Original Article

Comparison of the Efficacy of Continuous Positive Airway Pressure and Oxygen Therapy in Increasing Heart Rate Variability in Patients With Obstructive Sleep Apnea

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ABSTRACT

***Background*:** The risk of cardiovascular diseases is known to be increased in obstructive sleep apnea (OSA), the mechanism of which can be explained by the observation that the sympathetic tone increases during sleep due to repetitive apnea accompanied by hypoxia and arousal. Heart rate variability (HRV) represents the cardiac autonomic function and is mediated by respiratory sinus arrhythmia, baroreflex-related fluctuation, and thermoregulation-related fluctuation. The aim of the present study was to determine whether treatment by continuous positive airway pressure (CPAP) or O_2 could produce significant changes in HRV, especially in the time domain of HRV (SDNNs and RMSSDs), in patients with OSA.

***Method*:** Fifty-seven patients with OSA were participated in the current single-center randomized parallel-group clinical trial study. The patients were randomly divided into 2 groups: the CPAP group and the O_2 therapy group. Before treatment, the apnea-hypopnea index (AHI) was measured by polysomnography in each patient. HRV was assessed via 24-hour Holter monitoring, before and after 2 weeks of CPAP titration or O_2 therapy, and subsequently compared between the 2 groups. The Wilcoxon test and the T-test were used for the statistical analyses.

***Results*:** Our results demonstrated a reduction in the nocturnal SDNNs ($P < 0.001$) and RMSSDs ($P = 0.001$) and an elevation in the diurnal RMSSDs significantly ($P = 0.04$) following CPAP. In addition, O_2 therapy reduced the diurnal SDNNs significantly ($P = 0.01$) and elevated the nocturnal RMSSDs ($P < 0.001$).

Conclusions*:** Our findings demonstrated that CPAP was an effective treatment in comparison with O_2 therapy in improving HRV in our patients with OSA. Furthermore, correction of hypoxia by using nocturnal O_2 therapy was not sufficient to improve HRV indices. ***(Iranian Heart Journal 2017; 18(4):34-41)

KEYWORDS: Obstructive sleep apnea, Heart rate variability, SDNNs, RMSSDs, CPAP, Oxygen therapy

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Sleep is associated with a reduction in the level of consciousness, relatively suspended sensory perception, and inactivation of nearly all voluntary muscles at rest—thereby subjecting the activities of the body and mind to change. [1, 2] Insufficient sleep not only disrupts the body's natural rhythm but also diminishes the brain's ability. Studies have shown that more than 8 hours of sleep increases the risk of heart attack by 50%. [3] Many chronic diseases such as obstructive sleep apnea (OSA) are associated with increased sleep durations. [4]

OSA is a serious potentially life-threatening condition characterized by the repeated cessation of breathing while sleeping and is mostly in consequence of complete or partial pharyngeal obstruction. [5] OSA is recognized by a combination of symptoms such as repetitive apneas and hypopneas, which are accompanied by hypoxia, sleep arousal, and hemodynamic changes. [6] Moreover, the activation of the sympathetic nervous system during respiratory events potentiates vasoconstriction and increases blood pressure and heart rate. [2, 7] OSA is also allied to several cardiorespiratory problems such as loud snoring, load gasps, and daytime breathlessness. [8]

Overnight polysomnography (PSG) is the standard diagnostic test for OSA; it involves simultaneous recordings of multiple physiological signals during sleep. These recordings allow the identification and classification of sleep-related apneas and hypopneas. Apnea is defined as a complete cessation of the air flow for at least 10 seconds and hypopnea is defined as a clear decrease (>50%) in the amplitude of the oronasal flow for a minimum of 10 seconds. Sleep apnea severity is typically assessed with the apnea-hypopnea index (AHI), which is the number of apneas and hypopneas per hours of sleep. An AHI between 5 and 15 episodes per hour denotes a mild form of sleep apnea disorder, between 16 and 30 a moderate form, and more than 30 a severe form. [9]

The prevalence of OSA is approximately between 3% and 7% in men and between 2% and 5% in women. Obesity (the most important risk factor for OSA), gender (men twice more than women are affected), age (aging increases the risk of developing this disorder), race (at a certain body mass index, African Americans and Asians are at a higher risk), genetic predisposition and family susceptibility (risk of OSA increases in each person by an increase in the number of relatives affected), nasal obstruction, smoking, alcohol consumption, acromegaly, [10] hypothyroidism, polycystic ovary syndrome, use of benzodiazepines, and use of exogenous testosterone are the risk factors for sleep apnea disorders. [7]

Heart rate variability (HRV) analysis has been widely used for the noninvasive assessment of the cardiac autonomic function. Abnormal HRV is associated with increased mortality or adverse cardiac events; HRV analysis can, therefore, be a way of predicting sudden arrhythmic death, myocardial infarction, angina pectoris, stroke mortality, and even rapid prognosis of atherosclerosis in animals. [11] Changes in HRV parameters have also been reported in OSA syndrome patients, and that is why HRV analysis has been proposed as a screening tool for OSA syndrome. [12, 13]

We examined nocturnal HRV in patients with OSA to demonstrate whether treatment with continuous positive airway pressure (CPAP) or O_2 could effect significant changes in HRV, particularly in the time domain of HRV (standard deviation of normal-to-normal intervals [SDNNs] and root mean square of successive heartbeat interval differences [RMSSDs]), with a view to identifying and implementing appropriate treatment modalities for reducing cardiovascular complications in this group of patients.

METHOD

Subjects

The current single-center randomized parallel-group clinical trial recruited 57 patients with OSA from the Sleep Research Center of Baharloo Hospital in the Iranian capital, Tehran. The patients were divided into 2 groups: the CPAP group (n = 29) and the O_2 therapy group (n = 28). The mean age was 49.89 ± 12.76 years in the CPAP group and 46.11 ± 9.65 years in the O_2 therapy group. Before the commencement of the study, all the patients filled a questionnaire to determine clinical relevant data—including current medications, current medical problems, tobacco use, alcohol consumption, recreational drug use, height, and weight. The inclusion criteria comprised an ejection fraction more than 50 and absence of heart valve regurgitation. The patients who had a diagnosis of cardiovascular diseases and a history of surgery, CPAP, or O_2 therapy were excluded. To our knowledge, the existing literature lacks studies on the comparison of these 2 methods.

Nocturnal PSG

PSG is the method for monitoring and recording physiological parameters during sleep. This method specifies the relationship between the various stages of sleep by variations in parameters such as changes in heart rhythm, hypoxia, muscular attempts, and muscle fatigue due to hard work or snoring. The AHI and the respiratory distress time index are evaluated by this method. One of the parameters analyzed by PSG is the AHI, which is calculated by dividing the total sleep time by the total number of apneas (the complete cessation of breathing for at least 10 seconds) and hypopneas (reduced air flow for at least 10 seconds with blood desaturation or arousal). The AHI is drawn upon for the classification of the severity of OSA. Individuals with moderate OSA have an AHI greater than 15 but less than 30 and those with severe OSA have an AHI equal to or greater than 30. [23, 24]

PSG Under CPAP or O_2

Patients with OSA (N = 57) were randomly divided into 2 different groups: CPAP and O_2 therapy. The auto-adjusting CPAP system is a computer-based device that performs automatic pressure titration. It automatically increases or decreases the mask pressure in response to snoring, specific changes in the inspiratory airflow contour morphology, or the presence of apnea or hypopnea—thus acting to restore airway patency completely. In the process, a technician supervises and corrects the initial position and fitting of the mask. An initial CPAP of 4 to 20 cm H_2O is administered to the patient, and the titration of the pressure is controlled automatically while the patient is asleep. In the current study, 28 patients with OSA received O_2 therapy. In O_2 therapy, the amount of O_2 given to the patient is above its level in the atmosphere so as to prevent hypoxia. Oxygen is a drug and it should be used cautiously. In the present study, for a 2 week-period, nocturnal nasal O_2 was given to the patients with OSA for at least 6 hours at night and the O_2 flow was maintained between 3 and 4 liters per minute.

Analysis of HRV

Whole-night PSG electrocardiograms were recorded whether the patient was awake or asleep. Only ambulatory electrocardiograms of high quality (ie, free of extrasystoles [< 1%] and free of artifacts) were retained for the analysis. The HRV data were available from the Holter analysis software and were exported as text files for the analysis. Time domain analysis was applied at hours between 06:00 and 22:00 in the wakeful condition and at hours between 22:00 and 06:00 in the sleep condition. The reading of the Holter data was done in a blinded manner; in other words, the reader had no knowledge of the PSG data.

Time Domain Measures of HRV

The time domain measures of HRV were derived from normal-to-normal intervals (NNs), which were recorded directly between adjacent QRS complexes resulting from sinus node depolarization. [18, 19,20] The mean NN (ms), SDNNs (ms), SDNN index, percentage of the NNs that were different from the previous NNs by more than 50 ms (%), and RMSSDs (ms) [21] were computed. In the present study, after 2 weeks of treatment with CPAP or O_2, HRV was measured with Holter monitoring in the patients with OSA who had completed the treatment course. The time domain indices of HRV were compared between the 2 study groups. In the present study, among all HRV indicators, only SDNNs and RMSSDs were evaluated.

Statistical Analysis

All the statistical tests were performed using SPSS, version 16. The χ^2 test was used for the evaluation of the qualitative data and the T-test for the quantitative data with normal distributions. The quantitative data that had non-normal distributions but were relevant were assessed using the Wilcoxon statistical test. In all the cases, statistical significance was defined as a *P* value equal to or less than 0.05.

RESULTS

The study population was comprised of 57 patients with OSA, whose HRV were analyzed. Table 1 depicts the characteristics of the patients with OSA, who were randomly divided in 2 different groups based on the treatment with CPAP or O_2. The CPAP group comprised 29 participants at a mean age of 49.89 ± 12.76 years and a body mass index of 32.04 ± 4.39 kg/m^2, and the O_2 therapy group was composed of 28 patients at a mean age of 46.11 ± 9.65 years and a body mass index of 29.27 ± 3.53 kg/m^2. Comparisons between the 2 groups revealed no statistically significant differences in age and the body mass index (P = 0.22 for age and P = 0.24 for the body mass index). The time domain parameters were evaluated by Holter monitoring. The differences in the HRV time domains (SDNNs and RMSSDs) between the initial diagnostic PSG and the second PSG during CPAP titration and nocturnal nasal O_2 in the patients with OSA are demonstrated in Table 2. The nocturnal SDNNs were significantly decreased during the treatment with CPAP titration or O_2 (P < 0.001) (Table 2). Table 3 and Table 4 summarize a further comparison of the SDNNs and RMSSDs in the patients with OSA before and during nocturnal nasal O_2 and CPAP titration, respectively, at hours between 00:06 and 22:00 and at hours between 22:00 and 00:06. At hours between 00:06 and 22:00, the SDNNs were significantly decreased during O_2 therapy (P = 0.02) and overnight RMSSDs were significantly increased (P < 0.001). In the CPAP group, the SDNN index showed a significant reduction at night (P < 0.001), the diurnal RMSSDs were significantly increased (P = 0.04), and the overnight RMSSDs were significantly decreased (P = 0.001). Table 5 shows a comprehensive comparison of the SDNNs and RMSSDs between the CPAP and O_2 therapy groups.

Table 1. Patient characteristics

Variable	CPAP (n = 29)	O_2 Therapy (n = 28)	*P*
Age	49.89±12.76	46.11±9.65	0.22
BMI (kg/m^2)	32.04±4.39	29.27±3.53	0.24
Gender (male)	19	24	0.71

BMI, Body mass index; CPAP, Continuous positive airway pressure
Data are presented as means ± SDs or numbers.

Table 2. Time domain indices of HRV in the patients with OSA before and after CPAP and O_2 therapy

Variable	± SD	*P*
Diurnal SDNNs before treatment Diurnal SDNNs after treatment	96.46±29.36 94.68±26.89	0.2
Nocturnal SDNNs before treatment Nocturnal SDNNs after treatment	16.26±31.18 101.19±32.38	<0.001*
Diurnal RMSSDs before treatment Diurnal RMSSDs after treatment	39.84±20.74 39.79±22.58	0.9
Nocturnal RMSSDs before treatment Nocturnal RMSSDs after treatment	51.93±36.22 51.00±36.54	0.3

OSA, Obstructive sleep apnea; HRV, Heart rate variability; CPAP, Continuous positive airway pressure; SDNNs, Standard deviations of all RR intervals on electrocardiography; RMSSDs, Root mean square of successive heartbeat interval differences
Data are presented as means ± SDs.

Table 3. Time domain indices of HRV in the patients with OSA before and after O_2 therapy

Variable	± SD	*P*
Diurnal SDNNs before treatment Diurnal SDNNs after treatment	103.39± 32.73 98.96±27.13	0.02*
Nocturnal SDNNs before treatment Nocturnal SDNNs after treatment	114.25±33.48 114.68±33.25	0.7
Diurnal RMSSDs before treatment Diurnal RMSSDs after treatment	37.32±14.2 33.93±11.43	0.01*
Nocturnal RMSSDs before treatment Nocturnal RMSSDs after treatment	49.46±21.57 53.39±23.79	<0.001*

OSA, Obstructive sleep apnea; HRV, Heart rate variability; CPAP, Continuous positive airway pressure; SDNNs, Standard deviation of all RR intervals on electrocardiography; RMSSDs, Root mean square of successive heartbeat interval differences
Data are presented as means ± SDs.

Table 4. Time domain indices of HRV in the patients with OSA before and after CPAP therapy

Variable	± SD	*P*
Diurnal SDNNs before treatment Diurnal SDNNs after treatment	89.76± 24.43 90.55±26.46	0.7
Nocturnal SDNNs before treatment Nocturnal SDNNs after treatment	98.55±27.17 88.17±25.94	<0.001*
Diurnal RMSSDs before treatment Diurnal RMSSDs after treatment	42.28±25.38 45.45±28.75	0.04*
Nocturnal RMSSDs before treatment Nocturnal RMSSDs after treatment	54.31±46.52 48.69± 45.98	0.001*

OSA, Obstructive sleep apnea; HRV, Heart rate variability; CPAP, Continuous positive airway pressure; SDNNs, Standard deviation of all RR intervals on electrocardiography; RMSSDs, Root mean square of successive heartbeat interval differences
Data are presented as means ± SDs.

Table 5. Time domain indices of HRV in the patients with OSA, who received CPAP or O_2 therapy at hours between 00:06 and 22:00 hours and at hours between 22:00 and 06:00 for 2 weeks

Variable	CPAP Therapy	O_2 Therapy	*P*
Diurnal SDNNs	90.55±26.46	98.96±27.18	0.25
Nocturnal SDNNs	88.17±25.94	114.68±33.27	<0.0001*
Diurnal RMSSDs	45.45±28.75	33.93±11.43	0.002*
Nocturnal RMSSDs	48.69±45.98	53.39±23.79	<0.0001*

OSA, Obstructive sleep apnea; HRV, Heart rate variability; CPAP, Continuous positive airway pressure; SDNNs, Standard deviation of all RR intervals on electrocardiography; RMSSDs, Root mean square of successive heartbeat interval differences
Data are presented as means ± SDs.

DISCUSSION

OSA is a common disorder in adults, particularly in those who are overweight or obese. Nocturnal pathophysiological mechanisms such as increased sympathetic activity, decreased O_2 supply in tissues (especially the heart), decreased parasympathetic activity, and reduced intrathoracic pressure are activated in patients with OSA and might lead to cardiovascular diseases. [9] The best treatment for patients with OSA is widely believed to be CPAP. This treatment modality is shown to improve cardiovascular symptoms and reduce blood pressure, inflammatory markers, and insulin resistance. [14] HRV is the physiological phenomenon of variation in the time interval between heart beats. [25] HRV analysis has been widely utilized for the noninvasive assessment of the cardiac autonomic function and has become a predictive tool for angina and myocardial ischemia. [26] The SDNNs, one of the time domain indices of HRV, refer to the standard deviation of all R-R intervals. Roche et al [22] found that the SDNNs are higher in patients with OSA when they are asleep and it has been suggested as an inexpensive tool for the screening of OSA. [22] We found that the SDNNs were reduced by CPAP titration to eliminate respiratory events. [15]

The main hypothesis of the current study is that OSA causes damage to the myocardium, which in the long term can lead to cardiovascular events, arrhythmia, and heart failure. A reduction in the level of premature HRV causes these events. Oxygen therapy or CPAP can resolve the problem of O_2 supply in patients with OSA. Several studies have shown that CPAP therapy not only improves the quality of sleep by reducing apnea episodes during the night but also decreases the risk of cardiovascular diseases associated with this disorder. In the present study, we aimed to compare HRV time domain indices such as the SDNNs and RMSSDs between 2 groups of patients with OSA who were treated with either CPAP or O_2 therapy. We found that in the treatment with CPAP titration, the SDNNs were significantly decreased during the night ($P < 0.001$), the diurnal RMSSDs were significantly increased, and the nocturnal RMSSDs were decreased ($P = 0.001$). We also observed a significant reduction in the diurnal SDNNs ($P = 0.02$) and a significant elevation in the nocturnal RMSSDs ($P < 0.001$) in the group treated with O_2.

Our statistical comparisons of the 2 methods (Table 4 and Table 5) demonstrated that during the night, there was a significant difference with respect to the RMSSDs and SDNNs between the 2 study groups. To our knowledge,

the existing literature is devoid of research into comparisons of efficacy between CPAP and nocturnal nasal O_2 in improving HRV indices among patients with OSA. Our findings demonstrated that overnight CPAP was a more effective treatment than O_2 therapy in the reduction of the time domain indices of HRV such as the SDNNs and RMSSDs in our patients with OSA. Kufoy et al [17] reported that HRV (SDNNs) was decreased after the use of CPAP during the first night of treatment. Elsewhere, Gharabaghi et al [16] examined 36 patients with OSA in whom apnea had been confirmed via PSG. The authors divided their study population into 2 groups: patients with severe OSA (AHI $\geq$ 30) and patients with non-severe OSA (AHI = 5–29). They found that only the SDNNs (P = 0.026) and the O_2 desaturation index (P = 0.001) had significant differences between the 2 groups. Moreover, the AHI had the highest correlation with the HRV-triangular index (P = 0.022, r = 0.371) among the HRV indices and with the O_2 desaturation index (P = 0.001, r = 0.63) among all the parameters. Gharabaghi and colleagues also reported that HRV indices were not statistically significantly different between their 2 study groups and only the O_2 desaturation index differed significantly. Gala at al [27] recommended HRV as a screening tool for OSA and reported that the average indices of the SDNNs and RMSSDs were increased in patients with severe-to-mild OSA.

In light of our results, we can conclude that the correction of hypoxia by nasal O_2 is not sufficient to improve HRV, and CPAP is the treatment of choice in this group of patients.

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