cope M, Edwards AD, Wyatt JS, Delpy DT, Reynolds EOR. Quantification of adult cerebral hemodynamics by near-infrared spectroscopy. J Appl Physiol 1994; 77(6): 2753-60.

6. Elwell CE, Owen-Reece H, Wyatt JS, Cope M, Reynolds EO, Delpy DT. Influence of respiration and changes in expiratory pressure on cerebral haemoglobin concentration measured by near infrared spectroscopy. J Cereb Blood Flow Metab 1996; 16(2): 353-7.

7. Fantini S, Franceschini M, Gratton E. Semi-infinite-geometry boundary problem for light migration in highly scattering media: a frequency-domain study in the diffusion approximation. J Opt Soc Am 1994; B11: 2128-38.

8. Fishkin JB, Gratton E. Propagation of photon-density waves in strongly scattering media containing an absorption semi-infinite plane bounded by a straight edge. J Opt Soc Am 1993; A10: 127-40.

9. Franceschini MA, Fantini S, Paunescu LA, Maier JM, Gratton E. Influence of a superficial layer in the quantitative spectroscopic study of strongly scattering media. Appl Opt 1998; 37: 7447-58.

10. Franceschini MA, Zourabian A, Moore JB, Arora A, Fantini S, Boas DA. Local measurement of venous saturation in tissue with non-invasive, near-infrared respiratory-oximetry. Proc SPIE 2001; 4250: 164-70.

11. Fry JM, DiPhillipo MA, Curran K, Goldberg R, Baran AS. Full polysomnography in the home. Sleep 1998; 21(6): 635-42.

12. Hayakawa T, Terashima M, Kayukawa Y, Ohta T, Okada T. Changes in cerebral oxygenation and hemodynamics during obstructive sleep apneas. Chest 1996; 109(4): 916-21.

13. Hueber DM, Franceschini MA, Ma HY, Zhang Q, Ballesteros JR, Fantini S, Wallace D, Ntziachristos V, Chance B. Non-invasive and quantitative near-infrared haemoglobin spectrometry in the piglet brain during hypoxic stress, using a frequency-domain multidistance instrument. Phys Med Biol 2001; 46: 41-62.

14. Jöbsis FF. Non-invasive infrared monitoring of cerebral myocardial oxygen sufficiency and circulatory parameters. Science 1977; 198: 1264-7.

15. Lavie L, Perelman A, Lavie P. Plasma homocysteine levels in obstructive sleep apnea: association with cardiovascular morbidity. Chest 2001; 120(3): 900-8.

16. Lichty W, Sakatania K, Xie Y, Zuo H. Application of near-infrared spectroscopy to investigate brain activity: clinical research. PIE Proc Optical Sensing, Imaging, and Manipulation for Biological and Biomedical Applications 2000; 4082: 34-9.

17. Madsen PL, Secher NH. Near-infreared oximetry of the brain. Progress in Neurobiology 1999; 58: 541-60.

18. Marrone O, Bonsignore MR, Insalaco G, Bonsignore G. What is the evidence that obstructive sleep apnoea is an important illness? Monaldi Arch Chest Dis 1998; 53(6): 630-9.

19. Michalos A, Paunescu LA, Wolf M, Wolf U, Toronov V, Gratton E. Assessment of cerebral oxygenation and hemodynamics in obstructive sleep apnea syndrome. OSA Boimedical Topical Meetings 2000; 16: 163-5.

20. Michalos A, Safonova LP, Hueber DM, Wolf U, Wolf M, Choi JH, Gupta R, Polzonetti C, Barbieri B, Mantulin WW, Gratton E. Reduced cerebral hemodynamic response in sleep disorders: A NIRS frequency domain study. OSA Biomedical Topical Meetings 2002; 1: 248-50.

21. Michalos A, Safonova LP, Wolf U, Wolf M, Choi JH, Gupta R, Mantulin WW, Hueber DM, Barbieri B, Gratton E. Obstructive Sleep Apnea: Evaluation of Brain Oxygenation and Hemodynamics by Near-Infrared Spectroscopy. SLEEP 2002; 25: 547.

22. Mitler MM, Hajdukovic RM, Shafor R, Hahn PM, Kripke DF. When people die. Cause of death versus time of death. Am J Med 1987; 82(2): 266-74.

23. Neau JP, Paquereau J, Meurice JC, Chavagnat JJ, Gil R. Stroke and sleep apnoea: cause or consequence? Sleep Med Rev 2002; 6(6): 457-69.

24. Nielsen HB, Boesen M, Secher NH. Near-infrared spectroscopy determined brain and muscle oxygenation during exercise with normal and resistive breathing. Acta Physiol Scand 2001; 171: 63-70.

25. Okada E, Delpy DT. Effect of scattering of arachnoid trabeculae on light propagation in the adult brain. Biomedical Topical Meetings. OSA 2000; 256: 3.

26. O'Regan RG, Majcherczyk S. Role of peripheral chemoreceptors and central chemosensitivity in the regulation of respiration and circulation. J Exp Biol 1982; 100: 23-40.

27. Owen-Reece H, Elwell CE, Harkness W, Goldstone J, Delpy DT, Wyatt JS, Smith M. Use of near infrared spectroscopy to estimate cerebral blood flow in concious and anaesthtized adult subjects. Br J Anaesth 1996; 76: 43-8.

28. Palomaki H, Partinen M, Erkinjuntti T, Kaste M. Snoring, sleep apnea syndrome, and stroke. Neurology 1992; 42(7) Suppl 6: 75-81.

29. Peker Y, Hedner J, Kraiczi H, Loth S. Respiratory disturbance index: an independent predictor of mortality in coronary artery disease. Am J Respir Crit Care Med 2000; 162(1): 81-6.

30. Pressman MR, Schetman WR, Figueroa WG, Van Uitert B, Caplan HJ, Peterson DD. Transient ischemic attacks and minor stroke during sleep. Relationship to obstructive sleep apnea syndrome. Stroke 1995; 26(12): 2361-5.

31. Redline S, Strohl KP. Recognition and consequences of obstructive sleep apnea hypopnea syndrome. Clin Chest Med 1998; 19(1): 1-19.

32. Rolfe P. In vivo near-infrared spectroscopy. Annu Rev Biomed Eng 2000; 2: 715-54.

33. Sharabi Y, Scope A, Chorney N, Grotto I, Dagan Y. Diastolic blood pressure is the first to rise in association with early subclinical obstructive sleep apnea: lessons from periodic examination screening. Am J Hypertens 2003; 16(3): 236-9.

34. Toronov V, Franceschini M, Filiaci M, Wolf M, Fantini S, Gratton E. Near-infrared study of fluctuations in cerebral hemodynamics during rest and motor stimulation: spatial mapping and temporal analysis. Med Phys 2000; 27(4): 801-15.

35. Vernieri F, Rosato N, Pauri F, Tibuzzi F, Passarelli F, Rossini PM. Near infrared spectroscopy and transcranial doppler in monohemispheric stroke. Eur Neurol 1994; 41: 159-62.

36. Wolf M, von Siebenthal K, Keel M, Dietz V, Baenziger O, Bucher H. Tissue oxygen saturation measured by near infrared spectrophotometry correlates with arterial oxygen saturation during induced oxygenation changes in neonates. Physiol Meas 2000; 21: 481-91.

37. Young A, Germon TJ, Barnett NJ, Manara AR, Nelson RJ. Behavior of near-infrared light in the adult human head: implications for clinical near infrared spectroscopy. Br J Anaesth 2000; 84: 38-42.

38. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328(17): 1230-5.

39. Zhang G, Katz A, Alfano RR, Kofinas AD, Kofinas DA, Stubblefield PG, Rosenfeld W, Beyer D, Maulik D, Stankovic MR. Brain perfusion monitoring with frequency-domain and continuous-wave near-infrared spectroscopy: a cross-correlation study in newborn piglets. Phys Med Biol 2000; 45: 3143-58.
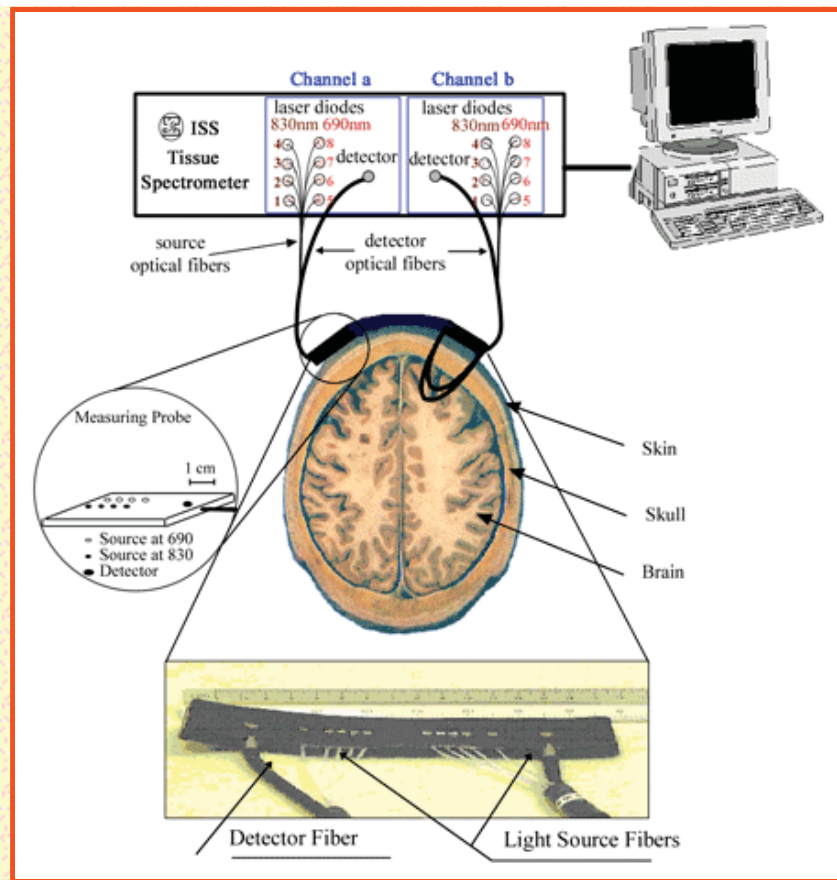
ACKNOWLEDGMENTS
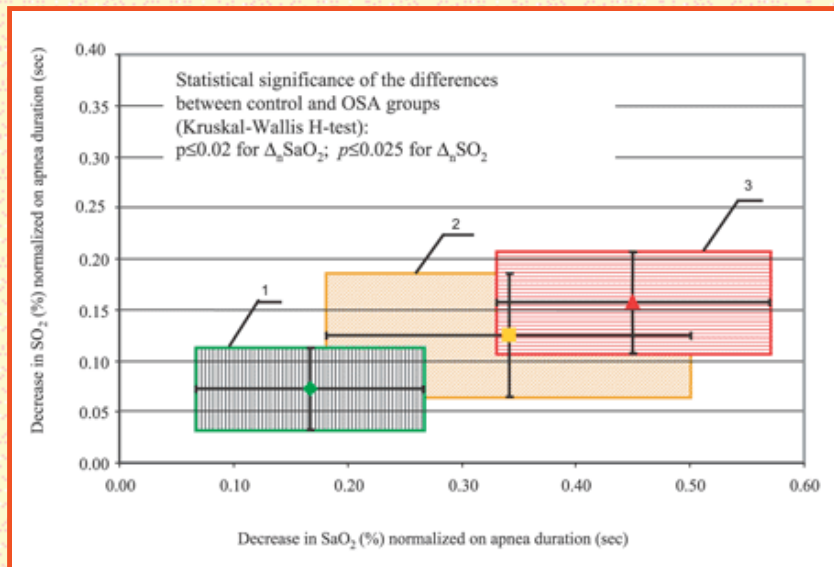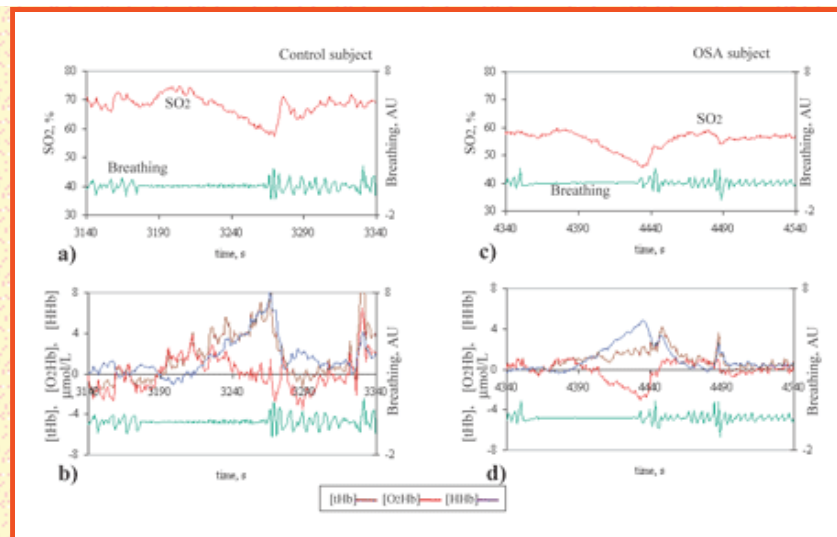
FIGURES

Figure 1.

Instrumental arrangement, sensor configuration, and dual sensor probe

Figure 2.

Characterization of subjects by decreases in $_2$ and SO_2 normalized on the duration of the hypoxic event, mean values and standard deviations. 1: control subjects during the breath holding exercises; 2: OSA subjects during breath holding exercises; 3: OSA subjects during diurnal napping.
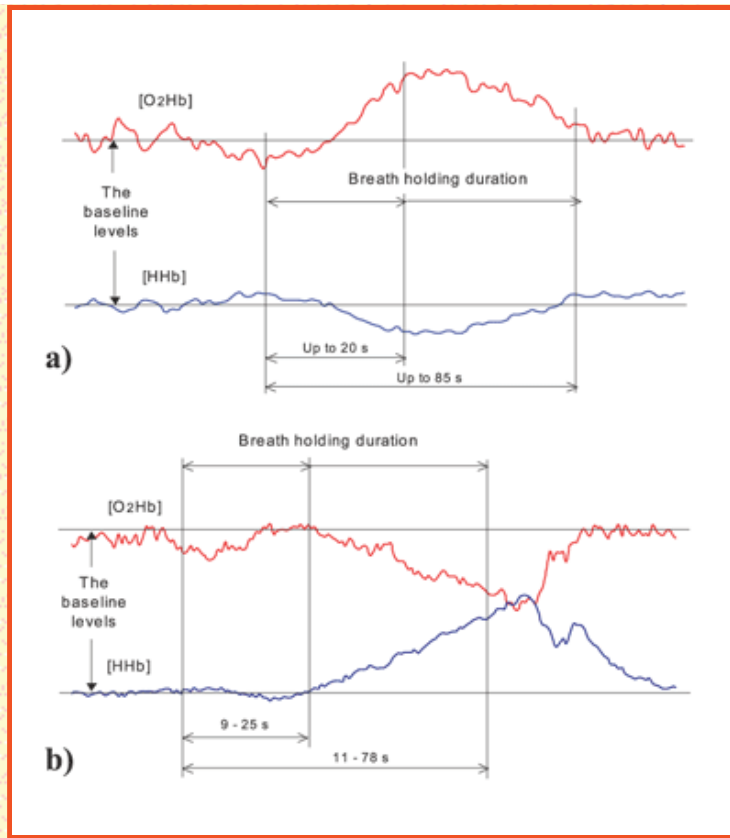
Figure 3.

Cerebral oxygenation (a,c) and changes in hemodynamics (b,d) as compared to baseline values in (a,b) a healthy control subject and in (c,d) an OSA subject during breath holding.
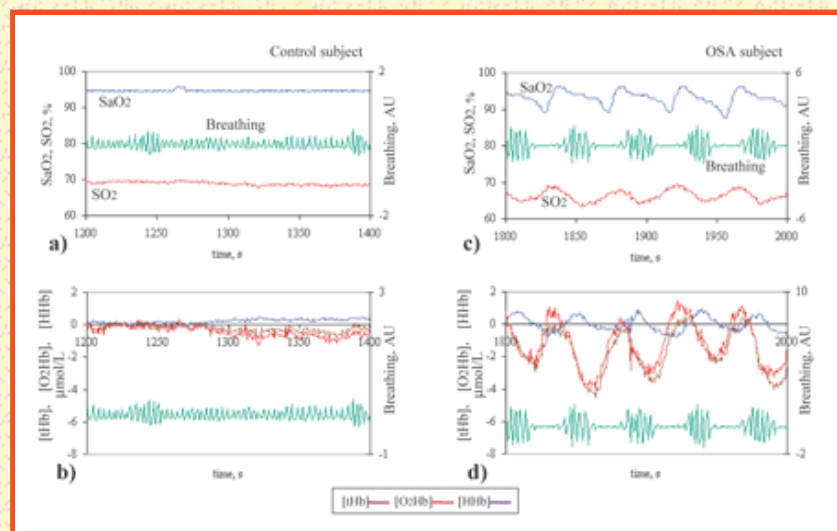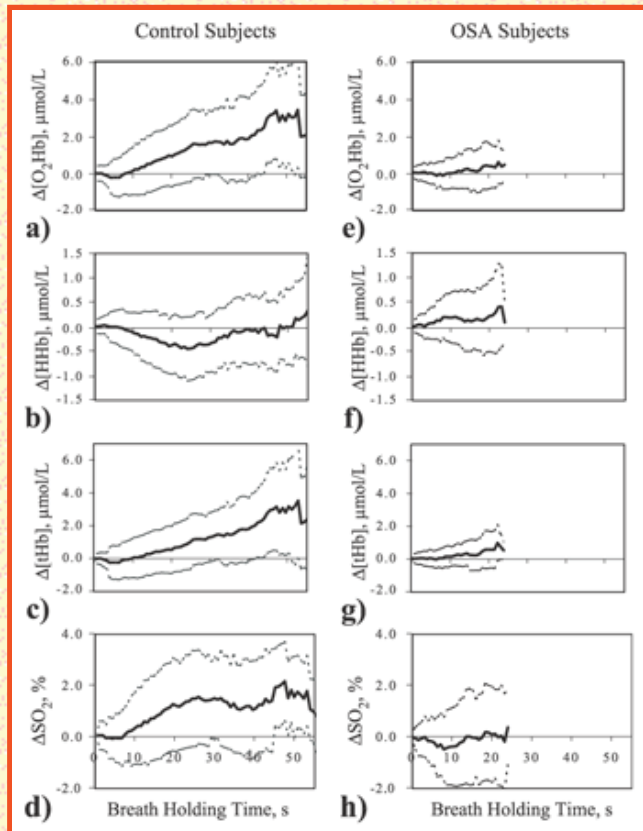

Figure 4.

Cerebral oxygenation (a,c) and changes in hemodynamic parameters (b,d) as compared to baseline values in a healthy control subject (a,b) and in an OSA subject (c,d) during diurnal napping.

Figure 5.

Dynamics of autoregulatory changes in [O₂Hb] and [HHb] with respect to the baseline values in a healthy control (a) and a chronic OSA patient (b) during breath holding.

Figure 6.

Means and standard deviations of changes in (a,e) [O_2Hb], (b,f) [HHb], (c,g) [tHb], and (d,h) SO_2 observed in 11 control subjects (a-d) and eight OSA subjects (e-h) during volunteer breath holdings.

TABLES

Table 1.

Brain tissue and arterial hemoglobin oxygen desaturation during hypoxic events. Normalized mean falls in arterial ($\Delta_n SaO_2$) and brain tissue ($\Delta_n SO_2$) hemoglobin oxygen saturation and corresponding standard deviations, (%/sec) as compared to baseline values.

Hypoxic Condition	Control Group (10 subjects/10 breath holdings)			OSA Group (8 subjects/11 breath holdings)		
	ta(s)	$\Delta_n SaO_2$	$\Delta_n SO_2$	ta(s)	$\Delta_n SaO_2$	$\Delta_n SO_2$
Sleep Apnea Events	–	–	–	12.7±2.4	0.45±0.12	0.16±0.05
Breathing Exercises	48.7±28.4	0.17±0.10	0.07±0.04	28.4±20.05	0.34±0.16	0.13±0.06