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Near-infrared spectroscopy (NIRS) as a useful tool to evaluate the treatment efficacy of positive airways pressure therapy in patients with obstructive sleep apnea syndrome (OSAS): A pilot study

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In obstructive sleep apnea syndrome (OSA) the periodic reduction or cessation of breathing due to narrowing or occlusion of the upper airway during sleep leads to an impaired cerebral vascular autoregulation that is associated with an increased cardiovascular risk, including stroke. Continuous positive airways pressure (CPAP) therapy at night is the most effective treatment for OSA and has been shown to reduce the cardiovascular risk in OSA patients. However, there is no suitable bedside monitoring method evaluating the recovery of cerebral hemodynamics during CPAP therapy. Near-infrared spectroscopy (NIRS) is ideally suited for non-invasive monitoring the cerebral hemodynamics during sleep due to its properties of local measurement, totally safe application and good tolerance to motion. In this pilot study, we monitored cerebral hemodynamics during standard CPAP therapy at night in three patients with severe OSA using NIRS. We found periodic oscillations in HbO_2, HHb, tissue oxygenation index (TOI) and blood volume (BV) associated with periodic apnea events without CPAP in all OSA patients. These oscillations were eliminated under the optimal CPAP pressures in all patients. These results suggested that the recovery of cerebral hemodynamics impaired by apnea events can be evaluated by bedside NIRS measurements in real time during all night CPAP therapy. NIRS is a useful bedside monitoring tool to evaluate the treatment efficacy of CPAP therapy in patients with OSA.

Keywords: Sleep; cerebral hemodynamics; hemodynamic oscillations; bedside monitoring.

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1. Introduction

Obstructive sleep apnea syndrome (OSA) is the periodic reduction (hypopnea) or cessation (apnea) of breathing due to narrowing or occlusion of the upper airway during sleep.[1,2] The main consequences of OSA are daytime symptoms and increased cardiovascular risks including hypertension, ischaemic heart disease and stroke.[3–5] In healthy humans, the cerebral blood flow (BF) should stay approximately constant when blood pressure varies, and adapt to changes in energy consumption and carbon dioxide and oxygen levels in the blood, and other factors. This regulation of BF is achieved primarily by arterioles dilating and contracting (vasomotion), under the influence of multiple complex physiological control systems which are termed as cerebral autoregulation mechanism.[6,7] Cerebral autoregulation is often interpreted as also encompassing the wider field of cerebral BF regulation, including neurovascular coupling and other aspects of cerebral hemodynamics. It has been well known that impairment of cerebral autoregulation mechanism involved in OSA contributes to the higher risk of stroke in OSA patients.[8,9]

Continuous positive airways pressure (CPAP) therapy is the most effective treatment for OSA to prevent apnea and intermittent hypoxia.[10,11] Standard CPAP therapy at hospital needs CPAP titration which is to identify an optimal pressure to maintain airway patency in all body positions and sleep stages and to eliminate respiratory events (apnea, hypopnea, snoring, etc.). Newer CPAP devices automatically adapt pressure levels based on embedded algorhithms (auto-CPAP). Currently, nasal and oral airflow changes together with respiratory effort signals and peripheral oxygen saturation (SpO_2) measured by pulse oximetry, are the most important systemic parameters for OSA diagnosis. They are also two key indicators for CPAP titration. However, SpO_2 and air flow measurements can only reflect the systemic hemodynamics during sleep; but are unable to provide information about cerebral hemodynamic changes and cerebral autoregulation. Thus, the questions whether CPAP efficacy in OSA is related to cerebral hemodynamics or whether optimal CPAP pressure derived from systemic parameters will restore or exacerbate the impaired cerebral autoregulation mechanism in OSA remain essentially unanswered. Addressing these questions has significant consequences for both clinical doctors and patients to improve future treatment strategies.

To monitor cerebral hemodynamic changes during CPAP therapy in real time is necessary to study these questions. Several well-established neuroimaging methodologies including computed tomography (CT), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), transcranial Doppler (TCD), and near-infrared spectroscopy (NIRS) have been widely used to study cerebral autoregulation mechanism under various physiological and pathological states in both healthy subjects and patients.[12–19] Several attempts to determine cerebral hemodynamics in OSA using these techniques faced some limitations. CT, fMRI, PET and SPECT are only suitable to study the cerebral hemodynamics in OSA patients during wakefulness,[20–22] but not during all night sleep due to obvious reasons including safety issues, radiation, high magnetic fields, loud noises, motion artifacts, compatibility of CPAP device, etc. TCD has been used to measure BF during sleep since 1990s.[23–26] However, TCD faces similar technical challenges of obtaining clean signals while patients were asleep, since the requirement to keep the Doppler probe in place in the medial cerebral artery during sleep was difficult.[27] In addition TCD reflects hemodynamics of the middle arteries but not of the arterioles, which are responsible for mediating cerebral autoregulation. NIRS can robustly measure oxygenated (HbO_2) and deoxygenated (HHb) hemoglobin (Hb), BF, blood volume (BV) and tissue oxygenation index (TOI) changes in local cerebral and muscular regions by calculating the distinct absorption spectrums of different chromophores.[28–35] The spontaneous low frequency oscillation (4–150 MHz) in these hemodynamic parameters further reflects vasomotion in cerebral tissue.[16,36–38] As a totally non-invasive and non-radioactive optical method, NIRS has sub-second temporal resolution and less motion restriction,[39,40] making it a powerful tool for all night sleep study. Although several studies with NIRS repeatedly reported an impairment of cerebral oxygenation in the patients with sleep apnea,[41–45] we still lack knowledge about the changes of cerebral autoregulation mechanism under CPAP therapy.

In this pilot study, we will characterize the changes of cerebral hemodynamic during all night

CPAP therapy in OSA patients using NIRS. Real time bedside monitoring of cerebral oxygenation changes will provide insight into the recovery mechanisms of cerebral autoregulation during CPAP therapy and improve our understanding of OSA associated risk of vascular diseases like stroke.

2. Method

2.1. *Subject*

Three patients with OSA (apnea–hypopnea index (AHI) > 4/h) were recruited at Sleep Center, Clinic Barmelweid, Switzerland. The basic information of these patients is shown in Table 1. The study has been proven by the local ethics committee, and all subjects gave their written informed consent to participate into the study. None of subjects has ischemic heart disease, chronic heart failure, or cerebrovascular disorders.

2.2. *Video-polysomnography (PSG) measurements*

An all-night Video-PSG (Embla RemLogic, Embla Systems LLC, USA) measurement was recorded from each patient during CPAP therapy at our sleep center. PSG is a comprehensive recording of the biophysiological changes during sleep, including cerebral electroencephalogram (EEG) at electrode locations of C3, C4, O1, O2, F3 and F4 according to 10–20 system, eye movement (electrooculogram, EOG), muscle activation (electromyogram, EMG), electrocardiogram (ECG), breathing functions (respiratory airflow and respiratory effort indicators), and peripheral oxygen saturation (SpO_2). Each patient was videotaped with an infrared camera to allow for subsequent assessment of subject's movement during sleep. A fully experienced neurophysiologist independently scored the sleep stages, respiratory events (apnea, hypopnea, and snoring), EEG arousals, and movements in 30-s epochs according to the newer American Academy of Sleep Medicine (AASM) scale,[46] based on the PSG measurements. OSA is defined as AHI higher or equal to 5/h, mild OSA is with AHI between 5 and 15/h, moderate OSA is with AHI between 15 and 30/h, and severe OSA has AHI higher than 30/h.

Table 1. Information of the three patients with OSA.

Subject no.	Gender	Age	Weight (kg)	Height (cm)	BMI (kg/m^2)	AHI (/h)
1	Male	36	134	179	41.8	160
2	Female	55	86	162	32	35
3	Male	65	115	163	43.3	21

Note: BMI: body mass index, AHI: apnea–hypopnea index.

2.3. *NIRS measurements*

A popular commercialized NIRS device (NIRO-300, Hamamatsu Photonics, Japan) based on spatially resolved spectroscopy (SRS) was used to monitor the hemodynamic changes during all-night sleep monitoring.[47] SRS method measures the light intensity as a function of the source-detector distance which is independent of the coupling between the optodes and the tissue. The NIRO-300 device uses four wavelengths of near-infrared light (775, 810, 850, and 910 nm), and the sensor contains three photodiodes placed at 4 cm from the source of emitting light. The emitting light will be coupled into a light transmitting fiber. The ends of the fiber and sensor are placed in a black light proof holder which fixes the detectors in the correct orientation relative to the light emitting point to ensure that the three photodiodes are at uniformly increasing distances (1 mm) from the source. The influence of the superficial layers of tissue which is a big contamination to the NIRS measurement with single source-detector distance is eliminated in the SRS approach, since the superficial tissue affects all the light bundles similarly and therefore their influences are cancelled out.[40] Based on SRS method, NIRO-300 can evaluate the tissue oxygen saturation changes by measuring the quantitative data of tissue oxygen index (TOI) in the unit of %, which is the ratio of HbO_2 to total Hb. NIRO-300 can use the Beer-Lambert method and provide the relative changes of HbO_2, HHb and total Hb. The NIRO-300 probe was kept in good contact with the left side of the subject's forehead via a medical adhesive and a soft medical bandage. The sample rate of NIRS measurement is 1 Hz. The raw analog signals of NIRO-300 measurements will be sampled by the data acquisition system of PSG, so that NIRS and PSG measurements can be synchronized.

2.4. *CPAP therapy*

One-hour baseline measurements were conducted without CPAP machine in every subject after

falling asleep with PSG and NIRS monitoring. After that patient was waken up and wore the mask of an auto-CPAP machine (S9 AutoSet^{TM} CPAP Machine, ResMed, Australia), then they can fall asleep again until next day morning. The CPAP pressure provided by the machine will be automatically adjusted according to its auto set algorithm which measured flow limitations such as snoring and apnea on a breath-by-breath basis. CPAP therapy started at a minimal pressure. When the patient's airflow showed signs of flow limitation, the auto set algorithm gently increased pressure based on the intensity and duration of the event until all the events were eliminated. Once the respiratory events resolved, pressures gradually decreased over a 20 min time frame. The all-night CPAP pressures were recorded in the machine.

2.5. *Data analysis*

Considering NIRS measures are usually severely contaminated by the movements during all-night sleep, several data preprocessing steps are needed:

(1) *Motion artifacts correction*. The raw NIRS data within 180 s after movements scored from PSG measurements will be discarded to eliminate the influences of motion artifacts.
(2) *Data segmentation and realignment*. The remaining NIRS data corresponding to baseline (without CPAP pressure) and optimal CPAP pressure (totally eliminated apnea events) measurements will be segmented into two data frames, i.e., data frame of baseline measurements and data frame of optimal CPAP pressure measurements. The NIRS data fragments in each data frame will be connected orderly.
(3) *Baseline adjustment*. The baselines of the data fragments in Step 2 usually varied. The jump of baselines between different data fragments will be eliminated by subtracting the value of the last data point of the former fragment from the succeed fragment.
(4) *Detrending*. To suppress the slow drifts, data will be subjected to detrending algorithm which subtracted the trends interpolated using piecewise cubic Hermite interpolation method.[48]
(5) *Bandpass filter*. A bandpass filter (type II Chebyshev filter, passband is 10–450 MHZ) will be used to further eliminate slow drifts.

Then the hemodynamic changing patterns under baseline and optimal CPAP pressure measurements will be compared visually by three experienced physicians. The standard deviations (SDs) of the hemodynamic changing curves corresponding to these two measurements will be calculated[49] to identify whether the cerebral hemodynamic oscillations induced by apnea events were suppressed by CPAP therapy.

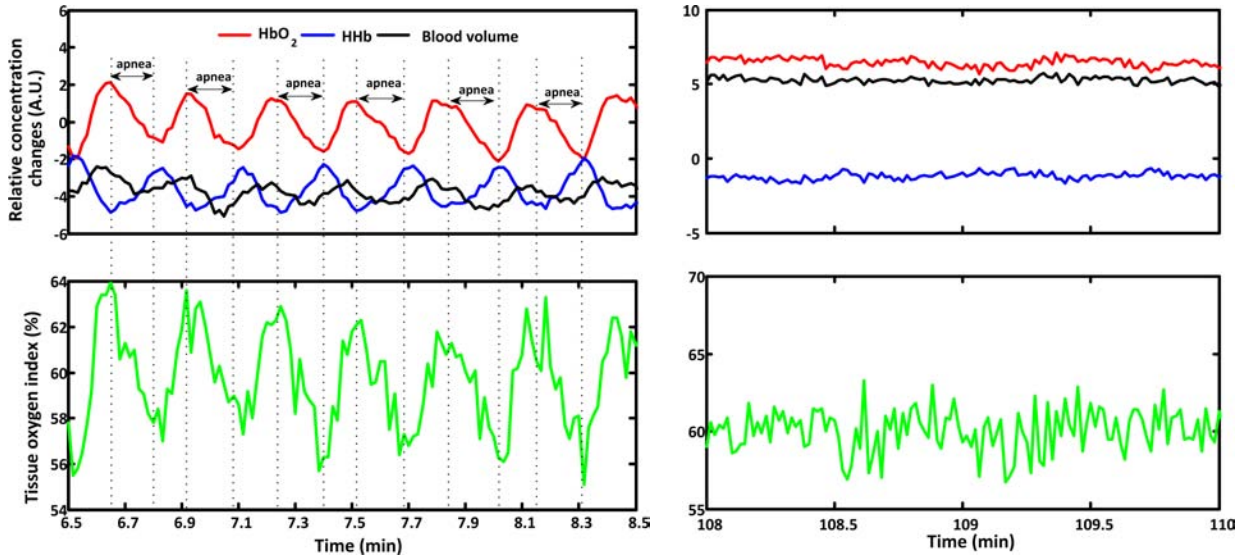
The Sign test was used to compare the SDs of the NIRS measurements under baseline and optimal CPAP pressure ($p < 0.05$). Statistical analysis was performed using SPSS (IBM Corporation, USA) computer programs.

3. Results

Typical fragments of cerebral hemodynamics during baseline measurements and optimal CPAP pressures measured from Subject 1 were shown in Fig. 1. HbO_2, HHb, TOI, and BV showed significant oscillations induced by apnea events without CPAP pressure in Fig. 1(a). HbO_2 and HHb showed reverse changing trends, while HbO_2 and TOI showed the same changing pattern. BV showed similar changing trend as HbO_2 but with some phase shifts. All the oscillations in cerebral hemodynamics were eliminated under optimal pressures (mean CPAP pressure was 12 cm H_2O) indexing recovery of cerebral autoregulation, as shown in Fig. 1(b). The similar changes were also clearly observed in Subjects 2 and 3, as shown in Fig. 2 and 3, respectively. The optimal pressures of the CPAP therapies for Subjects 2 and 3 are 8 cm H_2O and 10 cm H_2O, respectively.

Basic information about the sleep time, measurement periods under the baseline (without CPAP pressure) and optimal CPAP pressure were shown in Table 2. As stated in Sec. 2.4, about 1-h baseline measurements without CPAP pressure were conducted in every patient. Therefore, the baseline measurements after discarding the data contaminated by motion artifacts were between 50 and 60 min, and it was around 12%, 13%, and 14% of total monitoring time in each subject, respectively. The measurement time under optimal CPAP pressure was about 25%, 23%, and 16% of total monitoring time in each subject.

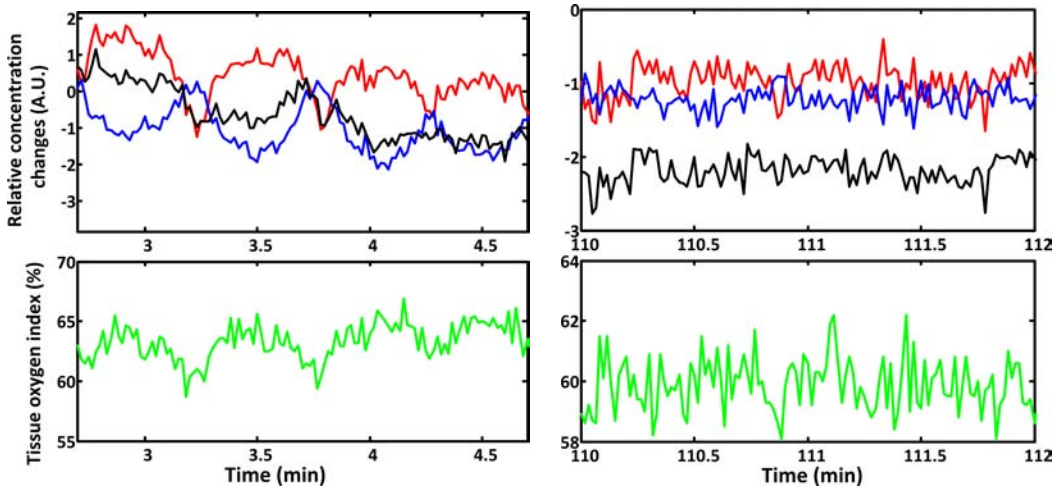
The SDs of the hemodynamic changing curves corresponding to the measurements under baseline



(a) (b)

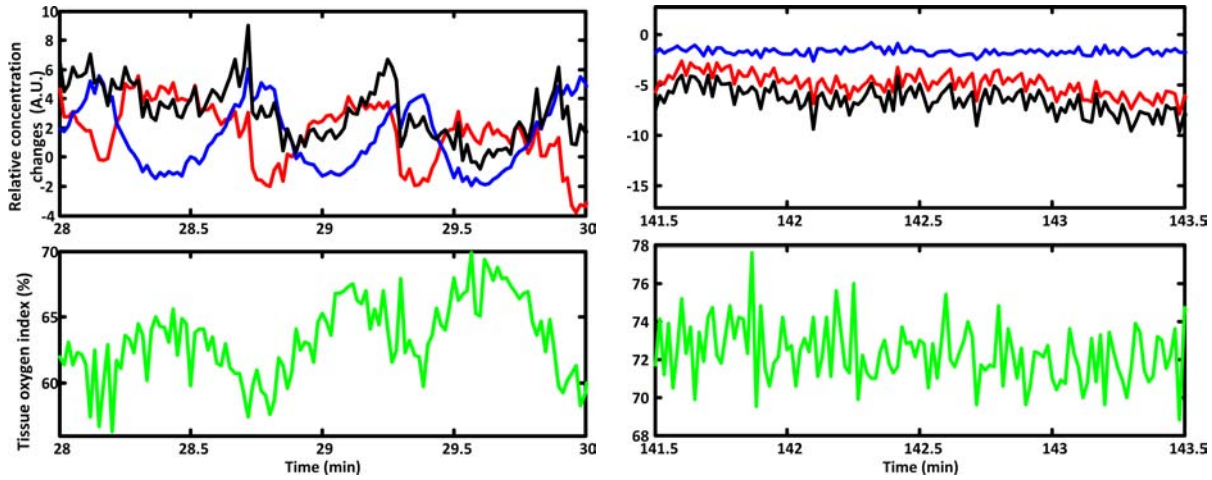
Fig. 1. Typical fragments of cerebral hemodynamics during baseline measurements (a) and optimal CPAP pressures (b) measured from Subject 1. The apnea events are marked by dash lines and double arrows shown in (a). BV, HbO_2 and HHb changes are expressed in arbitrary units (A.U.), as the mean value of first 60-s measurements was set at 0. During apnea events shown in (a), the BV, HbO_2 and tissue oxygen index signals show parallel decrease that are opposite to the HHb which increases after the initiation of apnea. Then an increase of BV, HbO_2 and tissue oxygen index, while a decrease of HHb appears after the termination of apnea. These apnea associated periodic oscillations in hemodynamic parameters are totally eliminated under optimal CPAP pressures, as shown in (b).

and optimal CPAP pressures were shown in Table 3. The SDs which approximately reflect the amplitudes of the hemodynamic oscillations,[49] were obviously decreased under optimal CPAP pressures compared to the baseline values. The Sign test showed that the oscillations of NIRS measurements induced by apnea events were significantly reduced under optimal CPAP pressures ($p < 0.05$).



(a) (b)

Fig. 2. Typical fragments of cerebral hemodynamics during baseline measurements (a) and optimal CPAP pressures (b) measured from Subject 2. The captions are the same as shown in Fig. 1.



(a) (b)

Fig. 3. Typical fragments of cerebral hemodynamics during baseline measurements (a) and optimal CPAP pressures (b) measured from Subject 3. The captions are the same as shown in Fig. 1.

Table 2. Sleep information of the three patients during measurements.

Subject no.	Total sleep time (min)	Measurements under baseline (min)	Measurements under optimal CPAP pressure (min)
1	470	55	118
2	470	62	107
3	383	53	60

Table 3. The SDs of cerebral hemodynamics during baseline measurements and under optimal CPAP pressures.

	Baseline measurements				Under optimal CPAP pressures			
Subject no.	BV (A.U.)	HbO_2 (A.U.)	HHb (A.U.)	TOI (%)	BV (A.U.)	HbO_2 (A.U.)	HHb (A.U.)	TOI (%)
1	0.8	1.4	1.1	2.7	0.4	0.5	0.3	1.5
2	0.7	0.8	0.6	1.5	0.2	0.2	0.2	1
3	3.2	3.1	3.1	3.5	1.3	1.2	0.5	2.2

Note: SD: standard deviation, BV: blood volume, TOI: tissue oxygen index, BV, HbO_2 and HHb changes are expressed in arbitrary units (A.U.), as the mean value of first 60-s measurements was set at 0.

4. Discussion

In this pilot study on three patients with OSA, we found that the cerebral hemodynamic oscillations induced by apnea events can be effectively eliminated by CPAP pressures. These results suggested that CPAP therapy can restore the impaired cerebral autoregulation mechanism in patients with OSA, thus it may prevent the high risk of cardiovascular disease such as stroke in these patients. NIRS is a useful bedside monitoring tool to evaluate the treatment efficacy of CPAP therapy in patients with OSA in real time.

The changes of cerebral hemodynamics during apnea events have been characterized by several previous studies.[44,45,50,51] All of these studies, reported a decrease in HbO_2 while an increase in HHb during apnea events, and a reverse changing tendency immediately after the end of the events, which is confirmed by our results. Furthermore, we found that the decline of HbO_2 was accompanied by a decrease in cerebral oxygen saturation (TOI)

indicating that desaturations induced by apnea events not only exist peripherally in SpO_2, but also occur in brain. By contrast reported changes of BV are more controversial. Several studies found BV to increase during apnea events[45,50]; while other studies[41,42,44] including ours, showed that BV decreased, as shown in Figs. 1–3. Urlesberger *et al.* found a decrease in BV in the majority of apnea events in 58 patients.[44] Olopade *et al.* argued that the lower cerebral tissue oxygenation in OSA compared to control subjects may be related to the age disparity between the two groups.[42] Therefore, further studies with more patients are needed to clarify the patterns of changes of BV in OSA more thoroughly taking multiple factors into account such as age, body mass index (BMI), AHI or gender.

In our study, the decrease of BV after the initiations of apnea events suggested the decreased oxygen supply to brain tissues. We therefore conclude that oxygen extraction increased to complement oxygen supply for neuronal activities, which may cause the decrease of HbO_2 and TOI, and the increase of HHb. Previous studies on BF changes with TCD found a decrease in cerebral BF during most of OSA events,[26] and these results are in line with the decrease of BV in our results of NIRS measurements. The deteriorated cerebral saturation and decrement in blood supply during apnea events will be terminated by a short abrupt awakening called arousal that mediated by increase of sympathetic activity. This increased sympathetic activity is also visible in the increase of heart rate. Arousal terminates apnea events. Patients with OSA remain unaware of such short time of arousal (normal between 3 and 10 s), but it is thought to reflect a kind of self-protection mechanism that is important for survival of the patients because arousal can restore the air flow that is ceased during apnea events. Then the recovery of breathing and increase in cerebral BV and HbO_2 generally overcame cerebral oxygen desaturation, leading to the decrease of HHb and increase of TOI. These apnea-induced periodic cerebral hemodynamic oscillations will interrupt the normal nocturnal sleep, disturb cerebral autoregulation and oxygenation during sleep, thus finally impair the autoregulation mechanism and contribute to high risk of cardiovascular diseases such as stroke.

As shown in Figs. 1–3, we found that the apnea-induced hemodynamic oscillations can be totally eliminated under optimal CPAP pressures in all patients. Optimal CPAP pressures are strong enough to prevent the occlusion of the upper airway during apnea events, so that the patients can inhale and exhale normally. As shown in Table 3, the SDs of hemodynamic changes which could reflect the amplitudes of hemodynamic oscillations,[49] were strongly suppressed under optimal CPAP pressures compared to the ones during baseline measurements in all hemodynamic parameters. Non-parametric statistical analysis, i.e., Sign test was chosen to test the differences between NIRS data under baseline and optimal CPAP pressure measurements, due to the limited number of subjects in this study. Sign test showed that all the hemodynamic measurements (four parameters) in these three subjects decreased under optimal CPAP pressure compared to baseline (totally $4 \times 3 = 12$ pairs to be compared, negative differences $= 12$, $p < 0.001$). It has been well known that optimal CPAP pressures can restore peripheral oxygen saturation in patients with OSA. Our data showed that they can also effectively restore cerebral tissue oxygenation. These results may support the hypothesis that CPAP therapy can prevent sleep apnea related comorbidities including stroke.[52,53]

One of the main limitations of this pilot study is that we only measured three patients with OSA. The limited number of subjects did not allow us to further investigate the relationships between cerebral hemodynamics, CPAP pressures, and other factors such as age, BMI, SpO_2. Another main limitation is that we still do not know the dynamic procedures of the restoration of cerebral hemodynamics under different CPAP pressures. Our further studies will investigate the dynamics of hemodynamic recovery with the increments of CPAP pressures in patients with OSA, to gain a better insight into the recovery mechanisms of cerebral autoregulation during CPAP therapy.

Although with several limitations, our pilot study still shed a light on the future application of NIRS in the clinical research field of sleep medicine. In 1977, Frans Jöbsis, who was educated in the field of optical techniques for monitoring tissues as a post-doctoral fellow in the Britton Chance laboratory, University of Pennsylvania, first reported the *in vivo* NIRS measurements on brain tissue.[54] Since then NIRS technique has been well developed for more than 30 years, thanks to the prominent work of the pioneers like Dr Britton Chance.[39,55–57] As an optical method, it has been demonstrated to be an ideal

complementary neuroimaging technology to fMRI, considering its properties of non-invasive and non-radioactive measurement, high temporal resolution, portability and less restriction to the subjects and measurement environment. Sleep is homeostatically regulated between immune, nervous, skeletal and muscular systems to maintain health, adaptability, and cognitive performance. Although humans spend approximately 1/3 time of their lives during sleep, the functions of sleep and effects of sleep related disorders remain enigmatic due to the limitations of current neuroimaging techniques as mentioned in the Introduction section above. Our work suggests that NIRS will provide a promising tool to investigate the pathological mechanisms of sleep disorders, and to evaluate the treatment efficacy in this research field in the future.

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