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Continuous Positive Airway Pressure Effectively Alleviates Arrhythmias in Patients with Obstructive Sleep Apnea: Possible Relationship with Counteracting Oxidative Stress*

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Summary: This work is aimed at exploring the clinical efficacy of continuous positive airway pressure (CPAP) in treatment of patients with arrhythmias combined with obstructive sleep apnea (OSA). Through evaluating serum native thiol, malonaldehyde (MDA) and nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) in these patients and describing the effects on oxidative parameters of CPAP therapy for 3 months, we confirmed the impact of oxidative stress on arrhythmias. A total of 64 patients with OSA combined with arrhythmias were collected from April 2014 to April 2017 with full clinical information. Patients were divided into two groups (paired experiment design): 32 patients in group A (control group), who received unchanged anti-arrhythmia treatment and 32 patients in group B, who were subjected to unchanged pharmacological anti-arrhythmia therapy combined with CPAP. OSA related parameters were compared between the two groups after 3-month therapy. And the levels of parameters of oxidative stress in patients were measured before and after CPAP therapy. After 3 months of CPAP therapy, compared with the control group, the percentage of sage N3 (NREM 3) and stage R (REM) in total sleep time was significantly increased, while apnea-hypopnea index (AHI) and the Epworth Sleepiness Scale (ESS) score were evidently decreased. Meanwhile, the lowest oxygen saturation ($LSpO_2$) was also elevated after CPAP treatment for 3 months. The CPAP therapy significantly prevented the occurrence of arrhythmias ($P<0.05$). Both the MDA level and NADPH oxidase levels were significantly lower in the group B than in the group A ($P<0.05$). But serum native thiol was improved by CPAP treatment ($P<0.05$). In conclusion, proper use of CPAP therapy provides significant benefits for the treatment of arrhythmia in patients with OSA.

Key words: obstructive sleep apnea; arrhythmias; oxidative stress; polysomnography; continuous positive airway pressure

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder and is characterized by recurrent cycles of hypoxemia, arousals and sleep fragmentation, which are caused by complete or partial obstructions of the upper airway. This disease has a prevalence of approximately 2%–6% of the overall middle-aged population, corresponding to 4% of middle-aged men and 2% of middle-aged women, which increases with age and obesity[1, 2]. OSA has been shown to be significantly related to several cardiovascular conditions including coronary artery disease, hypertension, and congestive heart failure, as well as with arrhythmias[2–5], especially nocturnal

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arrhythmias. Intermittent hypoxia and episodes of hypoxia/reoxygenation may induce intermediate mechanisms such as systemic inflammation, oxidative stress and activation of the sympathetic nervous system, responsible for cardiovascular conditions. Oxidative stress, defined as an excess of pro-oxidant species, which could not be counterbalanced by adequate endogenous and exogenous antioxidant defenses, represents a risk factor for cardiovascular conditions. Previous studies have shown that oxidative stress levels are elevated in OSA patients compared to healthy subjects by assessing levels of biomarkers, including proteins, modified lipids, and nucleic acids and, in this process, large amounts of reactive oxygen species (ROS) are released in the body[6–9]. Oxidative stress can be demonstrated by biomarkers. Thiols, commonly known as mercaptans, are important antioxidants; the sulfhydryl group (–SH) protects against oxidative stress. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is a peroxidase that plays a key role in the production of ROS. Malonaldehyde (MDA) is lipid peroxide, which is formed by the polyunsaturated fatty acids in the biofilm that initiate lipid peroxidation after being attacked by oxygen free radicals. The level of MDA directly reflects the degree of lipid peroxidation in the body.

Continuous positive airway pressure (CPAP) is effective for the improvement of the symptoms of sleep apnea[10–12] and is recognized as one of the therapeutic methods for OSA-associated congestive heart failure and hypertension among affected patients. In addition, some early reports have noted that CPAP is an effective strategy for prevention of the occurrence of arrhythmias in OSA patients. However, the therapeutic role of CPAP in the management of arrhythmia, which co-exists with OSA, has not attracted enough attention in clinical work as yet. Besides, biomarkers of oxidative stress have been intensively studied in recent years, but the real effects of CPAP on biomarkers have yielded controversial results mainly owing to different study designs and the presence of major confounders. To date, however, the relationship between oxidative stress and arrhythmias combined with OSA has been studied only sparingly. Therefore, the present study was designed to assess the effect of CPAP in order to offer an auxiliary therapy of pharmacological treatment on patients with OSA combined with arrhythmias.

1 MATERIALS AND METHODS

1.1 Study Design and Participants

All the patients were from the Sleep Medicine Center of the Provincial Hospital affiliated to Shandong University (China). We have introduced this trial to all enrolled patients and obtained written consent of the patients. All experimental operations and contents were reviewed by the ethics committee of the Provincial Hospital affiliated to Shandong University. This trial has obtained the consent of ethical approval and strictly complies with the Helsinki declaration. The inclusion criteria in the study were: (1) high pre-test suspicion of OSA: the features including apneas reported by mouth breathing, snoring, daytime sleepiness, obesity and so on; (2) at least one of the cardiac arrhythmias, including premature atrial complex, premature junctional complex, premature ventricular complex, sinus tachycardia, atrial tachycardia, ventricular tachycardia, atrial fibrillation, paroxysmal atrial fibrillation, bradycardia, sinus pause, second- or third-degree atrioventricular block.

Exclusion criteria were: (1) patients without signing the informed consent; (2) patients on nocturnal oxygen supplementation; (3) unstable cardiopulmonary, neurological, or psychiatric disease, hemodynamically unstable patient; (4) upper airway surgery; (5) using positive airway pressure therapy or oral appliances; (6) patients with a prescription for lipid-lowering drug, antioxidant, or psychotropic agent; (7) patients with craniofacial malformations; (8) patients with coronary heart disease; patients with valvular heart disease, cardiomyopathy and other cardiac morphological abnormalities or pericardial disease, the presence of a cardiac pacemaker or cardiac surgery within the previous 3 months.

The number of patients initially screened was 107. After exclusion and matching design, a total of 64 were enrolled. All the 64 patients with OSA combined with arrhythmias were recruited from April 2014 to April 2017, with full clinical information. Patients referred to these clinics routinely underwent overnight polysomnography (PSG) and dynamic Holter monitoring. These 64 patients were composed of 38 males and 26 females, and the age ranged from 19 to 70 years old, with an average of 53 years old.

The 64 patients were divided into two groups: 32 patients in group A (control group), who received unchanged anti-arrhythmia treatment and 32 patients in group B (test group), who were subjected to unchanged pharmacological anti-arrhythmia therapy combined with CPAP. And each group consisted of 18 patients with severe OSA, 8 patients with moderate OSA and 6 patients with mild OSA. There was no significant difference in the type of arrhythmia and pharmacological treatment between the two groups.

Group description (paired experiment design)[13, 14] was as follows: In order to ensure the homogeneity and comparability of patients in the two groups, patient screening and grouping were performed in advance. The first step was to classify all patients into severe OSA, moderate OSA and mild OSA according to the patient apnea-hypopnea index (AHI) score. The second step is

to further group the patients in each subgroup according to the types of arrhythmia: patients with single type of arrhythmia, patients with two types of arrhythmia, and patients with three or more types of arrhythmia; Third, in all the subgroups, the patients were paired according to their age, gender and medication status, and then the matched patients were randomly assigned to the group A and the group B.

The adherence to CPAP treatment was assessed at intervals of two weeks. Optimal adherence was defined as at least 4 h of CPAP use per night during the entire 12-week period.

Before and after CPAP therapy, we compared the difference of AHI, $LSpO_2$, percent of total sleep time in stage N3 (NREM 3) and stage R (REM), ESS and improvement of dynamic electrocardiogram arrhythmia between the test group and the control group. The levels of native thiols, NADPH oxidase and MDA were measured simultaneously.

1.2 Polysomnography and CPAP therapy

All participants voluntarily agreed to participate in this study and all gave written informed consent before PSG. A detailed history of complaints including snoring, witnessed apneas, mouth breathing, nocturia, disturbed nocturnal sleep, and morning headaches was collected. Daytime sleepiness was assessed by Epworth Sleepiness Scale (ESS). Details of all patients including height, weight, neck circumference, chest circumference, abdominal circumference were recorded. PSG recordings were started based on the usual domestic sleeping habits, and each patient was recorded for a minimum of 7 h[1, 15]. And the tests were scored by PSG technologists of our sleep center laboratory. We used the Kangdi E-Series Acquisition System to measure multiple physiological signals during sleep. The information we recorded included: electroencephalography, electrooculography, electro−cardiography, electromyography, airflow by a nasal pressure transducer, orinasal thermocouples, respiratory effort (thoracic and abdominal impedance), pulse oximetry, snoring (tracheal microphone), and sleep position.

All patients on the day of sleep monitoring were followed by dynamic electrocardiogram examinations. All the data were scored according to established criteria favored by the American Academy of Sleep Medicine (AASM). Obstructive apnea was defined as complete cessation (obstructive if respiratory efforts were present and central if respiratory efforts were absent) of nasal/oral airflow for at least 10 s, and the definition of hypopnea was an event of at least 10-s duration during which airflow was reduced by at least 30% from baseline with oxygen desaturation of at least 3% or arousal. The AHI was defined as the total number of apnea and hypopnea events per hour of sleep, and was commonly used as a diagnostic threshold for classifying the presence and severity of sleep apnea. Severity degree of OSA was defined according to commonly used clinical cutoffs, no OSA (AHI <5), mild OSA (AHI ≥5 but <15), moderate OSA (AHI ≥15 but <30), and severe OSA (AHI ≥30).

CPAP therapy was recommended for all patients with an AHI ≥30 and for patients with an AHI of 5.0 to 29.9 events per hour and coexisting daytime sleepiness that interferes with daily activities[15, 16]. CPAP treatment was prescribed on the basis of guidelines and it was titrated with either full standard PSG or an autotitrating CPAP device. A mean daily use of more than 4 hours per day was required to maintain CPAP prescription. After 12 weeks of treatment, polysomnography of patients in the two groups was reviewed under CPAP treatment and dynamic Holter monitoring. All data underwent computer playback, manual analysis and correction.

1.3 Blood Collection and Parameter Measurements

Venous blood samples from patients with OSA combined with arrhythmias were collected in the morning between 7 a.m. and 8 a.m. before CPAP therapy after a 12-h overnight fast. Further samples were obtained (from these patients) after 3 months of CPAP therapy. By means of peripheral venous blood analysis, the levels of native thiols, NADPH oxidase and MDA were determined in the biochemistry laboratory.

1.4 Statistical Analyses

Standard methods of statistical analyses were used for data analysis. All values were expressed as mean±standard deviation. Student's *t*-test and Chi-square tests were used for statistical analysis using SPSS 17.0. $P<0.05$ indicated the statistical significance.

2 RESULTS

2.1 Subject Characteristics

In the 64 patients with OSA combined with arrhythmias, the main presenting symptoms were snoring in 63 (98.4%), witnessed apneas in 34 (53.1%), mouth breathing in 63 (98.4%), nocturia in 49 (76.6%), disturbed nocturnal sleep in 47 (73.4%), morning headaches in 21 (32.8%) and daytime sleepiness in 56 (87.5%) with a mean ESS of 17.3. In those 64 patients, based on AHI score, 12 (18.75%) patients had mild, 16 (25.0%) had moderate, and 36 (56.25%) had severe OSA, respectively.

Table 1 Baseline characteristics of the study population

Groups	Age (years)	BMI (kg/m^2)	AHI	$LSpO_2$ (%)
A	51.57±10.05	29.65±4.04	41.92±22.94	71.47±12.08
B	51.59±9.51	29.67±4.08	42.05±22.70	71.56±12.27

AHI: apnea-hypopnea index; BMI: body mass index; $LSpO_2$: lowest oxygen saturation

The characteristics of the 64 patients at enrollment regarding, in terms of age, BMI, AHI, lowest oxygen saturation ($LSpO_2$), were presented in table 1. There were no significant differences in these indexes between the two groups (P>0.05).

The cardiac arrhythmia diagnosed in this cohort (fig. 1) was represented by bradycardia (49, 76.6%), followed by sinus tachycardia (45, 70.3%), atrial tachycardia (29, 45.3%), atrial fibrillation (29, 45.3%), premature atrial complex (26, 40.6%), premature ventricular complex (26, 40.6%), second- to third-degree atrioventricular block (19, 29.7%), ventricular tachycardia (17, 26.6%), sinus pause (16, 25.0%), paroxysmal atrial fibrillation (14, 21.9%) and premature junctional complex (12, 18.8%).

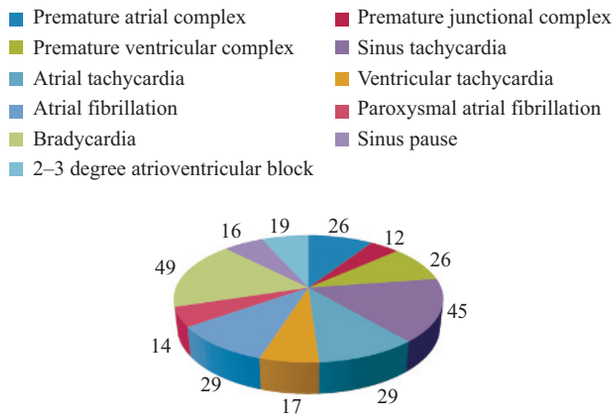

Fig. 1 Type of cardiac arrhythmias in patients included in the study

2.2 Effects of CPAP

After 3 months of CPAP therapy, as shown in table 2, compared with the control group, AHI and ESS score were significantly decreased, percent of total sleep time in stage N3 (NREM 3) and stage R (REM) was significantly increased, meanwhile, the lowest blood oxygen saturation was notably elevated. There were significant differences in these parameters between the two groups (P<0.05).

Table 3 showed that all types of arrhythmia are significantly reduced after CPAP treatment compared with drug treatment alone in patients with OSA (P<0.05). However, CPAP therapy was less effective for atrial fibrillation and paroxysmal atrial fibrillation than other types of arrhythmia, although the results were also statistically significant.

2.3 Alterations in Biomarkers of Oxidative Stress

Table 4 shows before CPAP treatment, there were no statistically significant differences in the oxidative parameters between the two groups (P>0.05). CPAP therapy for 3 months significantly attenuated the oxidative stress. The serum native thiol was improved by CPAP treatment (P<0.05). The MDA and NADPH oxidase levels were significantly lower in the CPAP-treatment group than in the control group (P<0.05).

Table 2 Comparison of ESS score and polysomnographic outcomes before and after treatment between the two groups

Parameters	Group A		Group B	
	Before therapy	After therapy	Before therapy	After therapy
AHI	41.92±22.94	41.99±23.04	42.05±22.70	3.19±1.73$^{*\#}$
$LSpO_2$ (%)	71.47±12.08	71.50±12.03	71.56±12.28	94.00±2.75$^{*\#}$
Stage N3 (%)	7.65±5.94	7.68±5.98	7.71±6.07	18.68±6.00$^{*\#}$
Stage R (%)	12.12±6.27	12.35±5.99	12.00±6.13	21.54±5.00$^{*\#}$
ESS	17.06±5.66	16.91±5.59	17.06±5.66	2.50±2.34$^{*\#}$

AHI: apnea-hypopnea index; $LSpO_2$: lowest oxygen saturation; Stage N3: stage NREM 3; Stage R: stage REM; ESS: Epworth sleepiness scale, $^{*}P$<0.05 *vs.* group A after therapy; $^{\#}P$<0.05 *vs.* group B before therapy

Table 3 Comparison of arrhythmia data before and after treatment between the two groups

Arrhythmias	Group A		Group B	
	Before therapy	After therapy	Before therapy	After therapy
Premature atrial complex	13	8	13	1
Premature junctional complex	5	4	7	1
Premature ventricular complex	12	10	14	3
Sinus tachycardia	22	14	23	5
Atrial tachycardia	15	10	14	2
Ventricular tachycardia	9	6	8	2
Atrial fibrillation	15	13	14	7
Paroxysmal atrial fibrillation	7	6	7	3
Bradycardia	24	14	25	3
Sinus pause	8	5	8	2
Second- to third-degree atrioventricular block	10	8	9	4
Total	140	98	142	33$^{*\#}$

$^{*}P$<0.05 *vs.* group A after therapy; $^{\#}P$<0.05 *vs.* group B before therapy

Table 4 Comparison of biomarkers of oxidative stress before and after treatment between the two groups

Biomarkers	Group A		Group B	
	Before therapy	After therapy	Before therapy	After therapy
Native thiol (μmol/L)	262.54±37.32	262.51±37.24	262.53±37.33*	319.35±43.57#&
NADPH oxidase (U/mL)	4.91±0.25	4.86±0.26	4.94±0.26*	3.22±0.16#&
MDA (nmol/mL)	13.48±0.82	13.41±0.79	13.49±0.81*	8.39±0.78#&

NADPH: oxidase nicotinamide adenine dinucleotide phosphate; MDA: malonaldehyde
*P>0.05 *vs.* group A before therapy; #P<0.01 *vs.* group A after therapy; &P<0.01 *vs.* group B before therapy

3 DISCUSSION

In the present study, we found that the association between arrhythmias and oxidative stress may be highly relevant in patients with OSA. And CPAP therapy significantly attenuated oxidative stress and reduced the incidence of arrhythmia in patients with OSA combined with arrhythmia. Furthermore, we confirmed that CPAP could change the levels of biomarkers of oxidative stress. Those findings indicate that CPAP treatment is able to lower the occurrence of arrhythmias. This effect may be achieved by reducing oxidative stress. Little information by far is available regarding arrhythmia in Asian patients with OSA. This study supports the conclusion that CPAP can effectively eliminate respiratory disturbance indexes, improve the symptoms of hyoxemia at night, and be effective for arrhythmias combined with OSA. The effects of CPAP on biomarkers of oxidative stress are complicated and previous results are inconclusive or even conflicting. Many early epidemiologic studies have demonstrated that OSA patients have a higher incidence of arrhythmia than non-OSA patients. Approximately, 58% of OSA patients have various types of arrhythmias, including almost all kinds of arrhythmias. Up to 48% of OSA patients suffered from arrhythmias, and arrhythmias have been considered as one of the factors contributing to their increased mortality[3, 4, 17–19]. Mehra *et al* demonstrated the association between OSA and a number of arrhythmias such as sinus tachycardia, bradycardia, atrial fibrillation, premature ventricular complex, and ventricular tachycardia[20]. However, other studies could not prove this association for some of these arrhythmias. Therefore, the relationship between OSA and certain types of arrhythmias remains controversial. In this work, we clearly demonstrated a high incidence of bradycardia, sinus tachycardia, atrial tachycardia and premature ventricular complex in OSA patients. However, it was also found that the effect of CPAP on atrial fibrillation and paroxysmal atrial fibrillation was not as significant as it on other types of arrhythmia, although the results of this study were statistically significant. This may be related to the special mechanism of atrial fibrillation.

With regards to the mechanisms likely involved in the development of arrhythmias in patients with OSA, previous studies hypothesized that various pathways triggered by hypoxia might have played a key role[21–23]. These disturbances, including sleep fragmentation, and chronic intermittent hypoxia caused by OSA, lead to a cascade of events related to the activation of systemic inflammation, oxidative stress and increase of catecholamine levels, all of which can influence the autonomic tension therefore result in an arrhythmias[22–25]. Hypoxemia and the cessation of respiration are essential in the development of arrhythmias[26]. Oxidative stress triggered by a combination of apnea and hypoxemia plays a key role. Intermittent hypoxia and hypoxia/reoxygenation may trigger ischemia-reperfusion injury. During hypoxemia, the antioxidant substances are down-regulated so that oxygen levels rise again, and more reactive oxygen species (ROS) or free radicals are produced[6, 27–29]. Therefore, we postulate that oxidative stress may contribute to the occurrence of bradycardia, sinus tachycardia, atrial tachycardia, atrial fibrillation and other arrhythmias. Oxidative stress has in recent years been studied extensively in OSA patients. However, the findings are controversial. The effect of CPAP on oxidative stress biomarkers is still unclear, and the majority of studies showed a significant reduction in oxidative stress and an increase in antioxidant capacity[30]. In our study, it is observed that antioxidant parameters of the oxidative stress including the native thiol were improved by CPAP treatment, but the MDA level and NADPH oxidase level were significantly lowered. Therefore, we believed that CPAP treatment decreased the occurrence of arrhythmias, possibly by attenuating oxidative stress. Further investigations are required to elucidate the mechanisms by which CPAP treats patients with arrhythmia combined with OSA.

CPAP has been accepted as the golden standard therapy for patients with OSA and its role is to expand the upper airway and maintain the upper airway open by acting as a pneumatic splint[18, 21, 23, 31]. In our research, PSG and dynamic Holter monitoring were employed simultaneously, which can record arrhythmias occurring in various respiratory events. The method can guarantee the accuracy and reliability of the study. Results of this research showed interruption of this chain of events induced by the episodes of apnea

and hypopnea can reduce the incidence of nocturnal arrhythmias. In our study, CPAP was shown to eliminate respiratory disturbances, improve the ESS score, AHI, stage N3 and stage R sleep time compared with control group, and the lowest oxygen saturation was elevated. The data obtained from our study indicated the therapeutic efficacy of CPAP in OSA-associated arrhythmias is definite. This effect seems likely as a result of an oxidative stress improvement in the body.

The influence of OSA on cardiovascular system can occur from the first apnea of OSA. However, most clinicians do not suspect this important comorbidity of arrhythmia in the beginning, resulting in delayed diagnosis of OSA. In clinical work, it is important to evaluate the presence of OSA in patients with clinical suspicion (obesity, daytime sleepiness and witnessed apneas) and associated arrhythmias, especially for these patients with intractable arrhythmia, nocturnal arrhythmias or the arrhythmia without a history of organic heart disease.

In conclusion, the findings from this work indicate CPAP therapy is effective in treating the patients with OSA combined with arrhythmias and, possibly, via counteracting the oxidative stress. In this regard, the proper use of CPAP therapy might offer an additional benefit to the patients with OSA combined with arrhythmias, though the precise mechanism by which CPAP exerts its efficacy is still not entirely clear.

Conflict of Interest Statement

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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