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Sleep Science

Changes in heart rate variability (HRV) in patients with severe and moderate obstructive sleep apnea before and after acute CPAP therapy during nocturnal polysomnography

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ABSTRACT

Introduction: Obstructive sleep apnea is an important risk factor for cardiovascular disease. Noninvasive positive pressure ventilation is the standard treatment of this disease, and it can reduce mortality in patients. Dysfunction of the autonomic system is one of the reasons for an increased risk of cardiovascular disease in these patients. The purpose of the present study was to investigate the effect of positive airway pressure (PAP) therapy on heart rate variability (HRV) indices. **Methods:** The study population was comprised of 55 patients, who underwent nocturnal polysomnography for the diagnosis of obstructive sleep apnea and PAP titration on the same night. The levels of continuous positive airway pressure (CPAP) and bilevel positive airway pressure were adjusted to relieve obstructive sleep apnea, hypopnea, and desaturation. The patients' heart changes and cardiac characteristics were recorded before and after the start of routine CPAP therapy. Finally, the cases' sleep and polysomnography tests were analyzed and interpreted in collaboration with a sleep specialist and their cardiac changes with the aid of a cardiologist before and after treatment with CPAP. **Results:** The participants were 55 patients at a mean age of 57.04±12.9 years. There were 34 (61.8%) male and 21 (38.2%) female cases. PAP therapy on the same night resulted in a decreased standard deviation of the N-N interval index (p=0.036) and a low-frequency index (p=0.021), as well as increased high-frequency index (p<0.001) and low frequency / high frequency ratios (p=0.008). **Conclusion:** Our findings indicate a relative improvement in the activity of the autonomic system in patients with obstructive sleep apnea after 1 night of PAP therapy. Overwhelming evidence suggests that improvement in the sympathetic balance can reduce the risk of cardiovascular disease in patients.

Keywords: Obstructive Sleep Apnea; Heart Rate; Positive-Pressure; Ventilation.

INTRODUCTION

Obstructive sleep apnea (OSA) is an obstructive event in the upper airways due to the complete or partial collapse of the upper airway during sleep, with a reduction in the airflow and repetitive episodes of shallow or paused breathing during sleep, and leading to frequent awakenings, loud snoring, disrupted sleep, and daytime sleepiness[1].

Polysomnography determines the relationship between changes in parameters such as heart rhythm, hypoxia, muscular effort, muscle fatigue, snoring, and the number of awakenings and different sleep stages through the simultaneous monitoring and recording of physiological parameters during *nighttime sleep*. OSA is defined by the presence of at least 5 apneas (respiratory arrest for 10 sec with relative hypoxemia or frequent waking with respiratory effort) or hypopnea during 1 hour of *sleep per* night (a 50% reduction in the respiratory flow along with respiratory effort) in patients with OSA symptoms[2].

The respiratory collapse in the obstructed airway causes a massive negative pressure fluctuation *within the chest*, initially increasing cardiac preload and afterload and, subsequently, leading to deformation and decreased cardiac function. Hypoxemia and imbalance between the sympathetic and parasympathetic nervous systems also cause *electrical cardiac abnormalities* and *myocyte injury*[3-5]. In patients with OSA, both sympathetic and parasympathetic systems cause *unstable heart rates*, resulting in increased parasympathetic activity during apnea, followed by increased sympathetic activity[6].

One of the easiest noninvasive methods for cardiovascular monitoring is to measure heart rate variability (HRV), which is defined as the variation in the time interval between heartbeats. HRV analysis is an appropriate method for determining the activity of the autonomic *system*, and it has a strong association with cardiovascular complications[6].

Continuous positive airway pressure (CPAP) is a common *therapeutic modality* for OSA that reduces the apnea-hypopnea index (AHI), HRV, and cardiovascular complications in patients.

MATERIAL AND METHODS

This *before-after study* was designed to investigate the effect of routine CPAP therapy for 1 *night* on HRV *indices* in patients suffering from moderate or severe OSA. The intervention in this study was part of the treatment process carried out by physicians according to available indications.

Between September 2016 and September 2017, the medical records of all patients with OSA who referred to the Sleep Laboratory of Imam Khomeini Hospital in Tehran for polysomnography during a sleep disorder were examined and OSA diagnosis was established. Following primary assessments on 350 patients, 55 cases fulfilled the inclusion criteria and were, therefore, considered eligible for enrollment in this study. Patients were excluded if they had the following *underlying diseases* affecting HRV: (I) any cardiac arrhythmia; (II) myocardial ischemia, cardiomyopathy, or myocardial infarction; (III) recent major surgery; (IV) other sleep disorders such as periodic limb movement disorder, restless limb syndrome, and narcolepsy; (V) any metabolic diseases such as diabetes mellitus and thyroid dysfunction; and (VI) treatment with antiarrhythmic, anticholinergic, or antidepressant medications.

For patients with an AHI > 15/h, the CPAP routine was set at 2 hours after sleep and started with 4 cm of water pressure. If 3 apneas or 5 *hypopneas* within 5 minutes were seen, CPAP was gradually increased to help apnea therapy or reach an AHI < 5/h. The pressure was raised to a maximum of 16 cm of water; and if apneas or *hypopneas were* not resolved, bilevel positive airway pressure was routinely performed. Additionally, the patients' cardiac changes and characteristics (HRV, rhythm, rate, arrhythmias, and QRS intervals) were recorded before and after routine therapy with CPAP. Finally, the cases' sleep and polysomnography tests were analyzed and interpreted in collaboration with a sleep specialist and their cardiac changes with the aid of a cardiologist before and after treatment with CPAP. As has been previously indicated, the percentage of HRV in patients with OSA is approximately 10%.

Data analysis

The questions and hypotheses of the current study were examined via descriptive and inferential statistics. The quantitative variables and qualitative variables were described using the mean (SD) and numbers (%), respectively. In addition, comparisons between HRV indices before and after the study were performed using the paired *t*-test. *A generalized* estimating equation (GEE) was used for multivariate data analysis after the effects of the variables of gender, age, and the body mass index (BMI) were eliminated. This model is commonly considered to analyze longitudinal/clustered data.

A p value < 0.05 was *considered statistically significant*. The statistical analyses were performed using *SPSS* Statistics, version *22*.0, and STATA *Statistical* Software, version 12.

RESULTS

A total of 55 patients at an average age of 57.04±12.9 years were included in this study. Of these, 34 (61.8%) were male and 21 (38.2%) were female. The mean (SD) of the BMI was 33.03±5.98, and the mean (SD) of the *AHI* was 61.58±32.69.

The mean (SD) of R-R intervals in the patients before PAP treatment was 874.59 (118.3), while it increased to 911.94 (114.5) after PAP treatment; this difference was statistically significant (p<0.001). After the elimination of the effects of age, sex, and the BMI in the GEE model, the changes in R-R intervals before and after the intervention were statistically significant (p<0.001). The effects of none of the variables of age, sex, and the BMI were significant (p>0.05). Moreover, the mean (SD) of the standard deviation of the N-N interval index (SDNNI) in the patients was 111.96 (86.9) before PAP therapy (Table1), whereas it reached 96.5 (76.5) after 1 night of treatment with PAP; therefore, this difference was found to be statistically significant (p=0.036). The SDNNI changes in the patients following the elimination of the effects of age, sex, and the BMI in the GEE model exhibited a statistically significant difference (p=0.049), where the aforementioned variables (age, sex, and the BMI) were not found to be significantly effective. The mean (SD) of the standard deviation of the average N-N intervals for each 5-minute segment of a 24-hour HRV recording (SDANN) in the patients before PAP therapy was 78.14 (57) ms, which rose to 89.8 (76.7) after treatment (p=0.473).

Based on the findings presented herein, the changes after the elimination of the effects of age, sex, and the BMI in the GEE model failed to constitute statistical significance (p=0.617). Furthermore, the variables of age and gender were not predictive of SDANN, while the BMI was revealed to be a poor predictor (B=-0.014, p=0.018). The number of adjacent R-R intervals that differed by more than 50 ms (NN50) was 1742.5 (1501.8) and 2298.5 (2577.7) before and after treatment with PAP, respectively, which was not statistically significant (p=0.093). In addition, the percentage NN 50 (pNN50) before treatment was determined to be 20.55 (20%), while this amount dropped to 18.1 (21.6%) after treatment (p=0.082). The changes in the 2 indices of the NN50 and the pNN50 were not statistically significant after the elimination of the effects of age, sex, and the BMI in the GEE model (p=0.165 and p=0.138). Only the variable of age was found to play a significant role as an NN50 predictor (B=−52.5, p=0.014).

On the other hand, the mean (SD) of the root mean square of successive R-R interval differences (RMSSD) was 121.6 (133.9) ms before PAP therapy, while the rate reached 105.75 (121.9) after 1 night with PAP (p=0.107). It is worth noting that the changes in the RMSSD index in the patients after the removal of the effects of age, sex, and the BMI were not statistically significant (p=0.132). In this regard, the variables of age, sex, and the BMI had no significant predictive value for the RMSSD index (p>0.05).

Prior to PAP therapy, the mean (SD) of the HRV triangular index was 23.32 (37.6), whereas this rate was 15.2 (9.6) after 1 night of PAP therapy (p=0.252).

The changes in the HRV triangular index in the patients did not show a significant difference (p=0.266) following the elimination of the effects of age, sex, and the BMI. Further, the variables of age, sex, and the BMI did not have a significant predictive value for this index (p>0.05).

The mean (SD) of the very-low-frequency band (VLF) index was 18306.25 (16527.8) ms^2 before PAP therapy, while this rate reached 17626.5 (13696.2) ms^2 after 1 night with PAP therapy (p=0.600). After the elimination of the effects of age, sex, and the BMI in the GEE model, the changes in this variable were not found to be significant in the patients (p=0.859). It is, however, deserving of note that the effect of the BMI on the value of this index was significant (B=−2.8, p=0.022). In addition, the mean (SD) of the low-frequency (LF) index was 13105.6 (9879.6) ms^2 before PAP therapy and the value was 11010.5 (6363.8) ms^2 after 1 night with PAP therapy (p=0.088). Following the elimination of the effects of age, sex, and the BMI, the changes in the LF index revealed no significant difference among the patients (p=0.334). The role of the 2 variables of age (B=−261.2, p=0.005) and the BMI (B=−1.6, p=0.033) was significant in predicting the LF index.

The ratio of the LF index (LF%) before treatment was 34.15% (7.06) in comparison with the total amount of power, whereas it decreased to 31.0% (6.1) after treatment (p=0.21). After the elimination of the effects of age, sex, and the BMI, the changes in LF% were found to be significant in the patients (p=0.042). The mean (SD) of the high-frequency (HF) index was 4470.32 (2263.1) ms^2 before PAP therapy, while an HF index value of 5549.6 (2764.3) ms^2 was obtained after 1 night of treatment with PAP (p<0.001) Table 2.

Table 1. Changes in the time-domain parameters of HRV indicators before and after a nocturnal treatment.

Variable	Pre-treatment	Post-treatment	Univariate p	Multivariate *p*
R-R interval	874.59 (118.3)	911.94 (114.5)	<0.001	<0.001
SDNNI	111.96 (86.9)	96.5 (76.5)	0.036	0.049
SDANN	78.14 (57.0)	89.79 (76.7)	0.473	0.617
NN50	1742.5 (1501.8)	2298.5357 (2577.7)	0.093	0.165
pNN50	20.55 (20.0)	18.1 (21.6)	0.082	0.138
RMSSD	121.61 (133.9)	105.75 (121.9)	0.107	0.132
HRV triangular index	23.32 (37.6)	15.18 (9.6)	0.252	0.266

Table 2. Changes in the frequency-domain parameters of HRV before and after an overnight PAP therapy.

Variable	Pre-treatment	Post-treatment	Univariate *p*	Multivariate *p*
VLF	18306.25 (16527.8)	17626.5 (13696.2)	0.600	0.859
LF	13105.6 (9879.6)	11010.5 (6363.8)	0.088	0.334
LF%	34.15 (7.06%)	31.0 (6.1%)	0.021	0.042
HF	4470.32 (2263.1)	5549.6 (2764.3)	0.001	0.016
HF%	15.17 (7.3%)	17.43 (7.2%)	0.052	0.088
LF/HF ratio	3.2 (2.8	2.2 (1.3	0.008	0.023

The mean (SD) of the SD1 index before PAP therapy and after 1 night was determined to be 54.6 (37.4) and 54.7 (47.5), respectively (p=0.972). No significant change was found in this index after the elimination of the effects of age, sex, and the BMI (p=0.517).

Following the elimination of the effects of age, sex, and the BMI, the changes in the HF index were significant in the patients (p=0.016). Further, HF% was 15.17% (7.3) before treatment in comparison with the total amount of power, which increased to 17.43% (7.2) after treatment (p=0.052). After the elimination of the effects of age, sex, and the BMI, the increase in this index was not statistically significant (p=0.088). The age variable did not play a significant role in the prediction of the HF index (B=−88.4, p=0.002).

The mean (SD) of the LF / HF ratio was 3.2 (2.8) before PAP therapy, and it reached 2.2 (1.3) after 1 night of PAP therapy (p=0.008). The changes in this index were significant after the elimination of the effects of age, sex, and the BMI (p=0.023).

The mean (SD) of the SD1 index before PAP therapy and after 1 night was determined to be 54.6 (37.4) and 54.7 (47.5), respectively (p=0.972). No significant change was found in this index after the elimination of the effects of age, sex, and the BMI (p=0.517).

The mean (SD) of the SD2 index was 101.9 (35.4) before PAP therapy and 106.4 (47.8) after treatment with PAP (p=0.458). Following the elimination of the effects of age, sex, and the BMI, no significant changes were found in this index (p=0.179).

The mean SD1 / SD2 index was 0.55 (0.3) before PAP therapy, whereas PAP treatment did not lead to significant changes (p=0.078). No significant changes were also revealed in this index after the elimination of the effects of age, sex, and the BMI (p=0.095) Table 3.

DISCUSSION

HRV is a relatively simple and accessible tool for monitoring the autonomic system, and it can predict the risk of cardiovascular events in patients. Of note, 24-hour HRV indices reflect cardiovascular fluctuations and responsiveness more optimally[7].

HRV *time*-domain parameters present heart rate changes by measuring the variation in the beat-to-beat interval. Among these indicators, which were also measured in this study, the SDNNI, the SDANN, the number and percentage of the NN50, the RMSSD, and the HRV triangular index can be mentioned. The SDNNI is the simplest index of HRV and is defined as the mean of the standard deviations of all the N-N intervals[8], where both parasympathetic and sympathetic systems play a role in this index. The SDNN is a gold standard for classifying patients vis-à-vis the risk of cardiovascular disease[9]. The SDNN measured in this study is the mean deviation of N-N intervals recorded for each 5-minute segment of a 24-hour HRV recording[10].

Gong et al.[11] evaluated the relationship between HRV and polysomnography in 25 patients with OSA and 27 healthy patients and found that the SDNNI had a significant positive correlation with the micro-arousal index and was one of the most important determinants of OSA in their patients. We found that the SDNNI significantly decreased in the patients following PAP-based nocturnal therapy. Since the SDNN and the SDNNI show the overall change during HRV measurement, it is believed that they are not suitable criteria for measuring sympathovagal balance in patients[7].

We observed no significant change in the SDANN index after treatment in this study. Furthermore, the BMI was a poor predictor of the SDANN index in our patients. Previous studies have published contradictory results on the relationship between the demographic characteristics of patients and the value of the SDANN index. Some studies have reported a decrease in this index following an increase in age and the BMI[11-19], while others have found no such a relationship in their patients[15]. The *NN50 and the pNN50, as the* time-*domain* HRV *indicators and the* representatives of changes in HF HRV differences, can be calculated as the difference between successive N-N intervals.

In the present study, the NN50 variable was significantly affected by the age of the patients inasmuch as age increased the NN50. This finding is consistent with other previous studies that have reported an inverse age association with the NN50[10,14,16] and can be justified by the fact that the activity of the parasympathetic system can be reduced by increasing age. The *RMSSD is considered* the root mean square differences of successive R-R intervals[9]. This index is one of the first time-*domain indicators to be* used for the evaluation of the vagal tone[10]. The use of this index is statistically superior to that of the NN50 and the pNN50[9]. In comparison with the SDNN, the RMSSD index is most affected by the parasympathetic system[16]. In a previous study, the RMSSD in the period of a respiratory tract accident was significantly higher in the presence of the respiratory event among patients with OSA than among those without it[20]. This increase can be secondary linked to the efforts of the parasympathetic system to adjust the rhythm of the heart during respiratory events[20]. Therefore, it can be concluded that a reduced RMSSD renders patients with OSA vulnerable to coronary heart disease. We did not find any significant changes in this index after 1 night of PAP therapy.

The HRV triangular index is calculated as the integral of the density distribution of *the* N-N *interval divided by its height*[9]. A number of studies have shown that this index also increases following a rise in the AHI and in the severity of OSA[7,12,21,22]. It has been indicated that both the HRV triangular index and the RMSSD are capable of distinguishing normal heart rhythms from arrhythmias[18]. A normal heart rhythm is considered when an HRV triangular index of ≤ 20.42 and an RMSSD of ≤ 0.068

Table 3. Changes in other HRV indices before and after 1 night of PAP therapy.

Variable	Pre-treatment	Post-treatment	Univariate *p*	Multivariate *p*
SD1	54.6 (37.4)	54.7 (47.5)	0.972	0.517
SD2	101.9 (35.4)	106.4 (47.8)	0.458	0.179
SD1/SD2	0.55(0.3)	0.5 (0.3)	0.078	0.095

are determined, while an HRV triangular index of > 20.42 is considered to be the arrhythmic heart rhythm. As was shown in the present study, the HRV triangular index was 23.32 before treatment as compared to 15.2 after therapy. Although these changes were not statistically significant, they could be indicative of the patients' heart rhythm modulation following a *decrease* in *respiratory events*.

The HRV axis frequency indicators are used to predict the absolute or relative power distribution. Frequency domain indicators, which were also included in the current study, are VLF waves, LF waves, and HF waves. The VLF spectrum includes waves at frequencies ranging from 0.003 to 0.04 Hz, which are associated with temperature regulation, circadian changes, and other less well-known variables[9,13]. According to available evidence, the nervous system of the heart and the sympathetic nervous system play the role of regulators. Investigations conducted on patients suffering from OSA have demonstrated higher levels of VLF and LF in these patients[7,12,23].

The nervous system control of the heart and the sympathetic nervous system play the role of a regulator for this index. Studies have shown a higher incidence of VLF and LF in patients with OSA[7,12,23]. Further, an increase in the severity of OSA has been shown to lead to a rise in the amount of VLF[19]. Previous studies have reported an association between power VLF and arrhythmic *death*[24]. We found no significant change in the VLF index after PAP therapy. LF power contains a spectrum of waves ranging from 0.04 to 0.15. The magnitude of this index is higher in patients with OSA in comparison with healthy subjects[17]. In addition, some previous studies have demonstrated that the power of LF is directly linked to the amount of *arterial oxygen unsaturation* and the AHI in patients[12,18,20,24]. The power of LF in patients with coronary heart disease is significantly higher when compared with healthy subjects[25]. These cases can be indicative of worse heart disease for the patient with an increased level of LF. Based on the data presented herein, the relative amount of LF (LF%) was decreased after PAP therapy. This finding can result in a reduction in the AHI index and improvement in oxygen saturation in patients. There was also an inverse correlation between age and the BMI of the patients and the amount of LF power, which could be due to the negative effect of age and the BMI on HRV indices[26].

The HF index has a frequency spectrum ranging from 0.15 to 0.4 Hz and is affected by the respiratory system and the parasympathetic system, where changes occur very rapidly[9]. Heart rate increases during the inhalation and shows a decreasing trend in the exhalation; hence, these changes affect the HF index. Moreover, the power of HF shows a rise during the night, while a decreased trend can be observed in its daily rate. HF has also been observed in patients suffering from anxiety and stress[10]. Previous studies have revealed low levels of HF in patients suffering from OSA in comparison with healthy subjects[24,27,28]. This suggests dysfunction in the parasympathetic system in patients, which can put them at risk for cardiovascular disease. In our study, the patients exhibited a significant increase in HF power with 1 night of PAP therapy.

The LF / HF ratio index is used to evaluate the activity of the sympathetic system in relation to the parasympathetic system[10]. According to the results of previous studies, the LF / HF ratio is higher in patients with OSA, and it is deemed one of the best HRV indices for distinguishing these patients from the normal population[7,12]. A higher index indicates the imbalance of the sympathovagal system where patients are *at increased risk* for heart disease[25]. As was indicated, the magnitude of this index in our patients was significantly reduced following therapy, denoting a moderating role for PAP therapy in the regulation of the sympathovagal system in patients with OSA.

The Poincaré plot is a geometrical and nonlinear approach for evaluating the dynamics of HRV. It is a diagram consisting of an R-R interval plot. The Poincaré plot has been used in a qualitative way where the plot is categorized into functional classes, exhibiting the degree of heart failure. The 2 indicators of SD1 and SD2 are calculated via this method. The SD1 index indicates the effect of breathing on the vagus system. The SD2 index is affected by other factors such as sympathetic, baroreflex, temperature regulation, and hormonal changes. Like the LF / HF ratio, the SD1 / SD2 index is also employed to evaluate the sympathetic balance[10]. There is little information available on the changes in non-linear *HRV indices* in patients with OSA. Our findings revealed no significant changes in any of these indices following PAP therapy.

Overall, based on the findings presented herein, a 1-night treatment with PAP changed the SDNNI and the frequency domain parameters of HRV (LF, HF, and the LF / HF ratio) in our patients with OSA. A study by Kuramoto et al.[29] showed that after 3 months of CPAP therapy in patients with OSA, HF power significantly increased, which is in agreement with our findings. However, contrary to the present study, a change in the LF / HF ratio was not found in the aforementioned study.

A change in the frequency domain parameters after 1 night of CPAP therapy, which was observed in the current study, was also observed by Karasulu et al.[30]. Gilman et al.[31] measured the effect of CPAP on the HF index in patients with concomitant heart failure and OSA and reported a significant increase in the HF index 1 month after CPAP treatment, which could improve prognosis in patients.

Grau et al examined the effect of 1-year CPAP treatment on HRV indices in patients with OSA[32] and reported changes in the number of the time-domain indicators (RMSSD) and the frequency-domain indicators (LF and HF) in these patients, which is *consistent* with our *findings*. In a similar study conducted by Chrysostomakis et al.[33], HRV indices were compared before and after CPAP therapy in patients with OSA. Contrary to the results of our study, the authors did not report any significant change in HRV indices following CPAP therapy. Another study indicated no significant change in the time-domain and the HRV frequency-domain indices after PAP therapy[34].

CONCLUSION

The results of this study indicate a relative improvement in the activity of the autonomic *system* in patients with

OSA following 1 night of PAP therapy. Improvement in sympathovagal balance can reduce the risk of cardiovascular disease in patients. In this study, OSA was associated with an increase in HRV indices, resulting in an increase in the activity of the sympathetic system caused by respiratory distress in the patients. Accordingly, improving respiratory function during the overnight CPAP therapy reduced sympathetic system activity and led to a decrease in HRV indices.

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