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Therapeutic effects of long-term continuous positive airway pressure treatment on improving leptomeningeal collateral circulation in obstructive sleep apnea syndrome patients

K. YU[1], Z.-H. JIANG[1], L.-G. ZHANG[2]

[1]Department of Otorhinolaryngology, Shengli Oilfield Central Hospital, Dongying, Shandong, P.R. China
[2]Department of Neurology, Shengli Oilfield Central Hospital, Dongying, Shandong, P.R. China

Abstract. – OBJECTIVE: This study aims to use methods of scoring collaterals on CT angiography to analyze changes in collateral circulation in untreated patients with moderate and severe OSAS before and after nasal continuous positive airway pressure (CPAP) treatment.

PATIENTS AND METHODS: Ninety-eight moderate and severe OSAS patients treated with nasal CPAP and seventy-four controls that weren't treated with CPAP, were involved in this study. Two independent neuroradiologists evaluated intracranial collaterals by using Miteff scale, modified Tan scale. Intracranial collaterals differences were compared between OSAS group (before and after treated) and control group. Correlations between intracranial collaterals and clinical parameters were analyzed.

RESULTS: Compared with pre-therapy of moderate and severe groups, apnea-hypopnea index (AHI), oxygen desaturation index (ODI), epworth sleepness scale (ESS) were lower after treatment. The lowest oxygen saturation, average blood oxygen saturation, Miterff scale, modified Tan scale in moderate and severe groups were significantly increased after treatment. We documented significant decrease of Miterff scale after two years in moderate and severe OSAS group without CPAP therapy (n = 32, $p < 0.01$). Conversely, mild OSAS group without CPAP therapy did not change Miterff scale after two years (n = 32, $p > 0.05$). Multivariate Logistic regression analysis showed that AHI had significant impact on Miterff scale and modified Tan scale. Severe OSAS were independently related with Miterff scale (odds ratio 0.343, 95% confidence interval 0.301-0.391, $p < 0.01$) and modified Tan scale (odds ratio 0.267, 95% confidence interval 0.095-0.754, $p = 0.013$).

CONCLUSIONS: Long-term CPAP treatment is a viable therapeutic choice for improving leptomeningeal collateral circulation in OSAS patients.

Key Words:
Continuous positive airway pressure, Obstructive sleep apnea syndrome, Collateral circulation, Apnea-hypopnea index.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a current major health concerning adults, which is characterized by repetitive episodes of upper airway obstruction during sleep. A recent study showed that OSAS increases the risk of ischemic stroke independently[1]. The Sleep Heart Health Study found that incidence of stroke increased in subjects with severe OSAS[2]. Treatment emphasis of the ischemic stroke was to improve collateral circulation. During focal cerebral ischemia, the degree of ischemic vascular injury can be minimized by collateral supply to vessels as well as brain tissue within the oligemic regions. In addition, good collateral formation has the potential to rescue brain tissue that exists within a poorly perfused ischemic penumbra surrounding infarct brain. In addition, good collaterals circulation, as seen on cerebral angiography, is recognized to influence clinical outcomes, infarct volume following ischemic stroke and recurrent cerebral infarction. Clinical researches[3,4] have demonstrated the vascular stenosis and cerebral hypo-perfusion were more pronounced in OSA individuals. Although they did not evaluate the collaterals circulation of the study participants, the results raise a possibility for subsequent pial collaterals assessment in OSAS patients.

Corresponding Author: Ligong Zhang, MD; e-mail: yyaoliu@yeah.net

Continuous and positive airways pressure (CPAP) therapy is a choice for OSAS treatment. Nevertheless, to our best knowledge, a change in pial collaterals among OSAS patients with CPAP treatment has not yet been investigated. Therefore, the aim of the present study was to investigate pial collaterals characteristic changes in OSAS patients during two years, and investigate the effects of two-years CPAP treatment on collaterals circulation in moderate to severe OSAS.

Patients and Methods

Patients

A total of 172 patients who visited the Sleep Center of Shengli Oilfield Central Hospital for diagnosed OSAS between January 2014 and July 2015 were enrolled in this study. The 172 OSAS patients included 34 females (19.8%) and 138 males (80.2%). The patients aged 59.53 ± 11.30 years, and had been diagnosed with OSAS according to Diagnosis of Obstructive Sleep Apnea Clinical Practice Guideline From the American College of Physicians[5].

Exclusion criteria for both patients and healthy volunteers were listed as follows: (1) younger than 18 years, (2) congestive heart failure, renal failure, pulmonary disease, (3) OSAS already diagnosed or course of treatment before sleep center, (4) any other sleep disorders, (5) presence or history of substance abuse, (6) inflammatory or infectious disease, (7) pregnant woman. This prospective cohort study was approved by the hospital institutional Review Board. The informed consent was obtained from the participants.

Patient Selection and Trial Grouping

All the patients were subjected to polysomnography (PSG). Patients with apnea-hypopnea index (AHI) ≥ 5 to 15 were categorized as having mild OSAS, those with AHI ≥ 15 to 30 were categorized as moderate OSAS and those with AHI > 30 were categorized as severe OSAS. Moderate and severe OSAS patients were scheduled for CPAP therapy.

In the present work, the patients (moderate and severe OSAS) were repeated collaterals circulation assessment after two years of useful CPAP treatment, and compared to control a group of OSAS patients with scarce compliance to CPAP treatment. Based on AHI, the control group was divided into a moderate and severe OSAS subgroup and a mild OSAS subgroup. All subjects had their medical records reviewed and a blood test. Patients had a craniocervical CTA performed at pre-therapy and two years.

Indices

The polysomnographic recordings from our unit met the guidelines of the American Academy of Sleep Medicine (AASM)[6], which lasted a minimum of 7 h. The polysomnography-montage was used to record nose and mouth airflow, chest and abdominal movement, body position, heart rate, oxygen desaturation index and snoring time and leg movement. Polysomnographic recordings were visually scored by specialized technicians using AASM criteria[7].

Epworth scale is an eight-item measure of daytime sleepiness that can be scored from 0 to 3 and assesses sleepiness during different daytime situations. The final score varies from 0 to 24. Responses are summed, and higher scores indicate greater sleepiness. A final score more than 10 suggests excessive daytime sleepiness[8].

The scale of Miteff is a 3-point score that grades middle cerebral artery collateral branches with respect to the Sylvain fissure9. The grades assigned are as follows: 3 (if the vessels are reconstituted distal to the occlusion), 2 (vessels can be seen at the Sylvian fissure), or 1 (when the contrast opacification is merely seen in the distal superficial branches). The modified scale of Tan was scored on a scale of 0-3. A score of zero indicated absent collateral supply to the occluded MCA territory. A score of 1 indicated collateral supply filling ≤ 50% but > 0% of the occluded MCA territory. A score of 2 was given for collateral supply filling > 50% but < 100% of the occluded MCA territory. A score of 3 was given for 100% collateral supply of the occluded MCA territory. The collateral grading system classifies the collaterals as "good" if seen in ≥ 50% of the MCA territory and "poor" when they are seen in < 50% of the territory[10]. These subjects were assessed at baseline and after a follow-up period of one and three months of CPAP therapy. Each patient's Epworth Sleepiness Scale (ESS) score was noted during the baseline and follow-up visits.

Statistical Analysis

SPSS 20.0 (SPSS Inc., Armonk, NY, USA) was employed to analyze the research data. Continuous variables were expressed as means ± standard deviation (SD), and categorical variables were expressed as frequencies and percentages. Numeric predictors were tested by using inde-

pendent *t*-tests, Mann-Whitney U test or one-way analysis. Categorical variables were evaluated by using x^2-test or Fisher exact test. The association between the total sleep parameters and collaterals circulation scale was evaluated using Pearman correlation analysis and linear regression analysis. In addition, multiple logistic regressions were used to evaluate the independent predictors or associated factors for migraine.

Results

Baseline Characteristics

There was significant difference between the CPAP group, moderate and severe OSAH subgroup and mild OSAHS subgroup with regard to TG (Table I, $p = 0.011$) and Body Mass Index (BMI) (Table I, $p = 0.004$). Other baseline characteristics of the OSAHS patients in the study group are shown in Table I.

Sleep Parameters and ESS Evaluation

A total of 98 patients with a beneficial two years treatment with CPAP participated in this study and composed CPAP group. There were no significant changes of sleep parameters and ESS at the baseline among moderate and severe OSAS patients (Table II). On the basis of AHI, we distributed controls group patients in two subgroups, mild OSAS (5/h ≤ AHI < 15/h, n = 42), moderate and severe OSAS (AHI ≥ 15/h, n = 32). At follow-up, AHI (p= 0.000), ODI ($p = 0.000$), SaO_2 min ($p = 0.001$), SaO_2 mean ($p = 0.000$), ESS ($p = 0.014$) in moderate and severe OSAS patients improved significantly after two years of CPAP therapy. There was a significant increase in the AHI ($p = 0.001$), ODI ($p = 0.002$) and SaO_2 min ($p = 0.012$) in the patients of moderate and severe OSAS subgroups after two years. We also documented a higher AHI ($p = 0.000$), and ODI ($p = 0.000$) in mild OSAS (Table II).

Collateral Circulation Assessment

There were no significant change of Miterff scale and modified Tan scale at the baseline among moderate and severe OSAS patients. After two years of CPAP therapy, Miterff scale and modified Tan scale in CPAP group patients improved significantly (2.40 ± 0.80, $p = 0.018$, and 2.53 ± 0.68, $p = 0.003$) (Table III). For mild OSAS subgroup, Miterff scale (2.62 ± 0.62, $p = 0.583$) and modified Tan scale (2.55 ± 0.71, $p = 0.5$) did not significantly change during the two years follow-up period. While Miterff scale (1.94 ± 0.84, $p = 0.036$) and modified Tan scale (1.50 ± 0.88, $p = 0.01$) were significantly lower in moderate and severe OSAS subgroup after two years (Table III).

Multiple Regression Analysis in OSAS Patients

The correlations were statistically significant between Miterff scale and changes in sleep parameters (Table IV AHI: $r = -0.279$, $p = 0.001$,

Table I. Baseline characterstics of CPAP group and Control group ($\bar{x} \pm s$).

Characteristic	CPAP group (n = 98)	Control group (n = 74)		F/χ^2	p
		Moderate and severe OSAHS	Mild OSAHS		
Male sex (%)	78/79.59	26/81.25	34/80.95	0.060	0.970
Smoker (%)	36/36.73	12/37.50	16/38.10	0.025	0.988
Alcohol (%)	23/23.47	7/21.88	9/21.42	0.084	0.959
Diabetes mellitus (%)	24/24.49	7/21.88	10/23.81	0.091	0.956
Hypertension (%)	61/62.24	20/62.50	25/59.52	0.105	0.949
Hyperlipidemia (%)	6/6.12	2/6.25	3/7.15	0.053	0.974
Age (years)	61.00 ± 11.74	56.38 ± 11.22	59.53 ± 11.30	2.285	0.105
SBP (mm Hg)	135.26 ± 19.43	139.34 ± 15.73	136.28 ± 18.88	0.563	0.571
DBP (mm Hg)	82.81 ± 13.27	87.69 ± 12.05	83.96 ± 12.56	1.843	0.162
FBP (mmol/L)	5.43 ± 1.27	5.38 ± 1.07	5.42 ± 1.44	0.018	0.983
TC (mmol/L)	4.63 ± 0.99	4.39 ± 0.84	4.62 ± 0.90	0.785	0.458
TG (mmol/L)	1.68 ± 1.47	2.32 ± 1.95	1.31 ± 0.53	4.662	0.011
HDL-C (mmol/L)	0.94 ± 0.32	0.99 ± 0.55	0.92 ± 0.23	0.354	0.703
LDL-C (mmol/L)	2.81 ± 0.81	2.61 ± 0.74	2.73 ± 0.61	0.867	0.422
BMI (kg/m^2)	27.32 ± 4.57	29.03 ± 3.81	25.68 ± 3.92	5.606	0.004

SBP: Systolic blood pressure, DBP: diastolic blood pressure, FBP: fasting blood glucose, TC: total cholesterol, TG: triglyceride, HDL-C: hjgh-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, BMI: body mass index.

Table II. Sleep parameters, ESS of CPAP group and Control group.

Index	CPAP group baseline	2-year follow-up	Control group moderate and Severe OSAS	2-year follow-up	Mild OSAS	2-year follow-up
AHI	40.75 ± 19.86	4.80 ± 1.72[a]	37.09 ± 15.89	49.91 ± 13.60[b]	8.98 ± 3.10	13.78 ± 5.31[c]
ODI	33.53 ± 22.39	3.29 ± 2.13[a]	41.74 ± 16.79	55.88 ± 17.45[b]	4.80 ± 2.87	8.56 ± 3.73[c]
SaO_2 mean	94.00 ± 4.88	96.06 ± 0.85[a]	94.22 ± 2.78	93.34 ± 2.57	95.52 ± 1.61	95.31 ± 1.55
SaO_2 min	77.03 ± 11.09	90.47 ± 2.43[a]	75.31 ± 8.02	70.06 ± 8.21[b]	83.12 ± 7.11	81.36 ± 6.81
ESS	9.89 ± 2.56	2.99±1.93[a]	9.56 ± 1.58	10.34 ± 1.84	8.02 ± 2.51	8.88 ± 2.17

AHI: apnea-hypopnea index, ESS: Epworth sleepiness scale, ODI: oxygen desaturation index, SaO_2 mean: mean oxygen saturation, SaO_2 min: lowest oxygen saturation. [a]OSAS group-CPAP *vs*. baseline, $p < 0.05$. [b]moderate and severe OSAS baseline *vs*. 2-year follow-up, $p < 0.05$. c mild OSAS baseline *vs*. 2-year follow-up, $p < 0.05$.

Table III. Assessment of collateral circulation in CPAP group and Control group.

Index	CPAP group baseline	2-year follow-up	Control group moderate and Severe OSAS	2-year follow-up	Mild OSAS	2-year follow-up
Miterff Scale	2.21 ± 0.89	2.49 ± 0.72[a]	2.41 ± 0.91	1.94 ± 0.84[b]	2.69 ± 0.56	2.62 ± 0.62
Modified Tan Scale	2.18 ± 0.90	2.53 ± 0.68[a]	2.13 ± 1.00	1.50 ± 0.88[b]	2.64 ± 0.58	2.55 ± 0.71

[a]OSAS group-CPAP *vs*. baseline, $p < 0.05$. [b]moderate and severe OSAS baseline *vs*. 2-year follow-up, $p < 0.05$.

ODI: $r = -0.231$, $p = 0.008$). Changes in the other factors also did not show a statistically significant correlation with Miterff scale. There was also correlation between modified Tan scale and AHI (Table IV, $r = -0.269$, $p = 0.002$), ODI ($r = -0.246$, $p = 0.005$). In moderate and severe OSAS patients, risk factors obtained by the method of automatic selection (stepwise forward) that were associated significantly with an increased risk of the poor collateral circulation included AHI (Table IV, $\beta = -0.046$, $p = 0.012$). The results of the linear regression models adjusting influence factor from the multivariable-adjusted models, for Miterff scale and modified Tan scale, with AHI as categorical variable. It was observed a significant association of severe OSAS (AHI ≥ 30/h) with Miterff scale (OR = 0.343, 95% CI: 0.301-0.391, $p < 0.01$) and modified Tan scale (OR = 0.267, 95% CI: 0.095-0.754, $p = 0.013$) (Table IV).

Discussion

In this study, we documented the significant positive effect of long-term useful CPAP therapy on intracranial collaterals in patients affected by moderate and severe OSAS. In particular, there

Table IV. Multiple regression analysis in OSAS patients.

							95% CI for OR	
	Factor	β	SE	Wald	p	OR	Lower	Upper
Miterff scale	AHI	-0.363	0.154	5.554	0.018	0.696	0.515	0.941
	Severe OSAHS	-1.319	0.529	6.210	0.013	0.267	0.095	0.754
	Moderate OSAHS	/	/	/	0.444	/	/	/
	Mild OSAHS	/	/	/	–	/	/	/
Modified Tan scale	AHI	-0.046	0.018	6.263	0.012	0.955	0.921	0.990
	Severe OSAHS	-1.071	0.067	6.237	0.000	0.343	0.301	0.391
	Moderate OSAHS	/	/	/	0.140	/	/	/
	Mild OSAHS	/	/	/	–	/	/	/

was significant association between intracranial collaterals scale and severe OSAS. Conversely, moderate and severe with respect to mild OSAS without a useful treatment by CPAP, was not conducive to cerebral collateral circulation during the two years follow-up period. Mild OSAS without CPAP therapy did not significantly affect cerebral collateral circulation. Leptomeningeal collaterals are a subsidiary vascular network of small blood vessels connecting distal regions of the intracerebral arterial system[11-13] and may provide residual blood flow to ischemic areas. The collateral circulation plays an important role in the fate of ischemic tissue. The preservation of flow through leptomeningeal collaterals is known to protect brain tissue against irreversible damage in case of acute ischemia. Presence of good leptomeningeal collateral flow has been associated with better functional outcomes, smaller risk of hemorrhagic transformation and smaller infarct volumes after a proximal arterial occlusion[14-19]. A growing body of evidence has suggested genetic factors[20] and the vascular risk profile, such as prior hypertension[21], old age[22], hyperlipidemia, metabolic syndrome[23], hyperglycemia[24] and circle of Willis completeness, to interfere the forming of leptomeningeal collateral circulation through impairing endovascular function. Taking into account that OSAS can facilitate endothelial cell injury and dysfunction, it is conceivable that OSAS patients may more frequently suffer from poor leptomeningeal collaterals. In fact, OSAS has been recently linked to intracranial atherosclerotic stenosis[25]. However, leptomeningeal collaterals circulation deficiency has been linked to the occurrence of OSAS. Moreover, the mechanisms through which OSAS may influence collaterals circulation have not been completely explained. The pathophysiological mechanisms may be related to OSAS-induced intermittent hypoxia. Intermittent hypoxia may cause endothelial oxidative stress, chronic inflammation, reducing NO availability and repair capacity, ultimately facilitating endothelial cell injury and dysfunction in patients with OSAS. Modified Tan scale and Miteff scale by using high-resolution multi-detector CTA, grade degree of leptomeningeal collateral supply in the MCA territory. The two scores provide a simple, reliably, and reproducible assessment of collateral status[26]. The modified collateral score would independently associate with ischemic penumbra and infarct volumes.

Sleep parameters may negatively affect intracranial collaterals circulation. In our regression model, AHI was related to the changes observed in Miteff scale and modified Tan scale in OSAS patients. Seif et al[27] found that patients with AHI $\geq$ 18.4 showed declining endothelial function, whereas for patients with AHI < 18.4, there was no statistically significant association between AHI and endothelial function. Our results also showed that severe OSAS was significantly associated with Miteff scale and modified Tan scale. These findings suggest that moderate and severe OSAS appears to independently contribute to endothelial dysfunction, leading to OSAS-mediated poor leptomeningeal collateral circulation. However, whether mild OSAS can damage endothelial function remains to be determined. The results suggest that moderate and severe OSAS can be an independent cause of poor leptomeningeal collateral circulation, however, the influence of mild OSAS on collateral circulation may be complicated by other factors, such as obesity and high TG. Therefore, taking into account that many methods have been used to treat OSAS, no one seems to be a sufficient treatment to improve collateral circulation in these patients. In this report, moderate and severe OSAS patients showed a significant improvement of collateral circulation after two years of CPAP therapy. It suggests that CPAP is a viable treatment for poor leptomeningeal collateral circulation in obese OSAS patients. Though this study received a few interesting results, there are also some limitations. This investigation only observed the therapeutic effects of long-term CPAP treatment on improving collateral circulation in OSAS patients. However, the improvement of the pulmonary function of OSAS patients undergoing CPAP treatment has not been investigated. In the following study, we would test the pulmonary function by conducting the spirometric measurement.

Conclusions

Moderate and severe OSAS can affect the leptomeningeal collateral circulation. These positive consequences are more evident in severe OSAS, and our study suggests that long-term CPAP treatment is a viable therapeutic choice for improving collateral circulation in OSAS patients. This work is a cohort study of 172 patients. The sample size might not be sufficient to detect the relationship between OSAS and leptomeningeal collateral circulation. These preliminary observations about the relationship be-

tween long-term CPAP treatment and improvement of collateral circulation need to be further substantiated by larger investigations. Moreover, we focused only on CPAP, which means that other prescriptions for OSAS treatment have been evaluation yet to affect leptomeningeal collateral circulation.

Conflict of Interest

The authors declare no competing financial or commercial interests in this manuscript.

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