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CASE REPORT

Impaired cerebral vasoreactivity may cause cerebral blood volume dip following obstructive sleep apnea termination

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Introduction

Near-infrared spectroscopy (NIRS) is a non-invasive technique for estimating cortical concentration changes of oxy- ($\Delta[HbO_2]$), deoxy- ($\Delta[HbR]$), and total ($\Delta[HbT]=\Delta[HbO_2]+\Delta[HbR]$) hemoglobin [1, 2]. Cortical $\Delta[HbT]$ is commonly used as an indicator of cerebral blood volume (CBV) changes. Obstructive sleep apnea (OSA) is characterized by apneas (pause in breathing lasting over 10 s) or hypopneas (reduced respiratory air flow lasting over 10 s, accompanied by blood oxygen desaturation of at least 4% or EEG arousal) during sleep. The resulting oxygen and sleep deprivation can lead to severe health problems ranging from fatigue to coronary artery disease and stroke [3].

In a recent study, transcranial Doppler sonography (TCD) was used to measure cerebral blood flow velocity (CBFV) during sleep in OSA patients [4]. The study concluded that cerebral vasoreactivity decreases during OSA sleep, and apnea termination is followed by a drop in CBFV. Several studies indicate that apnea-induced changes in CBFV should be associated with parallel changes in cerebral blood flow (CBF) and consequently also in CBV [3, 5, 6]. However, in a recent NIRS study, CBV was found to stay relatively constant after apnea termination [2]. Here, we show repeatable NIRS results from a single OSA subject that agree with the TCD results and suggest a hemodynamic response pattern not previously reported in NIRS OSA studies.

Materials and methods

Study design

A male subject (age 25, body mass index 25, no past medical history) participated in four overnight sleep measurements, during which he displayed repetitive drops in peripheral blood oxygen saturation (SpO_2) measured with fingertip pulse oximeter. The drops were accompanied by EEG arousals. The first two measurements did not include any respiration monitoring, so the other two measurements were carried out to confirm OSA.

In all measurements, polysomnography including EEG, EOG, EMG, and SpO_2 was carried out. A NIRS probe was positioned on the right forehead just below the hairline. In the third measurement, respiration was monitored with

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breathing mask spirometry, and in the fourth, with nasal tube capnography. A neurophysiologist scored the sleep into stages according to the Rechtschaffen–Kales system and confirmed the subject's OSA.

All oxygen desaturation events from the four measurements with at least a 4% decrease in SpO_2 were included in the final analyses. Apneas were present predominantly within the first 60 min of sleep during S2 stage, and the apnea–hypopnea index (AHI) during that time was 22–26 on three nights and 12 on one night.

Voluntary breath-hold measurements in supine position were carried out on the OSA subject and a control group of seven healthy volunteers (six males, one female, ages 20–29). The objective was to test the similarities of cerebral hemodynamic responses during OSA and voluntary breath-hold. In the experiment, each subject was asked to hold their breath after normal expiration for as long as they felt comfortable, then take 4–5 breaths and repeat the task 20 times. The subjects were monitored using pulse oximetry, breathing mask spirometry, and NIRS. The study design was approved by the local hospital ethics committee, and written consent was obtained from all subjects.

NIRS measurement technique and data analysis

The NIRS measurements were carried out with a frequency domain device designed at Aalto University [7]. The NIRS probe included one source position with two wavelengths (either 685 and 830 nm or 760 and 830 nm) and two detectors at distances of 1 and 4 cm from the source. The 1-cm detector measures primarily scalp hemodynamics, while the 4-cm detector measures a mixture of scalp and cerebral hemodynamics [8, 9]. For both detectors, $\Delta[HbO_2]$, Δ[HbR], and Δ[HbT] were estimated using the modified Beer–Lambert law with photon path length in tissue estimated from calibrated phase data [1, 7].

Principal component analysis (PCA) was used to estimate cerebral hemodynamic changes from dual-detector NIRS data by identifying and removing from the 4-cm NIRS signals the PCA components that represented scalp hemodynamics [8]. These were assumed to be the components with highest absolute correlation with the 1-cm NIRS signals.

OSA- or breath-hold-related hemodynamic changes were averaged for each measurement individually to improve the signal-to-noise ratio, after which PCA was applied to extract the cortical component from the averaged data. Before averaging, the data were time-aligned so that 0 s indicated resumption of breathing. In the first two OSA measurements, the apnea periods were time-aligned using a well-defined peak in the 1-cm [HbR] data (not shown here) that always occurred prior to the SpO_2 minimum. The [HbR] peak appeared to be associated with oxygen deprivation and heart rate increase during the apnea. After aligning, the SpO_2 and EEG events were verified to be in agreement with termination of apnea at 0 s.

Concentration means from three 10-s time periods were compared for statistically significant differences ($p<0.01$). The Kolmogorov–Smirnov test indicated that some of the data were not normally distributed, so a one-way Kruskal–Wallis test followed by post hoc Mann–Whitney U tests with the Bonferroni correction was used for the comparisons. The time periods started (A) immediately after onset of the respiratory event and (B) immediately and (C) 20 s after resumption of breathing.

Results

Figure 1 shows estimated cortical Δ[HbT], $\Delta[HbO_2]$, and Δ[HbR] responses to different respiratory events. The signals have been low-pass filtered (cutoff frequency at 1 Hz) for clarity. In the OSA measurements (Fig. 1a), all concentration levels change statistically significantly ($p<0.01$) from time period A to C and from B to C, but not from A to B. In the OSA subject's breath-hold measurement (Fig. 1b), all concentration levels change significantly ($p<0.01$) from A to B and from B to C but not from A to C. In the control group's breath-hold data (Fig. 1c), $[HbO_2]$ and [HbT] change significantly ($p<0.01$) from A to B, [HbR] and [HbT] from A to C, and all three hemoglobin species from B to C. Since the differences were demonstrated statistically, some of them may not be obvious from the graphical presentation.

During apnea, concentration changes are small (Fig. 1a). However, there is a prominent decrease in $[HbO_2]$ and [HbT] after the termination of apnea, with a return to pre-apnea levels occurring 30 s later. Conversely, both the apnea subject (Fig. 1b) and the control group (Fig. 1c) show an increase in $[HbO_2]$ and [HbT] and a slight decrease in [HbR] during the breath-hold, but 20–30 s after the breath-hold, hemoglobin concentrations have mostly returned to pre-breath-hold levels. Changes in $[HbO_2]$ and [HbT] during the first and last 10–20 s are most likely related to the previous or next breath-hold, as the breathing period between breath-holds typically lasted for 20–30 s (Fig. 1b, c).

The mean SpO_2 drop for the OSA subject is greater during apnea than during breath-holds of similar duration. This is most likely explained by the non-linearity of the oxygen–hemoglobin dissociation curve in the 96–99% SpO_2 range [10], which means that a given drop in the partial pressure of O_2 will cause a 2–4 times larger decrease in SpO_2 at 96–98% (the baseline for our OSA subject during sleep) than at 98–99% (the baseline for our OSA subject during wakefulness).

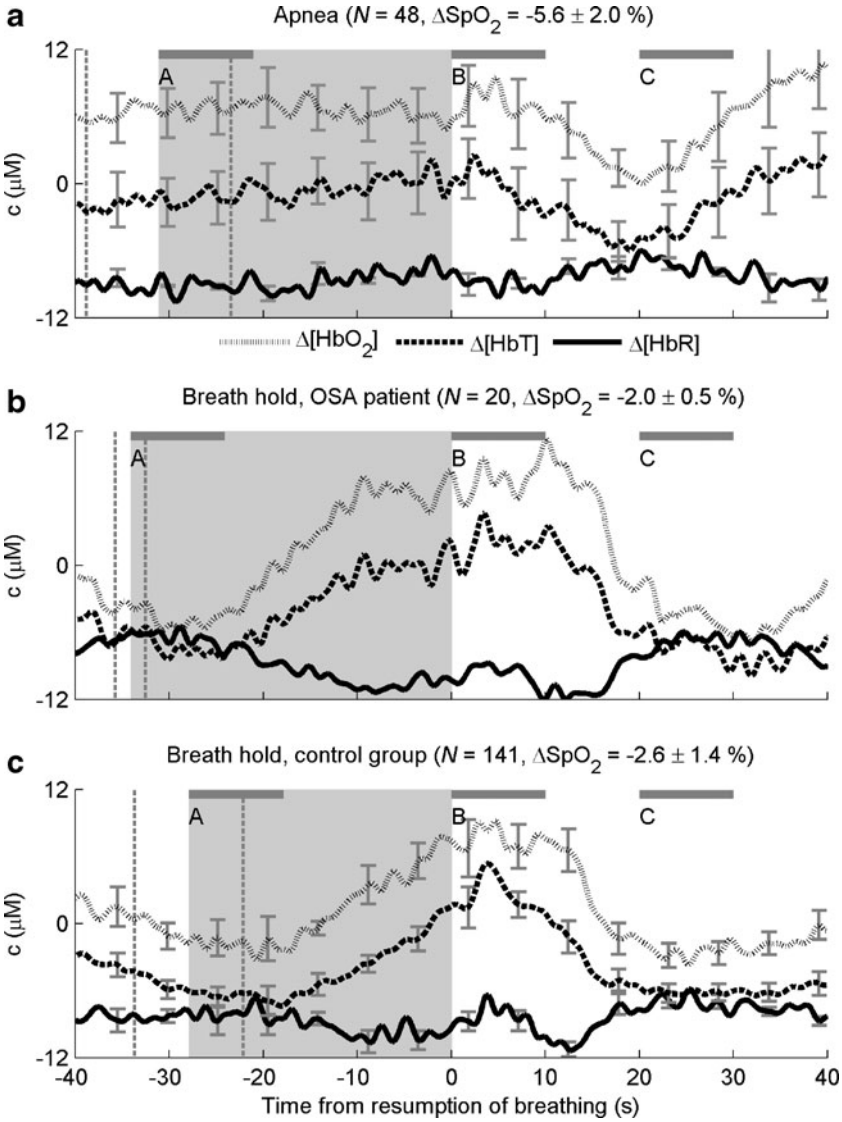

Fig. 1 Cortical hemoglobin concentration changes for the OSA subject during **a** apnea and **b** breath-hold, and **c** for the control group during breath-hold (*error bars* show standard error of the mean where multiple measurements were made). The time periods A, B, and C are indicated with *horizontal bars*. The zero levels of signals have been chosen to avoid signal overlapping. The number of respiratory events (*N*), mean event duration±standard deviation (STD) (*gray area*, *dashed vertical lines* show STD), and average drop in SpO_2±STD (ΔSpO_2) are given. For consistency with the breath-hold measurements, in **a**, the average duration is estimated only from the measurement where the breathing mask was used (N=11, ΔSpO_2=−5.4±1.6%)

Discussion

A recent NIRS study on OSA concluded that CO_2-induced cerebral vasodilation can compensate for the hemodynamic effects of mild apneas or hypopneas by increasing CBF, which causes an increase in CBV as indicated by Δ[HbT] [2]. In severe cases of OSA, this mechanism either fails or is insufficient, leading to a reduction in [HbO_2] and increase in [HbR] during apnea. However, our results indicate only minor hemodynamic changes during apnea but a statistically significant post-apnea decrease in [HbT] and consequently in CBV to well below pre-apnea levels. Such a drop has not been reported in previous NIRS OSA studies. Since both [HbT] and [HbO_2] decrease simultaneously, the most likely cause is a decrease in CBF.

Because this is a single-subject study, the prevalence of this phenomenon among OSA patients cannot be estimated here. However, the observed post-apnea decrease was both repeatable and prominent, as it was visible in all four OSA measurements and also in the raw (non-PCA-filtered) 4-cm Δ[HbO_2] and Δ[HbT] signals (not shown here). Also, while some of the OSA data presented were obtained without a respiratory measurement, we consider their inclusion in the analyses to be justified by SpO_2 and EEG evidence for apnea and positive apnea detection from respiratory signals in the later measurements.

Breath hold measurements were carried out to determine whether the observed changes are a response to blood CO_2 changes. Comparison of the OSA subject with the control group indicates a normal compensatory response to

elevated CO_2 in the wake state (CBF increase leading to CBV increase [5]), although in general, OSA severity has been shown to correlate with impaired cerebral autoregulation and vascular CO_2 reactivity during wakefulness [6]. For the OSA subject, CBV appears to stay constant after reaching maximal vasodilation, as would be expected in prolonged breath-hold. The brief and small cerebral [HbR] increase after breath-hold around 0 s probably indicates the point where blood deoxygenation starts to increase despite the compensatory response. After termination of breath-hold, CBV returns to pre-breath-hold levels, but no post-breath-hold CBV drop below pre-breath-hold levels is observed. Thus, the post-apnea CBV drop appears to be specific to the sleep state. The magnitude of the CBV drop in apnea is approximately half of the CBV increase during breath-hold.

The qualitatively different responses to breath-hold and apnea may be explained by differences in CBF regulation during wake state and sleep. Apnea is terminated by arousal, and CBFV measured with TCD has been shown to drop in response to arousals during NREM sleep [11]. This could indicate neurologically initiated post-apnea cerebral vasoconstriction, which would increase vascular resistance and lead to a reduction in CBFV, CBF, and consequently also CBV. In another study, CBFV was observed to decrease below baseline level after apnea termination, and cerebral vasoreactivity was observed to be severely impaired during OSA but partially recovered during normal sleep and wakefulness [4]. The inability of vascular diameter to promptly adapt to changes in other CBF determinants, such as blood pressure, could therefore also explain the post-apnea CBV drop. In any case, whether the CBV drop is caused by arousal or impaired vasoreactivity to CO_2, it exposes the brain to hypoxia. Since nocturnal cerebral hypoxia is a risk factor in many cardiovascular diseases, NIRS studies on OSA patients should investigate the prevalence of post-apnea CBV drop in the patient population.

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