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Original Article

# Low-frequency oscillations and vasoreactivity of cortical vessels in obstructive sleep apnea during wakefulness: A near infrared spectroscopy study

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ABSTRACT

*Objectives:* Effective nasal continuous positive airway pressure (CPAP) therapy reduces the cardiovascular outcomes associated with obstructive sleep apnea (OSA), but the mechanism behind this effect is unclear. We investigated if OSA patients during wakefulness showed signs of increased sympathetic activity and decreased vasoreactivity in cerebral cortical vessels as measured with near-infrared spectroscopy (NIRS), and if this may be reversed by CPAP treatment.
*Subjects and methods:* 23 OSA patients (mean age, 55 y) naive to CPAP were included in a prospective interventional study. The OSA patients received CPAP therapy for at least two months. Cortical low-frequency oscillation (LFO) amplitudes and vasoreactivity during a breath hold test were measured with NIRS and were compared between baseline and after CPAP treatment. Baseline values also were compared to 13 healthy controls (mean age, 52 y).
*Results:* We found a decrease in LFO amplitudes after CPAP therapy ($P = 0.022$) in OSA patients. We found no differences in LFO amplitudes between OSA patients and healthy controls ($P = 0.934$). There were no differences in peak vascular response following breath hold tests in OSA patients before and after CPAP therapy ($P = 0.158$) or compared to healthy controls ($P = 0.740$).
*Conclusion:* Our NIRS study revealed a decrease in LFO amplitude following two months of CPAP treatment in OSA patients, which may reflect a decrease in sympathetic activity affecting cortical vessels.


## 1. Introduction

In the general population the prevalence of obstructive sleep apnea (OSA) is high [1,2] and has been reported to be up to 33% [3]. OSA is more prevalent among men and increases with age [4,5]. OSA is characterized by repetitive episodes of partial or complete upper airway obstruction during sleep associated with intermittent oxygen desaturation, snoring and sleep fragmentation [6]. OSA is strongly associated with transitory ischemic attacks (TIA) [7] and cerebral infarction [7–9], independent of other risk factors. Effective nasal continuous positive airway pressure (CPAP) therapy reduces the cardiovascular outcomes associated with OSA [9], but the mechanism behind this effect is unclear.

During OSA episodes of intermittent hypoxia, recurrent arousals and intrathoracic pressure swings are suggested to induce sympathetic activation, which eventually may lead to endothelial dysfunction [10]. An increase in sympathetic activity in OSA patient may affect cortical cerebral vessels directly [11], but this theory has never been investigated before. Investigating cortical cerebral vessels in OSA patients may help to clarify the pathophysiologic mechanisms leading to ischemic vascular diseases in OSA.

Cerebral cortical vascular changes can be monitored non invasively in humans in vivo by near-infrared spectroscopy (NIRS), which can detect relative changes in oxyhemoglobin (oxyHb), deoxyhemoglobin (deoxyHb) and total hemoglobin (totalHb) [12]. So far, NIRS has been used to record oxyHb and deoxyHb changes during obstructive sleep apnea events in OSA patients [13,14]. Previous NIRS studies in awake patients and healthy subjects have investigated cortical low-frequency oscillation (LFO) oxyHb [11,15–17]. An increase in oxyHb LFO amplitude is posture dependent in healthy subjects and therefore is believed to increase during sympathetic activation [11]. NIRS also may detect cortical endothelial dysfunction by measuring vasoreactivity via a breath-hold test [18]. Therefore, NIRS may be applied to assess sympathetic activity and vasoreactivity in the cerebral cortical vasculature in awake OSA patients, but this hypothesis has not been previously investigated.

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In our study, we aimed to investigate if OSA patients during wakefulness have increased LFO amplitude in cerebral cortical vessels as a sign of increased sympathetic activity by employing NIRS. We investigated changes in cortical LFO amplitude in OSA patients following two months of effective CPAP treatment and in comparison to healthy controls. Furthermore, we explored changes in vasoreactivity in response to breath-hold tests in OSA patients following CPAP treatment and in comparison to healthy controls.

## 2. Subjects and methods

### 2.1. Subjects

Patients with moderate to severe OSA who had never received CPAP therapy were recruited from April 2011 to November 2011 at the Danish Center for Sleep Medicine, Glostrup Hospital, Denmark. OSA was diagnosed according to the International Classification of Sleep Disorders by the American Academy of Sleep Medicine [19] by sleep disorder specialists. OSA patients had an AHI (apnea–hypopnea index) $\geqslant$15 evaluated with either polysomnography (PSG) or cardiorespiratory monitory (CRM).

Healthy controls were recruited via internet advertising from the general population matching OSA for gender, age, body mass index (BMI), and time of recording. The healthy controls underwent a clinical interview and screening questions for snoring, witnessed apneas, and shirt size. All healthy controls were examined one night with CRM to exclude the presence of OSA or periodic nocturnal leg movements. PSG and CRM data were assessed by trained staff at the Danish Center for Sleep Medicine following the guidelines of the American Academy of Sleep Medicine [20].

Exclusion criteria for OSA patients and healthy controls were previous history of stroke, myocardial infarction, known stenosis of the carotid arteries (>50%), unstable chronic lung disease, anemia, present cardiac arrhythmia, central sleep apnea, rapid eye movement sleep behavior disorder, narcolepsy, medication with effects on the central nervous system, weekly alcohol use (more than 21 drinks for men or 14 drinks for women; 12 g of alcohol per drink), current use of illegal drugs, pregnancy, or breast feeding.

All subjects were examined with NIRS during daytime hours and OSA patients at a mean time of day of 12:15 PM (±0.42) and healthy controls at 12:16 PM (±0.56). OSA patients were reexamined with NIRS at the same time of the day within one hour following at least two months of CPAP treatment (IN551S, REMstar Auto A-flex w/SD CARD, Respironics Inc., Murrysville, USA). CPAP compliance was defined as CPAP used more than 50% of days at least four hours at night and was controlled by recording scripts from the patients' CPAP systems.

### 2.2. Near-infrared spectroscopy acquisition

Measurement of oxyHb, deoxyHb, and totalHb LFO was performed using continuous-wave NIRS (NIRS2; TechEn Inc, Milford, MA, USA). All recordings were performed by B.E.J. The NIRS optodes were placed bilaterally on the forehead with one source (two wavelengths, 690 nm and 830 nm) and two detectors on each side avoiding the frontal sinus. The distance between sources and detectors were three cm with the detectors lateral to the source. Thus, the detectors were measured at the frontal cortex supplied by the anterior cerebral artery or possibly the anterior cerebral artery or middle cerebral artery watershed areas.

LFO measurement was performed with the subjects in a comfortable supine position in a quiet room with a constant temperature (23 °C). The subjects were instructed to lie still and relax with their eyes open for 10 minutes. If subjects accidently fell asleep, they were gently awakened with a touch.

Breath hold was measured after a normal exhalation and subjects were instructed to hold their breath for up to 30-second tests, if possible. A maximum of four breath holds for each breath subject were recorded with two minute intervals. Breath holds lasting less than 15-seconds were excluded. To control that breath holds were properly performed subjects wore an open mask that caused no respiratory resistance to record $P_{ET}CO_2$ (ProPaq Encore; Welch Allyn Protocol, Beaverton, OR, USA). If any changes in $P_{ET}CO_2$ that indicated breathing were observed, the breath hold was excluded.

### 2.3. Data analysis

Postprocessing of NIRS data was performed by an expert who was blinded to the OSA and healthy control status of the subjects. Data processing was performed in MATLAB (The MathWorks Inc., Natick, Massachusetts, USA).

For the oscillation analysis, power spectra were estimated by computing the Fourier transform of the NIRS signal time series. NIRS intensity time series were first divided into windows of 100 seconds in duration with 50 seconds of overlap. Within each 100 s window, intensity variations at 690 and 830 nm were converted into relative changes in oxyHb and totalHb (ie, oxyHb + deoxyHb) using the modified Beer–Lambert Law [21] with a differential pathlength factor of six at both wavelengths. No correction for partial volume effect was employed because the NIRS measured oscillations are not expected to be very much localized. The oxyHb and deoxyHb signals were then Fourier transformed to obtain their power spectra (MATLAB function pwelch). The LFO frequency was defined as the frequency within the 0.05-Hz to 0.15-Hz range. To assess sympathetic activity the LFO amplitudes of oxyHb and totalHb were extracted as the value of the oxyHb spectrum at the LFO frequency. The values of oxyHb and totalHb amplitude were then averaged over all 100s windows and over the four NIRS channels.

For the breath-hold tests intensity variations at 690 and 830 nm also were converted into relative changes in oxyHb and totalHb as described above. Data collection was down sampled to 25 Hz and automatic motion detection was applied. The data also were low pass filtered at 0.5 Hz (to remove cardiac and high-frequency noise) and high-pass filter at 0.01 Hz (to remove slow drifts). The cortical cerebrovascular reactivity was assessed as the maximal increase in oxyHb and totalHb relative to baseline within the first 30 seconds of breath hold. The mean of four breath holds was used for analysis. Baseline was defined as the 10 seconds before breath hold instruction and was normalized to one.

### 2.4. Statistics

Data are presented as mean value ± standard error of the mean (±SEM). Sample size could not be properly determined before the study, as there is no previously known variation coefficient for the NIRS measurements performed in our study. However, other studies investigating cerebrovascular reactivity to hypercapnia included between eight and 20 subjects [22,23] and similar studies investigating LFO and cerebral oscillatory hemodynamics included between 10 and 38 subjects [11,24]. Gender match between OSA group and controls was analyzed with the Pearson $X^2$ test. Age, BMI, time of recording, and time between somnography and NIRS recordings between OSA patients and healthy controls were analyzed with the Mann–Whitney *U* test. Time of recording, changes after CPAP treatment in LFO oscillations, breath-hold data, and breath-hold duration within OSA patients were tested using the Wilcoxon signed rank test. Differences in oscillation, breath-hold data, and breath-hold duration between OSA patients and healthy