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ORIGINAL ARTICLE

Cerebral hemodynamic changes in obstructive sleep apnea syndrome after continuous positive airway pressure treatment

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Abstract
Background Patients with obstructive sleep apnea syndrome (OSAS) are at increased risk for cerebrovascular diseases. The underlying mechanisms remain obscure. It may occur through a reduction in cerebral vascular reactivity. Continuous positive airway pressure (CPAP) is effective in reducing the occurrence of apneas. We hypothesized that treatment with CPAP improves cerebral vascular reactivity.
Methods This is a prospective study with OSAS patients. The apnea test (ApT) was calculated as an increase of mean artery velocity during apnea: [Artery velocity in apnea minus Resting artery velocity]/Resting artery velocity expressed as percentage. After 2 years of CPAP treatment, the test was repeated.
Results Seventy-six patients represented the study pool. After 2 years of treatment with CPAP, we were able to conduct a reassessment in 65 patients. Of the 65 patients who finished the clinical study, 56 were men, and 9 were women, with an average age of 48.1±10.4 years. There was an improvement in the ApT after CPAP treatment (30.8± 12.1 vs 39.8±15.1; *p*:0.000). The values of cerebral blood flow velocities, diastolic blood pressure in apnea, and basal heart rate decreased.
Conclusions Cerebral vascular reactivity in OSAS patients measured by ApT improved after 2 years of CPAP.

Keywords Obstructive sleep apnea syndrome · Continuous positive airway pressure · Cerebral hemodynamic · Transcranial Doppler · Middle cerebral artery

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Introduction

Obstructive sleep apnea syndrome (OSAS) is a disorder affecting 2–4 % of the adult population and with high prevalence of undiagnosed patients [1]. The disorder is characterized by daytime hypersomnolence, nocturnal snoring, obesity, and frequent cessation of breathing during sleep. Fragmented sleep results in decreased quality of life and increased risk of injuries from motor vehicle crashes and industrial injuries [2]. Recently, OSAS has been implicated as an independent risk factor for the development of stroke [3, 4].

The pathogenesis of the neurological abnormalities is incompletely understood. Putative links between OSAS and stroke include arterial hypertension [5], systemic inflammation [6], coagulation factors [7], and changes in cerebral blood flow [8]. Continuous positive airway pressure (CPAP) has been effective in reducing symptoms of sleepiness and in improving quality of life in people with moderate and severe OSAS [9]. CPAP treatment in OSAS

prevents new vascular events after an ischemic stroke [10] and reduces blood pressure [11].

Cerebral autoregulation is the ability to maintain constant cerebral blood flow despite changes in the cerebral perfusion pressure. The first studies of brain perfusion were measurements done at different blood pressures, whereas nowadays, transcranial Doppler (TCD) is used to evaluate dynamic cerebral autoregulation in humans. TCD testing of cerebrovascular reactivity (CVR) measures changes in cerebral blood flow velocities (CBFV) in response to a vasodilatory stimulus such CO_2 inhalation or acetazolamide administration. CVR can also be estimated by measuring the change in the CBFV that occurs in response to endogenous collection of CO_2 such as apnea test (ApT). Some authors [12] have found severe disturbances of cerebrovascular reactivity indicated by CBFV hyporeactivity, especially during consecutive respiratory events. These changes are likely to impair cerebral circulation. Impaired CVR may cause cerebral blood volume dip following obstructive sleep apnea termination [13]. Some studies have demonstrated that in healthy awake volunteers, the CBFV decreased significantly after CPAP treatment [14]. We hypothesized that the CVR in the middle cerebral artery (MCA) measured by the apnea test improves after 2 years of CPAP treatment.

Patients and methods

Patients

This is a prospective study with consecutive patients with OSAS evaluated in the Sleep Laboratory in Albacete University Hospital. The exclusion criteria were cardiopulmonary diseases, previous cerebrovascular disease, extracranial carotid stenosis or occlusion, intracranial artery stenosis, lack of temporal bone acoustic window, and β-blocker treatment. Patients with central apnea syndrome and mixed were excluded. All patients were 18 years old or above. The study protocol was reviewed and approved by the Ethics Committee of our Hospital, and all subjects gave written informed consent to participate in the study.

Vascular risk factor (arterial hypertension, smoking, hyperlipidemia, and diabetes mellitus), body mass index (BMI), and Epworth Sleepiness Scale (ESS) were registered. Hypertension was defined as a detection of one or more of the following: resting systolic blood pressure of at least 140 mmHg, resting diastolic pressure of at least 90 mmHg, or treatment with antihypertensive medications.

Polysomnography

Full-night attended polysomnography was obtained using a 16-channel polygraph (SleepLab 1000P, Aequiton Medical Inc., Minneapolis, MN, USA), including three EEG channels (C4-A1, Cz-O2, and C3-A2), two electro-oculogram channels, submental electromyogram (EMG), and tibialis anterior EMG in both legs. Respiratory efforts were monitored using chest and abdominal respiratory belts, as well as nasal oral airflow. The level of oxygen saturation was set using a pulse oximeter.

Apnea was defined as a complete cessation of airflow for ≥10 s, and hypopnea was defined as a reduction ≥30 % in airflow for 10 s associated with ≥4 % desaturation. The apnea–hypopnea index (AHI) was calculated as the sum of the number of apnea and hypopnea events per hour of sleep. Percentage of total sleep time spent with an oxygen saturation <90 % (T90) was visually scored. OSAS was confirmed by polysomnography using a threshold of IAH ≥ 10.

Cerebrovascular reactivity

All subjects undergone cervical and transcranial Doppler ultrasonography (Multi-DOP B+, DWL Elecktronische Systeme, Germany), which excluded extra- and intracranial vessel stenosis. Patients were instructed not to smoke or drink caffeinated or alcoholic beverages for 24 h before their assessment. Accordingly, the clinical study was performed in a quiet room, with subjects lying in a comfortable supine position without any visual or auditory stimulation.

The breath-holding maneuver was performed according to the simplified test of cerebral perfusion reserve of Ratnatunga [15]. The apnea test was calculated as an increase of mean artery velocity during apnea: [Artery velocity in apnea minus Resting artery velocity]/Resting artery velocity expressed as percentage. Transcranial Doppler involve curve was registered in the M1 segment of the right MCA at a depth of 53 mm. We made the ApT to all subject in the study before use of CPAP.

First, the basal mean blood velocity was assessed for 1 min until it reaches a stable value. Then, subjects were asked to hold their breath for at least 30 s. The mean blood velocity in apnea was assessed as the highest value during apnea or in the first minute after the apnea.

Mean blood pressure (BP) and heart rate (HR) were continuously monitored using a blood pressure monitor (BCI 3100, BCI International, Waukesha, WI, USA), and values at rest and at apnea were achieved.

ApT, ESS, and BMI were repeated after 2 years with CPAP treatment. The optimal pressure of CPAP was estimated by employing the predicted formula of Miljeteig [16]. Utilization of CPAP was recorded from the CPAP machine system to confirm that the patient used their machines regularly.

Statistical analysis

Continuous data were presented as mean ± standard deviation. We confirmed that the data were normally distributed

by the Kolmogorov–Smirnov test. Categorical data were expressed as percentages. The pre- and post-CPAP value variations of the variables were measured as the change percentage over pre-CPAP values. We hypothesized that the CVR in the MCA measured by the apnea test improves after 2 years of CPAP treatment. We made the assessment at 2 years to determine if the improvement in CVR demonstrated in other studies was maintained.

Comparison between pre-CPAP and post-CPAP values of hemodynamic cerebral parameters was performed by Student's *t*-test for paired variables. Pearson correlations were implemented to determine the linear relationship between selected dependent variables. Univariate analysis of variance (ANOVA) was used to determine the main effects of candidate predictors including age, sex, BMI, T90, occurrence or not of hypertension, smoking, diabetes mellitus, and hyperlipidemia on ApT improvement. Variables with a main effect of $p<0.20$ in the univariate ANOVA were included in multiple linear regression analysis to predict ApT improvement. The level of significance was set at $p<0.05$ for all statistical comparisons. Statistical analysis was performed using statistical software (SPSS version 15.0, Chicago, IL, USA).

Results

Five of 81 participants were excluded because of inability to obtain an adequate Doppler signal. Seventy-six patients represented the study pool. After 2 years of treatment with CPAP, we were able to conduct a reassessment in 65 patients. Of the 11 patients who did not complete the study, 7 did not tolerate the CPAP, 2 died in traffic accidents, 1

Table 1 Anthropometric, clinical, hemodynamic, CPAP, and polysomnographic characteristics of OSAS patients

Anthropometric and clinical parameters	Mean or percentage	Standard deviation
Age (years)	48.1	10.4
Male/female gender (number)	56/9	–
Hypertensive (%)	27.7	–
Hyperlipidemia (%)	26.2	–
Diabetic (%)	3.0	–
Current smokers (%)	33.8	–
Basal BMI (kg/m^2)	31.0	4.2
Post-CPAP BMI (kg/m^2)	31.1	4.4
Basal ESS	12.8	4.1
Post-CPAP ESS	5.78	3.2
Hemodynamic, BP, and HR parameters		
Apnea test pre-CPAP (%)	30.8	12.1
Apnea test post-CPAP (%)	39.8	15.1
CBFV pre-CPAP (cm/s)	53.8	9.1
CBFV post-CPAP (cm/s)	49.9	12.7
Resting SBP pre-CPAP (mm Hg)	144.1	22.2
Resting SBP post-CPAP (mm Hg)	141.5	19.0
Resting DBP pre-CPAP (mm Hg)	87.1	13.3
Resting DBP post-CPAP (mm Hg)	81.5	11.8
Apnea SBP pre-CPAP (mm Hg)	148.0	21.5
Apnea SBP post-CPAP (mm Hg)	144.0	18.2
Apnea DBP pre-CPAP (mm Hg)	90.0	14.8
Apnea DBP post-CPAP (mm Hg)	81.0	11.6
Resting HR pre-CPAP (beats/min)	80.6	13.8
Resting HR post-CPAP (beats/min)	72.6	12.2
Apnea HR pre-CPAP (beats/min)	74.9	12.4
Apnea HR post-CPAP (beats/min)	71.8	12.4
CPAP and polysomnographic parameters		
CPAP measured use (h)	4.29	1.8
CPAP pressure (cm H_2O)	7.95	0.9
AHI	56.9	24.2
T90	20.3	26.7

BMI body mass index, *CPAP* continuous positive airway pressure, *ESS* Epworth Sleepiness Scale, *CBFV* cerebral blood flow velocity, *PI* pulsatility index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *AHI* apnea–hypopnea index, *T90* oxygen saturation <90 %

died of a cerebral hemorrhage, and 1 suffered from a non-fatal ischemic stroke. Of the 65 patients who finished the clinical study, 56 were men, and 9 were women, with an average age of 48.1±10.4 years. Anthropometric, clinical, hemodynamic, CPAP, and polysomnographic variables are shown in Table 1.

The statistical analysis performed shows an improvement in the ApT after using CPAP treatment (30.8±12.1 vs 39.8±15.1; *p*: 0.000). The results in other hemodynamic, BP, and HR parameters are shown in Table 2. These data show a decrease in resting CBFV between pre-CPAP values (53.8±9.1 cm/sg) versus post-CPAP values (49.9±12.7 cm/sg) with a *p*:0.046. The apnea diastolic BP and resting HR were statistically different.

The statistical analysis in BMI change between pre- and post-CPAP values shows no significant discrepancies (31.0±4.2 vs 31.1±4.4; *p*:0.597), while ESS improvement was clearly significant (12.8±4.1 vs 5.78±3.2; *p*: 0.000).

Table 3 shows the results of the univariate analysis between ApT improvement and anthropometric, clinical, CPAP, and polysomnographic parameters.

Table 3 Univariate analysis (Spearson's test) between improvement in apnea test and anthropometric, clinical, CPAP, and polysomnographic variables

Variable	*R*	*p*
Age	+0.048	0.712
Sex	−0.172	0.184
Hypertension	+0.225	0.081
Hyperlipidemia	+0.229	0.076
Smoking	+0.104	0.356
AHI	−0.014	0.917
T90	−0.070	0.590
BMI	+0.184	0.155
ESS	+0.062	0.711
CPAP use	+0.104	0.510
CPAP pressure	+0.058	0.725

BMI body mass index, *CPAP* continuous positive airway pressure, *ESS* Epworth Sleepiness Scale, *AHI* apnea–hypopnea index, *T90* oxygen saturation <90 %

Discussion

Our clinical study shows that the treatment with CPAP after 2 years in OSAS patients improves the cerebral vasomotor reactivity analyzed by apnea test at the MCA. Treatment with CPAP also decreases CBFV and diastolic BP in apnea and resting HR.

Hypercapnic cerebrovascular reactivity is evaluated by ApT, and it is considered an index of the capability of cerebral vessels to adapt to the metabolic demands of the brain. Any reduction in this property could be interpreted as an increased susceptibility to ischemic injury [17]. OSAS can provoke important cerebral hemodynamic changes. A few previous clinical studies have investigated the change on cerebral blood flow in OSAS patients [8], paying particular attention to hemodynamic effects on apneic events during nocturnal sleep and their relationship with sleep stages [18, 19]. Diomedi et al. [20] showed an improvement in cerebral hemodynamics in patient with OSAS in the first day and first month of using CPAP treatment. In our study, we observed that the improvement of cerebrovascular reactivity persisted after 2 years of treatment. The largest sample size of our study gives more reliability to the results than previous studies with less number of patients. In addition, this clinical study also included women who showed an ApT improvement, and this population was not studied by Diomedi et al. [20].

Our group also observed an improvement in the ApT at the basilar artery in OSAS patients after CPAP treatment [21]. Reichmunth et al. have demonstrated that vasodilator responses to the chemical stimuli in the cerebral circulation and the forearm are impaired in many patients with OSAS and, in some of these impairments, they can be improved with CPAP [22].

We found a decrease in CBFV after CPAP treatment, which probably reflects the normalization of pathologically

Table 2 Statistical analysis of hemodynamic, BP, and HR variable changes between pre-CPAP and post-CPAP

Variable	Pre-CPAP		Post-CPAP		*p*
	Mean	Standard deviation	Mean	Standard deviation	
Apnea test	30.8	12.1	39.8	15.1	0.000
CBFV	53.8	9.1	49.9	12.7	0.046
Resting SBP	144.1	21.5	141.3	19.2	0.602
Resting DBP	87.2	13.5	81.4	11.9	0.052
Apnea SBP	148.4	20.6	143.8	18.4	0.374
Apnea DBP	90.2	14.7	80.9	11.8	0.029
Resting HR	80.7	14.5	72.4	12.2	0.002
Apnea HR	75.6	13.1	71.7	12.6	0.301

CBFV cerebral blood flow velocity, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate

high velocities. High speeds in OSAS could be conditioned by high blood pressure, as well as cerebral vasoreactivity change. Other authors also showed that OSAS have high speeds [18] and can double its values during apnea [23]. This increase in speed could reflect a change in cerebral microcirculation [24], and it is possible that CPAP treatment could reverse this situation [25].

Consistent with previous studies [11, 26], we found a reduction in blood pressure that was statistically significant in the values of apnea diastolic BP. Our clinical study has also disclosed a decrease in resting HR after CPAP treatment. These findings on BP and HR would reflect a sympathetic hyperactivity and its value normalization after using CPAP treatment [27], although patients in our trial have shown an improvement in hypertension because they are more compliant with diet changes and BP control. This is unlikely because there is no decrease in BMI, so probably, the improvement in the BP is a direct effect of CPAP treatment.

Pathophysiologic mechanisms by which the cerebral vasoreactivity is altered in patients with OSAS would be a sympathetic hyperactivity [28, 29] and an endothelial dysfunction [30, 31]. Prevention of apneic events using CPAP might attenuate sympathetic nerve activity by decreasing the sensitivity and tonic activity of the chemoreflex [32, 33] and also reverses endothelial dysfunction [34, 35]. We used Doppler ultrasound to measure blood flow velocity in the MCA. Although this is not a direct measurement of cerebral blood flow, we believe that it is a reasonable estimate because the diameter of the MCA varies by less than 4 % during changes in arterial pressure and CO_2 tension.

Previous studies have demonstrated an impaired cerebral vascular response to hypoxia in OSAS and its correction with CPAP [36]. The change in the cerebral blood flow response to hypoxia after CPAP therapy was greatest in those with the highest apnea–hypopnea index, suggesting that patients with severe OSAS may most likely benefit from treatment with CPAP [22]. These authors believe that the alteration in cerebrovascular regulation is characterized by impaired endothelium-dependent vasodilatation [37–39].

Our study has some limitations. First, although all patients were newly diagnosed OSAS, the time from onset of symptoms is highly variable and, in most cases, inaccurate. Therefore, these data had not been analyzed. Second, there is no control group, although each patient serves as his/her own control. It would raise ethical concerns to keep patients with OSAS without treatment with CPAP. Third, the tolerance to CPAP was assessed by patient's statement, but in patients who were continuously on CPAP, we are not sure if apnea was abolished.

The early diagnosis of OSAS patients and the administration of CPAP treatment are essential in reducing the occurrence of cerebrovascular diseases. The reduction of stroke events will be implicated by several pathophysiological mechanisms, including a disorder in cerebral vasomotor reactivity, as shown this clinical study. Our findings provide the basis for future studies that will advance our understanding of the pathogenesis of stroke in patients with sleep apnea and thereby improve the management of this important complication.

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