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Original Article

Original Article

How does obstructive sleep apnea alter cerebral hemodynamics?

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Abstract

Study Objectives: We aimed to characterize the cerebral hemodynamic response to obstructive sleep apnea/hypopnea events, and evaluate their association to polysomnographic parameters. The characterization of the cerebral hemodynamics in obstructive sleep apnea (OSA) may add complementary information to further the understanding of the severity of the syndrome beyond the conventional polysomnography.

Methods: Severe OSA patients were studied during night sleep while monitored by polysomnography. Transcranial, bed-side diffuse correlation spectroscopy (DCS) and frequency-domain near-infrared diffuse correlation spectroscopy (NIRS-DOS) were used to follow microvascular cerebral hemodynamics in the frontal lobes of the cerebral cortex. Changes in cerebral blood flow (CBF), total hemoglobin concentration (THC), and cerebral blood oxygen saturation (StO_2) were analyzed.

Results: We considered 3283 obstructive apnea/hypopnea events from sixteen OSA patients (Age (median, interquartile range) 57 (52-64.5); females 25%; AHI (apnea-hypopnea index) 84.4 (76.1-93.7)). A biphasic response (maximum/minimum followed by a minimum/maximum) was observed for each cerebral hemodynamic variable (CBF, THC, StO_2), heart rate and peripheral arterial oxygen saturation (SpO_2). Changes of the StO_2 followed the dynamics of the SpO_2, and were out of phase from the THC and CBF. Longer events were associated with larger CBF changes, faster responses and slower recoveries. Moreover, the extrema of the response to obstructive hypopneas were lower compared to apneas ($p < .001$).

Conclusions: Obstructive apneas/hypopneas cause profound, periodic changes in cerebral hemodynamics, including periods of hyper- and hypo-perfusion and intermittent cerebral hypoxia. The duration of the events is a strong determinant of the cerebral hemodynamic response, which is more pronounced in apnea than hypopnea events.

Key words: obstructive sleep apnea; diffuse correlation spectroscopy; near-infrared spectroscopy; cerebral hemodynamics; sleep disorder

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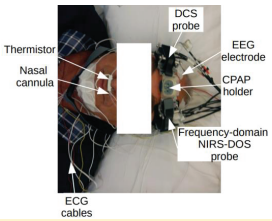
Graphical Abstract

How does obstructive sleep apnea alter cerebral hemodynamics?

BACKGROUND:
Apnea/hypopnea events alter:
- Arterial oxygen saturation
- Intrathoracic pressure
- Sympathetic activation
- Macrovascular blood flow
- Sleep architecture



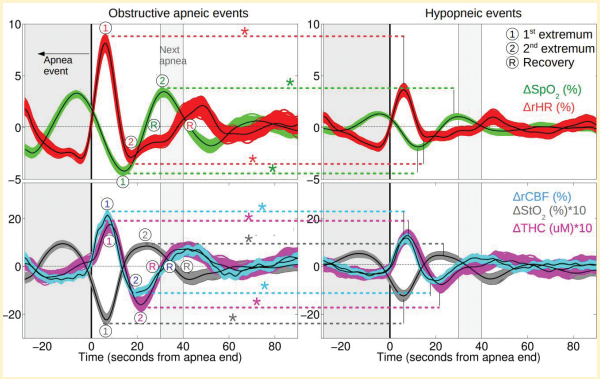
OBJECTIVES:
- Characterize the cerebral hemodynamic response to obstructive sleep apnea/hypopnea events
- Evaluate their association to polysomnographic parameters

METHODS:
- 16 obstructive sleep apnea patients studied during night sleep
- Diffuse optical techniques,
  used to measure frontal microvascular cerebral hemodynamics:
  - Diffuse correlation spectroscopy (DCS)
  - Frequency-domain near-infrared diffuse correlation spectroscopy (NIRS-DOS)
- Parameters measured, changes in:
  - Cerebral blood flow (CBF)
  - Total hemoglobin concentration (THC)
  - Cerebral blood oxygen saturation (StO_2)
  - Hear rate (HR)
  - Peripheral arterial oxygen saturation (SpO_2)

RESULT 1: A biphasic two extrema response is observed for each cerebral hemodynamic variable (CBF, THC, StO_2), heart rate (HR) and peripheral arterial oxygen saturation (SpO_2)

RESULT 2: Longer events were associated with larger CBF changes, faster responses and slower recoveries

RESULT 3: The extrema of the response to obstructive hypopneas were lower compared to apneas



CONCLUSION: Obstructive apneas/hypopneas cause profound, periodic changes in cerebral hemodynamics

Statement of Significance

Time-traces of the systemic and cerebral hemodynamic parameters were recorded during night sleep in severe obstructive sleep apnea patients. Each obstructive event was identified and characterized in detail. The resulting information provides a deeper understanding of the interplay between different physiological parameters, the cerebral hemodynamics and blood oxygenation in response to obstructive apnea and hypopnea events. This information and these tools could be utilized to improve the understanding of the pathophysiology of obstructive sleep apnea and may be relevant to its management. Finally, in the longer term, it may allow the clinicians to develop preventative measures to minimize the impact of this condition on cerebrovascular disease.

Introduction

Obstructive sleep apnea (OSA) is a prevalent disorder [1] characterized by the intermittent collapse of the upper airway during sleep that results in transient dips in arterial oxygen saturation (intermittent hypoxia), increased respiratory effort, sympathetic activation, and disruption of the sleep architecture [2–4].

OSA has a negative impact on the patient quality of life, is related to cognitive impairment and has several metabolic and cardiovascular consequences [5–10] such as increased prevalence of ischemic stroke. Obstructive apneas are associated with profound changes in cerebral blood flow [11–15] and apnea-induced hypoxia combined with reduced cerebral perfusion may predispose the brain to nocturnal cerebral ischemia. The continuous measurement of cerebral hemodynamics during sleep as part of a comprehensive study may provide additional and relevant information about the impact of OSA, and, in the future may arise as a valuable tool in monitoring response to treatment.

Previously, nocturnal microvascular cerebral blood oxygenation changes due to OSA events have been measured and characterized by near-infrared diffuse optical spectroscopy (NIRS-DOS) [16–20]. In these studies, the changes of microvascular total hemoglobin concentration and/or cerebral blood oxygen saturation were reported in response to individual apneic events. This change which was observed close to the end of the apnea was found to be associated with the event duration, the sleep stage and the peripheral arterial oxygen saturation [16, 20]. Other works have studied the apnea-induced changes of the macrovascular cerebral blood flow velocity (CBFV) in the middle cerebral artery by transcranial Doppler (TCD) [11–15]. Interestingly, Bålfors et al. [11] found that CBFV and the mean arterial blood pressure showed a biphasic pattern consisting on a gradual increase close to the apnea end followed by a sudden decrease. However, TCD can directly insonate only proximal vascular segments of large arteries and only indirectly provides information about more distal vascularity and microvascular cerebral blood flow (CBF) [21].

A technique that combines the measures of the microvascular CBF with the microvascular cerebral blood oxygenation changes by NIRS-DOS would be desirable to understand the complete picture of the cerebral oxygen metabolism during apneas. Near-infrared diffuse correlation spectroscopy (DCS) can address this gap by measuring microvascular CBF locally on the brain cortex in a noninvasive manner at the point-of-care (DCS) [22, 23]. DCS uses near-infrared light like NIRS-DOS but relies on the speckle statistics of the laser light to characterize the red blood cell motion. Hou et al. [24] attempted to measure night sleep changes by DCS and NIRS-DOS in OSA patients but without characterizing

the response to individual apneic events. Recently, we have demonstrated that DCS is a suitable technology for bed-side and continuous monitoring of the microvascular CBF during the polysomnographic study [25]. We were able to obtain sufficient signal-to-noise ratio for characterizing the typical shape of the microvascular cerebral blood flow changes, which followed the biphasic pattern observed previously with TCD [11].

In this study, we report further analysis and interpretation with previously unpublished parts of data from our original work Ref [25].[1] In this analysis, we have utilized data from DCS, NIRS-DOS, and polysomnography signals simultaneously to characterize the individual obstructive apnea/hypopnea-induced changes of cerebral hemodynamics in patients with severe OSA. We have hypothesized that the cerebral hemodynamic changes are associated with the characteristics of the respiratory events (type and duration) and OSA severity.

Methods

Study design and participants

This study was conducted at the Sleep Unit of the Department of Respiratory Medicine, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain. The study protocol was approved by the local ethical committee (EC/11/001/1166). All participants gave their informed written consent. The data presented here is based on the same set that was previously utilized in a proof-of-concept study (see Supplementary Materials section "Clarification of data-set and comparison to the previous studies" for details).

The subjects were referred to a sleep study because of being at a high risk of severe OSA according to the Epworth sleeping scale [26], their clinical symptoms and the results of a previous home-use nocturnal pulse oximetry study [27].

The exclusion criteria were being older than 80 years, previous or current continuous positive air pressure (CPAP) treatment, chronic obstructive pulmonary or neuromuscular diseases, previous ischemic stroke, or refusal to participate in the study.

A preestablished questionnaire was used to collect demographic variables including their medical history, cardiovascular risk factors, and current medications.

Patients were asked to arrive at the Sleep Unit at 19:00 on the study day. Caffeinated or alcoholic beverages were to be avoided for twenty-four hours before the measurement. Optical and polysomnographic (PSG) data were simultaneously acquired during the night sleep.

Sleep studies

Polysomnographic (Siesta Compumedics, Melbourne, Australia) sensors were wirelessly connected to the monitoring room and included the recording of the oronasal flow (by a thermistor and a nasal cannula), the thoracic and abdominal movements (by respiratory inductance plethysmography bands), the heart rate (HR; by electrography chest leads and calculated from the electrocardiogram as described by Solà-Soler et al. [28]), the electromyographic activity (by submental and pretibial electromyography), the eye movements (by electrooculography), the global neural electroencephalographic activity (by electroencephalography (EEG)), the arterial oxygen saturation (SpO_2; by pulse oximetry), and the body position (by mercury switches).

The data were analyzed manually according to the Spanish Sleep group normative [29] and the American Academy of Sleep Medicine guidelines [30]. The diagnosis of OSA and the degree of severity were established according to number of apneas and hypopneas per hour (AHI). Other parameters calculated were the percentage of total sleep time with SpO_2 lower than 90% (CT90) and the four per cent oxygen desaturation index (ODI4). Also, arousals were identified as previously described [31].

The clinical technician fixed a CPAP mouth-nose mask to find the correct air pressure for preventing obstructive events if the AHI was larger than 30 after about four hours of sleep split-night PSG. Only the data recording of the first four hours of night sleep prior to CPAP usage was used for the analysis in this work.

Optical methods and instrumentation

Optical monitoring was performed with a portable, hybrid platform combining DCS and frequency-domain NIRS-DOS as previously described [32]. DCS data were acquired at 785 nm with eight detection channels. The frequency-domain NIRS-DOS module (Imagent, ISS, Champaign, USA) consisted of lasers at 690, 785, or 830 nm (five each).

Only three lasers, one of each wavelength, were used continuously during the night study and the diffuse light from each was detected by one detector. The frequency-domain NIRS-DOS and DCS worked simultaneously by each one utilizing a different cerebral hemisphere. For that we have assumed that the hemodynamic changes in the brain are homogeneous bilaterally and fixed the DCS probe on the right forehead and the frequency-domain NIRS-DOS on the left one. PSG variables were also coregistered as previously described [25].

Diffuse optical data were continuously assessed with a range of 0.9-3.1 second time-resolution for DCS which was adjusted depending on the signal level, and, with a time-resolution of 0.2 seconds for frequency-domain NIRS-DOS.

Two optical probes for the night measurement were made of custom-built fibers. One source-detector separation of 2.5 cm was used for both probes. The use of 2.5 cm was justified by previous validation studies [23, 33]. The probes were placed bilaterally on the temporal margin of the patient forehead superior to the frontal sinuses as shown in Figure 1.

The data were analyzed using previously described methods to derive a continuous blood flow index (BFI) from DCS measurements [22, 25, 32]. The BFI is a parameter that reflects the motion and the amount of red blood cells mainly in arterioles, capillaries, and venules. It is derived based on the model of the propagation of photons in tissues, how their interactions with red blood cells impinge changes on the statistics of the resultant laser speckles and, finally, a model of this motion in the complex tissue vasculature. The resultant parameter has been shown to both correlate and agree with microvascular blood flow in comparison to different modalities [23, 33, 34]. The output of the four DCS channels was averaged at each time point for improved signal-to-noise ratio.

Similarly, the modified Beer-Lambert law [35–38] was used for the frequency-domain NIRS-DOS to obtain continuous traces of the changes in oxyhemoglobin ($\Delta HbO_2(t)$) and deoxyhemoglobin ($\Delta Hb(t)$). Furthermore, at the start of the study a probe with multiple source-detector separation (the Adult Flexible Sensor by ISS, Champaign, USA) with four three-fiber bundle sources at distances of 2.5, 3, 3.5, and 4 cm from a detector was used to obtain the baseline absolute measurements by using a tissue simulating phantom as a calibration for five minutes [39, 40]. This allowed us to add the changes that were measured continuously to the baseline values to further obtain total hemoglobin concentration (THC) as the sum of HbO_2 and Hb concentrations,

[1] For further details about the differences between this work and our original work see Supplementary Material section "Clarification of data-set and comparison to the previous studies."

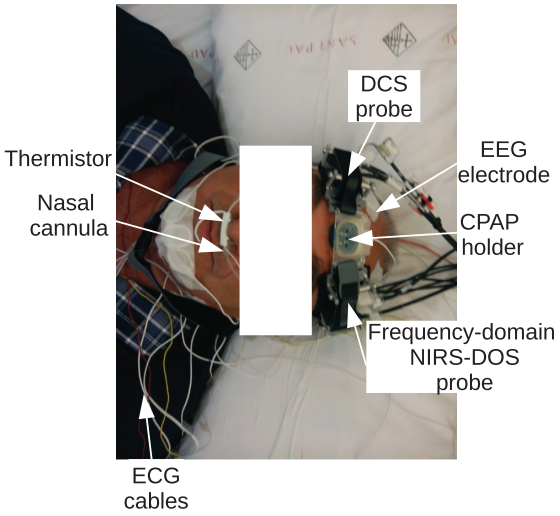


Figure 1. The optical probes for each technique and the polysomnographic sensors that are placed on the subject's head. DCS, diffuse correlation spectroscopy; EEG, electroencephalography; CPAP, continuous positive airway pressure; NIRS-DOS, near-infrared diffuse optical spectroscopy; ECG, electrocardiography.

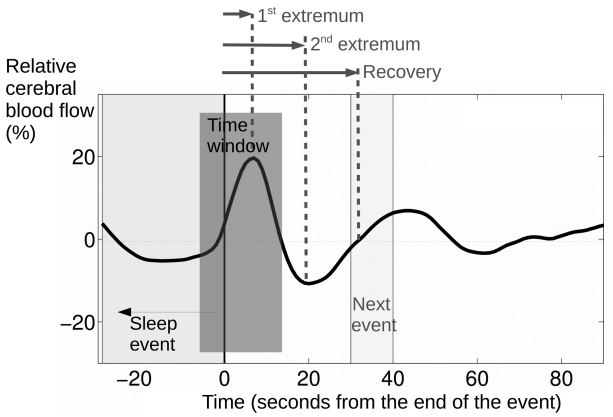


Figure 2. Visualization of the parametrization of the relative cerebral blood flow response to a single event. The first light gray region indicates the sleep event and the second, the possible following event. The dark gray region indicates the time window used to find the first extremum. The first and the second extrema and the parameters at recovery are labeled.

and cerebral blood oxygen saturation (StO_2) as HbO_2 divided by THC. Frequency-domain NIRS-DOS was averaged to 1 second for improved signal-to-noise ratio.

Statistical analysis

Quantitative variables were expressed as median and interquartile range (median (Q1, Q3)), and, categorical variables as the number of cases and percentages per category. The percent relative CBF change (ΔrCBF) has been defined as $\Delta rCBF = (BFI(t)/BFI_{bl} - 1) \times 100$, where BFI_{bl} is the average of the BFI and included the thirty seconds before the start of the sleep event. This choice for BFI_{bl} was used to correct for slight changes in the probe position during the whole night measurement. We note that this is different compared to our earlier analysis [25], in this work it has been adapted to improve our analysis by minimizing the effects of overlapping apnea periods. Similarly, ΔStO_2 was defined as $\Delta StO_2(t) = StO_2(t) - StO_{2bl}$, ΔTHC as $\Delta THC(t) = THC(t) - THC_{bl}$, ΔrHR as $\Delta rHR(t) = (HR(t)/HR_{bl} - 1) \times 100$, and ΔSpO_2 as $\Delta SpO_2(t) = SpO_2(t) - SpO_{2bl}$.

To identify measurements with poor signal quality and with movement artifacts during the measurement, all responses were studied by previously developed methods for outlier detection [41, 42] as described in [25]. These outliers were removed from further analysis.

Bootstrapping was performed for all variables with thousand iterations of resampling and an alpha significance value of 0.05 to check and control the stability of the results and show its dynamics. The bootstrapping procedure was implemented by R [43] using the "fda.usc" package.

To characterize the night sleep events and following the protocol paved in our previous work [25], we have considered the apnea end as a pivot point (time = 0) and parametrized each parameter. Each event was considered as a function dependent on time (ΔrCBF(t), $\Delta StO_2(t)$, ΔTHC(t), ΔrHR(t), and $\Delta SpO_2(t)$), and then, the first two relative extrema of these functions along a specific time interval were calculated. A third time parameter ("recovery") indicated when the measured variable recovered to the baseline value and was analyzed following the two first extrema.

The time windows to find the first extrema were from −5 to 15 seconds for the ΔrCBF (see Figure 2 as an example), from 0 to 15 seconds for the ΔStO_2, from 0 to 13 seconds for the ΔTHC, from 0 to 15 seconds for the ΔrHR, and from 5 to 35 seconds for the ΔSpO_2. These time windows were selected from the literature [11, 44] and also by the visual observation of all the events plotted together from −30 seconds to 90 seconds to include the majority of the first extrema. This procedure was partially (for ΔrCBF, ΔrHR, and ΔSpO_2) utilized in our previous work in Ref. [25]. For each event, the second extremum was found following the first extremum, and as mentioned, the recovery time was found following the second extremum. This analysis was performed with Matlab (Mathworks, MA, USA).

Once the events were parametrized, the associations between the mean calculated values at the extrema, and, the recovery values with different polysomnographic and clinical parameters (one by one) were analyzed by performing simple linear models. The polysomnographic and clinical parameters were the fixed effect and the mean calculated measured values for the different variables (ΔrCBF, ΔStO_2, ΔTHC, ΔrHR, and ΔSpO_2) were the predictors.

Similarly, associations between the calculated extrema and the recovery parameters of all events between different variables, event duration and also the presence of arousals were analyzed by performing linear mixed-effect models [45] as previously described in [25].

The student's *t*-test was used to assess the difference between obstructive apneic and hypopneic parameters, ignoring repeated events from the same individuals. This analysis was performed with R programming language and environment [43]. A *p*-value $< .05$ was considered as the threshold for rejection of the null hypothesis for all statistical tests.

Results

Baseline characteristics

A cohort of sixteen ($n = 16$) subjects was recruited and all subjects were diagnosed as having severe OSA after being studied with a split-night PSG ($n = 14$, 88%) or by an overnight PSG ($n = 2$, 12%). These subjects were also reported on our previous work [25].

Table 1a summarizes the demographic and clinical characteristics of the subjects. It is a population with homogeneous clinical

characteristics showing prevalent obesity in all patients. Four patients received beta blockers which could influence the heart rate response [46], but no further analysis has been performed due to the small sample size of this subgroup.

Night sleep clinical and optical results

Table 1b shows a summary of the PSG findings. 3817 respiratory events were identified by the PSG. Only obstructive apneas (n = 1365, 36%) and hypopneas (n = 1918, 50%) have been included in the analysis as per the study protocol. Central and mixed events were excluded due to the differences in their pathogenesis and immediate consequences (especially in intrathoracic pressure changes).

DCS recordings were discarded in two patients for this analysis due to a synchronization failure between the PSG and the DCS module. Also due to technical reasons, the frequency-domain NIRS-DOS recording of one patient was discarded. Finally, the SpO_2 recording in one patient was discarded due to the inadequate signal of the pulse oximeter during the main part of the recording.

The outlier analysis was implemented separately for obstructive apneas and hypopneas as mentioned above. The clarification of the total number of events considered for the analysis is given in Supplementary Material Table 1.

Figure 3 shows three minutes of data relating nasal airflow to optically measured cerebral hemodynamics (BFI, StO_2, and THC) and systemic physiological variables (HR and SpO_2) as an example of the apnea effect. In this characteristic time period, with frequent obstructive apneas, it is noted how when breathing stops (shaded gray area), there are visible changes in all parameters. For example, it can be observed that while cerebral blood oxygen saturation decreases (similar to SpO_2) after the breathing restarts following an apnea, the BFI starts to rise.

Parameterization of the cerebral hemodynamic response to obstructive sleep apnea events

The majority of the events (80%, n = 3054) have a preceding event at equal or less than thirty seconds prior to its start. This implies that the expected hemodynamic responses due to a given event have a high chance of overlapping with the start of the following event as also illustrated in Figure 3. We have, therefore, characterized the measured parameters at the end of the apnea and in the post-apnea period (as explained in methods section).

Figure 4 shows the results obtained for HR, SpO_2 and cerebral hemodynamics from ten seconds before the end of obstructive apnea or hypopnea events to ninety seconds after the end of the event. HR, CBF, and THC show first a positive extremum close to the apnea end followed by a negative extremum. Both SpO_2 and StO_2 show first a negative extremum close to the apnea end followed by a positive extremum. The second extremum is followed by a recovery to baseline levels for all variables.

Associations between cerebral hemodynamic parameters and clinical parameters

The associations between the cerebral hemodynamic parameters versus clinical and polysomnographic parameters were tested considering both the apnea and hypopnea events collectively and also separately. For simplicity, the results including apnea and hypopnea events together are shown in this section.

Table 2 shows the slopes and the coefficients of determination of the statistically significant associations between the mean cerebral hemodynamic parameters and event duration, SpO_2 and heart rate. The p-values are shown in Supplementary Material Table 2. Below we detail some of the salient findings.

Longer[2] events were associated with a larger response (increment (max) or decrement (min)) of the cerebral blood flow changes. The first extremum has been found to be associated

Table 1. Study group a) demographics, clinical, and b) polysomnographic characteristics. *Arousals information was gathered in fourteen patients. OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; SpO_2, arterial oxygen saturation; CT90, % of measured night sleep time when SpO_2 is lower than 90%; ODI4, number of times where SpO_2decreases 4% due to an apnea; REM, rapid eye movement.

a)	OSA patients (n = 16)
Age (years), median (interquartile range)	57 (52-64.5)
Males, n (%)	12 (75)
Body mass index (kg/cm²), median (interquartile range)	33.9 (31.8-37.5)
Epworth, median (interquartile range)	9.5 (7.5-15.5)
Arterial hypertension, n (%)	10 (62.5)
Smokers, n (%)	13 (81)
Diabetes, n (%)	5 (31.25)
Dyslipidemia, n (%)	3 (18.75)
b)	
AHI (n./hour), median (interquartile range)	84.4 (76.1-93.7)
Mean SpO_2 (%), median (interquartile range)	92 (90.5-93.5)
CT90 (%), median (interquartile range)	23 (12.4-32.7)
ODI4 (%), median (interquartile range)	73.8 (64.6-85.4)
Total number of apneas by polysomnography, n	3817
Obstructive apneas, n (%)	1365 (36)
Hypopneas, n (%)	1918 (50)
Mixed apneas, n (%)	358 (9)
Central apneas, n (%)	176 (5)
Time on stage 1 (%), median (interquartile range)	26 (19.5-30)
Time on stage 2 (%), median (interquartile range)	57 (45-65)
Time on stage 3 (%), median (interquartile range)	9.2 (3.85-25)
Time on REM (%), median (interquartile range)	0.2 (0-4.55)
Index Arousals/hour *, median (interquartile range)	12.3 (6.0-23.1)

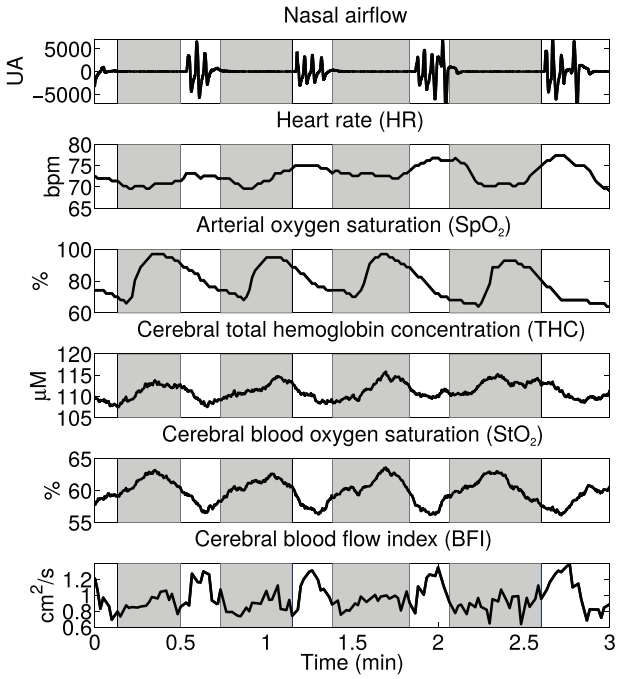


Figure 3. Nasal airflow, heart rate, arterial oxygen saturation, total hemoglobin concentration, cerebral blood oxygen saturation and blood flow index dynamics for three minutes of night sleep for one representative obstructive sleep apnea subject. See the text for details. The gray regions between two vertical lines indicate obstructive apneic events.

with the event duration by a 0.5%/sec increase, which means that for an event of 10 seconds, the first extremum would be found to be a 5% CBF change from the baseline. Similarly, for the second negative extremum, we have observed a 0.2%/sec decrease. About the timing of the response, longer event duration was associated to a faster (negative slope) occurrence of the first extremum of –0.1. On the contrary, longer event duration was associated to a slower (positive slope) recovery (time to recover to baseline levels after an event) with a slope of 0.1.

Apnea duration, the presence of arousals, the SpO_2 and the HR changes were found to be one by one associated to cerebral hemodynamics. However, only apnea duration was the significant factor in the resulting linear mixed-effects model.

On the other hand, larger CBF extrema were associated to larger SpO_2 and HR responses (Table 2). In general, the longer the cerebral blood flow took to reach an extrema, the longer it took for SpO_2 and HR too.

For THC and StO_2, similar associations to cerebral blood flow were found, for event duration, SpO_2 and HR parameters. Interestingly, StO_2 and SpO_2 parameters were associated among themselves.

Table 3 shows the slopes and the coefficients of determination of the statistically significant associations between the mean cerebral hemodynamics, gender, age, smoking, mean SpO_2 and AHI. CT90% was also tested but statistically

[2] For clarity, we note here that from this point on, "longer" corresponds to an increased duration, i.e. larger changes in time, and "larger" corresponds to an increased magnitude of the observed change.

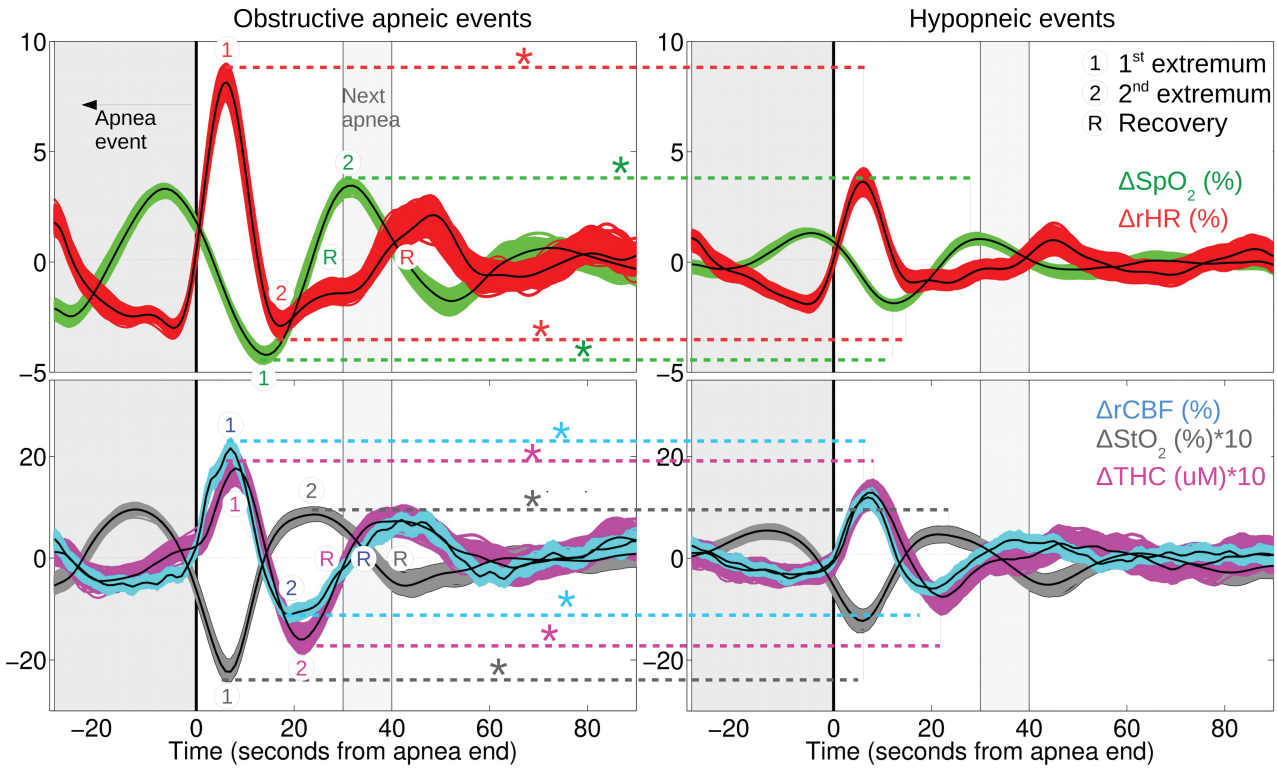


Figure 4. (Top row) The dynamics of systemic variables, i.e. heart rate (ΔrHR) and peripheral arterial oxygen saturation (ΔSpO_2) and (Bottom row) those of the cerebral microvasculature, i.e. relative cerebral blood flow (ΔrCBF), total hemoglobin concentration (ΔTHC) and blood oxygen saturation (ΔStO_2) are shown for both obstructive apnea and hypopnea events. The data is averaged over all patients and the shaded area shows the variability due to bootstrapping. The first and the second extrema and the recovery points are further labeled. For clarity, the results for ΔStO_2 and ΔTHC are multiplied by ten (x10).(*) indicates statistically significant association (<0.001) of the extrema between apneic and hypopneic events.

Table 2. Slopes and coefficients of determination of the statistically significant linear models between cerebral hemodynamic parameters versus polysomnographic parameters considering obstructive apneic and hypopneic events together. Here only those associations that were tested are shown. Empty slots imply that the association was not tested. The values of the slopes and the coefficients of determination (slope (R^2)) are shown only for the statistical significant associations. The units of the slope are given by the unit of the corresponding row (y) divided by the unit of the corresponding column (x). All extrema are considered in absolute values, and we have indicated on the table if these were originally positive (indicated as "max") or negative (indicated as "min"). n.s. = non-significant association; Ext. = extremum. The p-values are shown in Supplementary Material Table 2.

y=slope·x slope (R^2)	Event duration (s)	Presence of arousal	Arterial oxygen saturation, SpO_2					Heart rate, HR				
			1st ext. (min) (%)	2nd ext. (max) (%)	Time-to-1st ext. (s)	Time-to-2nd ext. (s)	Time-to-recovery (s)	1st ext. (max) (%)	2nd ext. (min) (%)	Time-to-1st ext. (s)	Time-to-2nd ext. (s)	Time-to-recovery (s)
Cerebral blood flow, CBF												
1st ext. (max) (%)	0.5 (0.08)	2.18 (0.01)	2.5 (0.29)					0.9 (0.33)				
2nd ext. (min) (%)	0.2 (0.01)	n.s.	0.6 (0.01)	0.9 (0.01)				0.2 (0.01)	0.7 (0.01)			
Time-to-1st ext. (s)	–0.1 (0.04)	–1.36 (0.04)	n.s.		0.1 (0.02)			n.s.		0.3 (0.06)		
Time-to-2nd ext. (s)	n.s.	–0.45 (0.03)	n.s.			0.1 (0.01)		–0.1 (0.03)			0.2 (0.03)	
Time-to-recovery (s)	0.1 (0.02)	n.s.	–0.4 (0.02)				0.1 (0.01)	0.2 (0.05)				0.2 (0.06)
Total hemoglobin concentration, THC												
1st ext. (max) (uM)	n.s.	n.s.	0.1 (0.02)					0.1 (0.05)				
2nd ext. (min) (uM)	0.01 (0.01)	-0.41 (0.01)	0.2 (0.01)	0.2 (0.01)				0.1 (0.02)	0.1 (0.01)			
Time-to-1st ext. (s)	–0.1 (0.02)	n.s.	n.s.		n.s.			n.s.		n.s.		
Time-to-2nd ext. (s)	n.s.	–1.36 (0.02)	n.s.			0.1 (0.01)		–0.1 (0.04)			0.2 (0.01)	
Time-to-recovery (s)	n.s.	n.s.	0.4 (0.01)				n.s.	–0.2 (0.02)				0.1 (0.02)
Cerebral blood oxygen saturation, StO_2												
1st ext. (min) (%)	0.1 (0.13)	-0.64 (0.06)	0.3 (0.37)					0.1 (0.37)				
2nd ext. (max) (%)	0.1 (0.06)	0.23 (0.02)	0.1 (0.1)	0.3 (0.48)				0.1 (0.26)	0.1 (0.3)			
Time-to-1st ext. (s)	0.01 (0.01)	–1.20 (0.03)	n.s.		0.1 (0.09)			n.s.		0.1 (0.3)		
Time-to-2nd ext. (s)	n.s.	n.s.	–0.3 (0.01)			0.5 (0.13)		0.2 (0.03)			n.s.	
Time-to-recovery (s)	0.2 (0.02)	n.s.	–0.6 (0.02)				0.7 (0.43)	0.5 (0.12)				n.s.

significant associations were not found. As explained in methods, the events were averaged for each patient to be introduced in this analysis. The p-values are shown in Supplementary Material Table 3.

Older age was associated with a longer time between the extrema of CBF. The time to the second extremum has been found to be associated with age by a factor of 0.2%/years. For example, for a patient of 50 years of age, the time to the second extremum would be found at 10 seconds after the end of the event (+10 seconds).

For total hemoglobin concentration, females showed larger (maximum) THC extrema to the events. Smokers showed a larger reduction in THC at the second extremum and a slower recovery to baseline values. Interestingly, larger AHI was associated to a larger (maximum) THC first extremum and to a faster (negative sign) second time extremum.

Cerebral blood oxygen saturation was also associated to AHI. Faster occurrence of StO_2 extrema (minimum) and faster recovery to baseline levels were associated to a larger AHI.

No statistically significant associations were found between the BMI nor the Epworth scale versus the cerebral hemodynamic parameters. The association of REM vs non-REM period is not included due to the non-normality of the residuals of the linear model fit.

Table 3. Slopes and coefficients of determination of statistically significant linear models between cerebral hemodynamic parameters versus patient polysomnographic and clinical parameters considering the mean (per patient) of obstructive apnea and hypopnea events. Please see Table 2 caption for definitions and details. The p-values are shown in Supplementary Material Table 3.

y=slope·x slope (R^2)	Gender effect *(being female)*	Age *(years)*	Smoking *(yes)*	Mean night SpO_2 *(%)*	AHI *(n apneas/hour)*
Cerebral blood flow, CBF					
1st ext. (max) (%)	n.s.	−0.5 (0.37)	n.s.	n.s.	n.s.
2nd ext. (min) (%)	n.s.	n.s.	n.s.	n.s.	n.s.
Time-to-1st ext. (s)	n.s.	n.s.	n.s.	n.s.	n.s.
Time-to-2nd ext. (s)	n.s.	0.2 (0.34)	n.s.	n.s.	n.s.
Time-to-recovery (s)	n.s.	n.s.	n.s.	n.s.	n.s.
Total hemoglobin concentration, THC					
1st ext. (max) (uM)	1.9 (0.55)	n.s.	n.s.	n.s.	0.1 (0.4)
2nd ext. (min) (uM)	2.01 (0.76)	n.s.	1.9 (0.47)	n.s.	0.1 (0.35)
Time-to-1st ext. (s)	1.0 (0.38)	n.s.	1.7 (0.68)	n.s.	n.s.
Time-to-2nd ext. (s)	n.s.	n.s.	n.s.	n.s.	−0.1 (0.53)
Time-to-recovery (s)	−4.6 (0.4)	n.s.	n.s.	n.s.	−0.1 (0.4)
Cerebral blood oxygen saturation, StO_2					
1st ext. (min) (%)	n.s.	n.s.	n.s.	n.s.	n.s.
2nd ext. (max) (%)	n.s.	n.s.	n.s.	n.s.	n.s.
Time-to-1st ext. (s)	n.s.	n.s.	n.s.	n.s.	n.s.
Time-to-2nd ext. (s)	n.s.	n.s.	n.s.	1.1 (0.39)	n.s.
Time-to-recovery (s)	n.s.	n.s.	n.s.	1.7 (0.44)	−0.3 (0.42)

Difference in the cerebral hemodynamic response between obstructive apneas and hypopneas

In Figure 4, we have compared the cerebral hemodynamic responses between apnea or hypopnea events. The first and the second extrema are statistically significantly different ($p < .001$), where obstructive apneas show larger responses than hypopneas. However, no statistically significant differences have been found in the extrema time responses with the exception of SpO_2. The p-values are shown in Supplementary Material Table 4.

Discussion

Our results show that the hybrid diffuse optical techniques can characterize and parameterize the changes of microvascular, cerebral hemodynamics in response to individual apnea and hypopnea obstructive events during sleep. To the best of our knowledge, this is the first study to provide a complete characterization and a graphical representation of cerebral hemodynamic behavior in the long (~ +50 seconds) post-apnea period in response to obstructive events measured with DCS, NIRS-DOS and polysomnography, simultaneously. Overall, we have observed a biphasic response in CBF, THC, HR, SpO_2, and StO_2 with intermittent decrease in cerebral perfusion and oxygenation due to obstructive events. The event duration was the parameter with strongest association with cerebral hemodynamic changes. Moreover, hypopnea responses were significantly lower for all extrema changes compared to those of the obstructive apneas. The intermittent fluctuations in cerebral perfusion and oxygenation could cause hypoxic brain injury, especially if cerebral vasoreactivity and autoregulation were impaired [47] or if the time-to-respond was too long.

As shown in Figure 4, a clear biphasic response has been observed with an initial increase, a posterior fall and a recovery in CBF, HR, and THC. Similarly, but on the opposite direction, this response was found for SpO_2 and StO_2. CBF, HR, and SpO_2 followed the expected dynamics of the first extrema responses according to the literature [16, 17, 20, 25, 44].

The first and second CBF extrema behaved according to the literature as indirectly estimated by the middle cerebral artery CBFV [11, 14, 15] showing a peak close to the end of the apnea. This behavior was previously reported in our work in Ref [25]. We stress here that due to methodological differences in data analysis the values of changes reported differ between the current work and that in Ref [25]. However, overall biphasic behavior is the same. Different factors have been implicated in this response, especially the changes in gas exchange and the arterial blood pressure [47].

Arterial blood pressure has been reported to increase during the apnea event and to fall below baseline after the cessation of the event in different studies [11, 12, 48]. Bålfors et al. [11] found a correlation between percent change in mean arterial blood pressure and in CBFV during and after an apnea event. Moreover, the sensory, sympathetic, or parasympathetic nervous system arteries innervates cerebral arteries and could influence CBF on events during OSA [47, 49]. However, except during some pathological states, activation of the sympathetic nervous system does not have a big effect on the cerebral circulation [47, 49, 50]. In our study, cerebral blood flow changes are associated to SpO_2 and HR, and larger CBF extrema responses are associated to larger SpO_2 and HR responses. Unfortunately, neither pCO_2 nor arterial blood

pressure were monitored. These are not part of the standard clinical nocturnal evaluation.

Total hemoglobin concentration and cerebral blood oxygen saturation are also associated to both HR and SpO_2. Particularly, parameters of cerebral blood oxygen saturation were associated to its reciprocal parameter of peripheral oxygen saturation. The relationship between relative changes in peripheral saturation and cerebral NIRS parameters has already been described during obstructive apneas [51] and suggests a failure of autoregulatory brain mechanism.

The event duration was the parameter with the strongest association with cerebral hemodynamics, SpO_2 and HR changes. Previous studies [16, 20, 52] have reported the association of event duration to the first extremum of SpO_2, THC and StO_2 variables. Here, we report an association to microvascular CBF, as well as an association with the second extremum and, relevantly, with the time-to-recovery.

The presence of arousals has been shown to be associated with CBF, THC and StO_2 changes [13]. However, the presence of arousals was not significant in our study.

The gender effect that was observed should be further studied since the 75% of the population were males, i.e. only four female participants. Older age has been associated to smaller SpO_2 response to apnea being the opposite as predicted in the literature [53]. No previous studies were identified discussing the time to the response (time-to-extremum) which was found to be slower both for the time to the second extremum and for the recovery in older age patients.

Most of our patients (81%) were former or current smokers. Smoking also was shown to affect the THC second extremum with larger reduction and the time-to-recovery to baseline levels. There are few studies that analyze the relationship between chronic smoking and cerebral blood flow changes. Generally, they report an association between smoking and reduced CBF. Recently, differences in behavior between former and current smokers have been described [54], suggesting that distinct compensatory mechanisms may be involved depending on the timing and history of smoking exposure. Unfortunately, we do not have this information in our sample. Future studies should include more information about smoking and cumulative measures.

Larger AHI was associated to a larger (maximum) THC value of the first extremum and to a faster (negative sign) occurrence of the second THC extremum. Olopade et al. [18] did not characterize each event, but instead, calculated the mean over a sleep period with sleep events, and considering this analysis, they did not find a correlation between AHI and THC. Faster response could be adaptive in more severe patients, but a larger sample is needed to validate this hypothesis.

Larger AHI was also associated to faster (negative sign) recovery responses in cerebral blood oxygen saturation. Olopade et al. [18], in the same analysis previously mentioned, found that the magnitude of StO_2 was correlated to AHI; however, the response rate was not studied.

Contradictory to previous findings [55], we did not observe any body-mass-index effect. The body-mass-index values of our group were narrow in range, from 32 to 37.5, which may have obscured this relationship.

Different studies have found associations between the REM versus non-REM sleep stages and the event duration, HR, SpO_2, THC, and StO_2 changes [16, 20, 56]. However, due to the severity of our OSA cohort, only 0.2% of the total time of study was during REM stage with a total of twelve events. Therefore, we were not able to properly evaluate this effect.

A differentiated response between hypopneas and apneas has been observed in the literature. Kulkas et al. [52], as in our study, demonstrated a relationship between the duration of obstructive events and the severity of the related desaturation but, compared to hypopnea, apnea events led to more severe desaturations. These findings further support the idea that the biological and physiological effects of apneas and hypopneas are not equivalent and are also consistent with the hypothesis that overall AHI, an index that estimates the severity of OSA by quantifying only the rate at which respiratory events occur, does not fully reflect the severity of the disease.

In fact, AHI does not consider the duration of individual events, which shows a significant variation between patients. For example, Asano et al. [57] showed that in mild and moderate OSA patients, integrated area of desaturation is higher in the patients with cardiovascular events compared to patients without cardiovascular events, whereas AHI showed no differences between the groups. The intensity of the desaturation which in turn is related to the duration of the event, predicts better the degree of endothelial impairment, which is one of the main factors involved in cerebral dysfunction in OSA, than the number of apneas and hypopneas [47]. Moreover, several observational studies have demonstrated that measures of nocturnal hypoxemia predict cardiovascular disease and all cause mortality better than the AHI alone does [58].

Our study has potential limitations to consider. The signals of the diffuse optical monitor could have been contaminated by extracerebral tissue contributions as is the case for all such instruments. Future implementation could utilize a probe with multiple source-detector separations and the so-called pressure modulation algorithms which would allow for accounting for these effects [59]. However, we note that a source-detector separation of 2.5 cm has been found to be a good compromise and was validated in numerous studies [23, 33, 60]. The driving reasons for this omission of a short source-detector separation were to maximize the signal-to-noise ratio by averaging different output signals at the same source-detector separation and to utilize a simple probe for the night-sleep.

Second, we note that NIRS-DOS and DCS data from this study and the literature in general studies are mainly limited to the frontal lobes. One could only speculate how this is related to the response of the other brain areas in healthy and pathologically altered brain with a broader head-coverage. It has been shown that for systemic events such as the obstructive sleep apnea, this type of point measurements reflects the global, cortical response when compared to imaging methods such as magnetic resonance imaging (MRI) in the healthy brain [23, 33, 34]. In case of pathological alterations, this is clearly no-longer true and it has to be studied. Larger head-coverage is becoming more widely available for both techniques, albeit with additional technical complexity and reduced subject comfort. The latter is sometimes a limiting factor in this type of studies.

Third, absolute values were not recorded continuously but only at the beginning of the measurement. This has hindered our ability to evaluate the effect of different sleep stages on cerebral hemodynamics as was previously done for CBFV using TCD [61]. Another shortcoming due to relative measurements is that our results depend on the choice of the baseline for normalization.

Finally, our findings correspond to a group of patients with very severe OSA and male predominance, which implies that these results are not necessarily extrapolated to the different

OSA severities. The results should be validated in a large sample of patients with a wider range of severity. The study of cerebral hemodynamic changes due to obstructive events may be interesting in patients with moderate OSA, in which case AHI may not accurately estimate disease severity and predict its outcomes (e.g. cardiovascular, metabolic, and neurocognitive disorders) [57, 62]. Moreover, cardiovascular and neurovascular diseases should be recorded as a part of the clinical patient data to include this information in future analysis.

Nevertheless, our findings pave the way for future studies using these methods and provide the framework for a more thorough understanding of the obstructive sleep apnea pathophysiology and consequences, mainly about the mediation of OSA to cerebrovascular disease risk. Moreover, our findings provide new tools to improve the assessment of disorder severity which, nowadays, is only based on very simplistic AHI cut-offs. Finally, future research should analyze the changes in cerebral hemodynamics after the different therapeutic interventions that would allow to develop preventive measures to minimize the impact of this condition on cerebrovascular disease.

Conclusions

In summary, we were able to characterize and analyze the hemodynamic changes that occur at the level of cerebral microcirculation in response to obstructive events during sleep. We have found that apnea-/hypopnea duration is a key parameter on the cerebral hemodynamics on-time-response to the sleep events. Moreover, the response is more pronounced in obstructive apnea than in hypopnea events in the cerebral hemodynamic variables, and also in HR and SpO_2.

Supplementary material

Supplementary material is available at *SLEEP* online.

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Author Contributions

Clara Gregori-Pla analyzed the data, and wrote the manuscript. Mercedes Mayos and Turgut Durduran devised the study, supervised the clinical aspects, contributed to the clinical interpretation, and revised the manuscript. Peyman Zirak and Igor Blanco devised the optical data acquisition and acquired the data. Isabel Serra, Pau Bramon, Jordi Solà-Soler and Beatriz F. Giraldo Giraldo contributed to the analysis. Ana Fortuna, Gianluca Cotta and Anna Mola contributed to the recruitment and in the acquisition of the clinical data.

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Herewith the following current or potential financial relationships are disclosed. ICFO has equity ownership in the spin-off company HemoPhotonics S.L. which commercializes relevant technologies. Potential financial conflicts of interest and objectivity of research have been monitored by ICFO Knowledge & Technology Transfer Department. No financial conflicts of interest were identified.

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The authors of the manuscript are or have been involved in other research projects and topics of relevance to this research. The publication of these results is supportive of these activities. The potential conflicts of interest and objectivity in all research activities are continuously monitored by the relevant departments in their institutions. No issues have been identified.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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