Original Article

ISSN: 1735-0344 *Tanaffos 2024; 23(4): 371-375*

TANAFFOS

Heart Rate Variability in Obstructive Sleep Apnea: Association with Excessive Daytime Sleepiness and Cardiovascular Risk

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Received: 29 October 2023
Accepted: 7 July 2024

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Background: Obstructive sleep apnea (OSA) is associated with increased vagal activity, sympathetic nervous system activation, and cardiovascular complications. Excessive daytime sleepiness (EDS) in OSA patients is a predictor of cardiovascular and all-cause mortality. Heart rate variability (HRV) can be used to assess cardiac autonomic modulation, which is affected by OSA. This study aimed to evaluate the relationship between HRV and daily sleepiness in OSA patients based on the excessive sleep scale (ESS) scores.

Materials and Methods: The study included 70 patients with OSA, divided into two groups: those with EDS (ESS ≥ 11) and those without sleepiness (ESS < 11). Time and frequency domain parameters were evaluated. The results were compared and analyzed between the two groups.

Results: Patients with OSA and EDS had higher cardiovascular risk, as indicated by different HRV parameters (higher low-frequency parameter and higher time domain parameters), compared to non-sleepy OSA patients. A significant positive correlation was found between ODI and AHI with VLF, and significantly higher LF and VLF in EDS patients.

Conclusion: OSA patients with EDS had higher cardiovascular risk, as indicated by different HRV parameters, compared to non-sleepy OSA patients. A significant positive correlation was found between ODI and AHI with VLF, and significantly higher LF and VLF in EDS patients. Further studies are needed to better understand the relationship between HRV and daily sleepiness in patients with OSA.

Keywords: Obstructive Sleep Apnea; Heart Rate Variability; Excessive Daytime Sleepiness

INTRODUCTION

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder, characterized by the sleep-dependent periodic collapse of the upper airway, resulting in irregular episodes of reduced or interrupted ventilation, accompanied by hypoxia, hypercapnia, autonomic fluctuation, arousal from sleep, or sleep fragmentation (1). Enhanced vagal activity during apnea and hypopnea events is associated with the activation of the sympathetic nervous system, leading to electrical remodeling and cardiac arrhythmogenesis (2).

Patients with severe OSA are at high risk for all-cause mortality and cardiovascular comorbidities, such as systemic hypertension, coronary artery disease, and arrhythmias, with the potential for negative feedback (e.g., OSA causing hypertension that can worsen OSA) (3).

Daytime sleepiness is a common feature of OSA; however, non-sleepy OSA is also prevalent. Daytime sleepiness phenotype has been related to higher levels of cardiovascular and metabolic comorbidity (4). Excessive daytime sleepiness (EDS) is a statistically significant predictor for cardiovascular and all-cause mortality, although the association is modest (5).

The primary contributing factor to these adverse outcomes is sympathetic overactivity, which can be evaluated using heart rate variability as a marker of shifts in the autonomic nervous system. HRV is a non-invasive method for the assessment of cardiac autonomic modulation that describes the oscillations between consecutive electrocardiogram R-R intervals (6). HRV includes three different frequency-based components: a very low frequency (VLF) component, a low frequency (LF) component, and a high frequency (HF) component, as well as time domain indices such as standard deviation of normal-to-normal RR intervals (SDNN), SDNN index (SDNNI), and triangular index (7). Autonomic function impairment is more evident in patients with severe OSA, and during sleep, low frequency can be strongly related to autonomic dysfunction in OSA (8).

Although sleepy individuals with OSA may have increased sympathetic nervous system activity and higher cardiovascular complications (9), the effect of non-sleepy and sleepy OSA on HRV has not been investigated. Therefore, this study aimed to evaluate the relationship between HRV and daily sleepiness in patients with OSA based on the excessive sleep scale (ESS) scores.

MATERIALS AND METHODS

Participants and study design

Patients who were referred to Imam Khomeini Hospital Sleep Clinic due to a history suggestive of sleep apnea with an Apnea-Hypopnea Index (AHI) ≥ 15 events/hour on an overnight polysomnogram (PSG) were included in this study. Patients were excluded if they had a history of cardiovascular disease (cardiac surgery or acute coronary syndrome in the previous three months, heart failure, atrial fibrillation), were drug or ethanol abusers, were under treatment that affects heart rate, had received Continuous Positive Airway Pressure (CPAP) for OSA treatment, or had received central nervous system stimulants or depressants at the time of the PSG. All participants provided written informed consent. The study was conducted in accordance with the ethical standards outlined in the 2013 Declaration of Helsinki. The ethical committee of Imam Khomeini Hospital approved this study and granted the ethical code [IR.TUMS.IKHC.REC.1402.039].

The demographic information of the participants and their related medical and drug history were recorded. The Epworth Sleepiness Scale (ESS) 10 was calculated for all participants who had subjectively answered all eight questions to measure their daytime sleepiness immediately before PSG. Scores can be interpreted as Lower Normal Daytime Sleepiness (0-5), Higher Normal Daytime Sleepiness (6-10), Mild Excessive Daytime Sleepiness (11-12), Moderate Excessive Daytime Sleepiness (13-15), and Severe Excessive Daytime Sleepiness (16-24). We divided patients into the excessive daytime sleepiness group (ESS≥11) and non-sleepy patients (ESS < 11).

Objectives and outcome measures

Heart Rate Variability: HRV indices were obtained by PSG amplifier (Embla N7000, Natus, USA) for each patient. Specific HRV indices recorded included time-domain measures (mean heart rate, SDNN, SDNNI, and triangular index) and frequency-domain measures (LF, HF, and the ratio of low-frequency power to high-frequency power (LF/HF)). These indices were calculated using Kubios HRV software (version 3.5.0, University of Eastern Finland, Finland) and were based on 5-minute segments of artifact-free RR intervals during non-REM sleep stages 2-4.

Sample size and statistical analysis

Considering the effect size of 0.72 based on the previous studies (10), with a power of 80% and a significance level of 0.005, 62 patients were required (31 in

each group). The planned sample size was determined to be 72, with an assumed 10% dropout rate.

Categorical variables were reported with frequencies or percentages as appropriate. Quantitative variables were reported as either median (interquartile range) or frequency (percentage). The Shapiro-Wilk test was used with the variable boxplot to assess the normality. Group comparison was performed using the Chi-square test (or Fisher's exact test if cell count<5) for qualitative variables. One-tailed Student's t-test was used for normally distributed quantitative variables, and one-tailed Mann–Whitney U test was used for not normally distributed variables. The sample size estimation was carried out using G*Power (version 3.1), and the data analysis was processed using SPSS (version 21.0, Chicago, IL, USA).

RESULTS

Patient disposition and characteristics

In this prospective cross-sectional study, a total of 85 patients with OSA were screened, of which 70 were eligible for inclusion and were entered into the study. The study population included 36 patients with EDS and 34 non-sleepy patients. There were no significant differences in terms of age, body mass index (BMI), sex distribution, or medical or drug history between the two groups. The baseline characteristics of these patients are summarized in Table 1.

Table 1. Baseline characteristics of the patients examined, grouped based on ESS

Parameter	EDS (n=36)	Non-EDS (n=34)	*P-value*
Age (mean ± SD)	56.11 ± 12.54	51.24 ± 14.04	0.61[a]
Female/ male ratio	14/22	13/21	0.95[b]
BMI (mean ± SD)	33.77 ± 6.00	34.55 ± 9.08	0.67[a]
ESS score (mean ± SD)	14.25 ± 4.81	5.71 ± 5.02	**< 0.05** [a]

Abbreviations: AHI = Apnea Hypopnea Index, BMI = Body Mass Index, EDS= excessive daytime sleepiness, ESS = excessive sleepiness scale
a: independent T-test, b: Chi-square test

Outcomes

The EDS group had a significantly higher AHI than the non-EDS group (median AHI: 51.5 vs. 23.5, $p < 0.05$). Other PSG data were not significantly different between the groups .

Time and frequency domain parameters were evaluated in the current study. The results showed that LF, VLF, SDNN, SDNNI, and triangular index were significantly different between the two groups (Table 2).

The correlations between the Oxygen Desaturation Index (ODI) and AHI with different HRV indices are presented in Table 3. This shows a significant positive medium correlation between ODI and AHI with VLF and a medium negative correlation with SDNNI (Pearson's Correlation Coefficient±0.30 and ±0.49, respectively).

Table 2. Time domain and frequency domain of HRV indexes and oxygen desaturation index

Parameter	EDS (n=36)	Non-EDS (n=34)	*P-value*
AHI (Median (IQR))	51.5 (42.3)	23.5 (32.9)	***0.006****
ODI (Median (IQR))	43.1 (49.12)	23 (28.65)	*0.11**
Frequency-based parameters			
LF (Median (IQR))	4833.5 (6338.0)	3402 (4050.3)	***0.09****
HF (mean ± SD)	3076 ± 1983	3082 ± 1955	*0.93***
VLF (Median (IQR))	6735.5 (10296.0)	3149.5 (3576.0)	***0.04***
Time-based parameters			
SDNN (Median (IQR))	262.0 (9940.0)	9098.5 (10328.0)	***0.06****
SDNNI (Median (IQR))	260.0 (7965.0)	7411.0 (9275.0)	***0.04****
Triangular index (Median (IQR))	21.0 (1542)	564.5 (1542)	***0.05****

Abbreviations: AHI = Apnea Hypopnea Index, EDS = excessive daytime sleepiness, ESS = excessive sleepiness scale, ODI = oxygen desaturation index, LF = Low frequency, HF = low frequency, VLF = Very low frequency, SDNN = Standard deviation of normal to normal (NN) interval time series, SDNNI = SDNN index
*Mann–Whitney U test, ** Independent T-test

Table 3. The correlations between ODI and AHI with different HRV indices

		ODI	LF	HF	VLF	SDNN	SDNNI	Triangular Index
ODI	Correlation Coefficient	1.000	.296*	-.039	.424**	-.338**	-.340**	-.286*
	P-value*	.	.013	.750	.000	.004	.004	.016
	N	70	70	70	70	70	70	70
AHI	Correlation Coefficient	.868**	.295*	-.015	.444**	-.350**	-.346**	-.332**
	P-value *	.000	.013	.903	.000	.003	.003	.005
	N	70	70	70	70	70	70	70

***P** value Pearson correlation coefficient

DISCUSSION

OSA is closely associated with several cardiovascular diseases. It is thought that this relationship may be due in part to enhanced nocturnal sympathetic nerve activity (SNA) that can result in wakefulness (11). However, the specific mechanisms by which OSA is linked to cardiovascular disease are not fully understood.

One possible factor that may contribute to the development of cardiovascular disease in patients with OSA is chronically reduced heart rate variability (HRV), which is a marker of autonomic imbalance and parasympathetic dysfunction (12). Previous studies have suggested that changes in HRV predict poor cardiovascular outcomes, indicating that HRV may be a useful indicator of cardiovascular risk (12). Higher SDNN, SDNNi, HF, and TI values may reflect a healthier autonomic nervous system balance and a lower risk of cardiovascular disease (CVD). Decreased SDNN, SDNNi, HF, and TI values may suggest an imbalance with increased sympathetic activity and potentially higher CVD risk. Increased LF and LF/HF ratio may indicate sympathetic dominance and higher CVD risk (13). VLF represents long-term modulations, possibly influenced by thermoregulation and hormonal factors. The exact role of VLF in CVD is still being studied (14). In a recent meta-analysis of 22 studies involving 2565 patients with obstructive sleep apnea and 1089 healthy controls, HRV outcomes were analyzed to evaluate autonomic function. The study found that patients with OSA had reduced parasympathetic function compared to controls. Specifically, patients with severe OSA had significantly lower parasympathetic function, HF, root mean square of the successive differences between normal heartbeats, and SDNN, and higher LF and LF/HF. Patients with moderate OSA had significantly higher LF and LF/HF compared to controls. Furthermore, patients with OSA had significantly higher LF and ratios of LF/HF at night, significantly lower parasympathetic function, HF, root mean square of the successive differences between normal heartbeats, and SDNN, and a higher ratio of LF/HF during the day than controls. The study suggests that autonomic function impairment is more severe in patients with severe OSA and that LF can reflect the impairment of autonomic function in OSA, and the ratio of LF to HF may be useful in obstructive sleep apnea diagnosis (8).

Our study found a significant positive medium correlation between ODI and AHI with VLF. Additionally, we found significantly higher LF and VLF in patients with EDS. LF primarily reflects sympathetic activity. Increased LF may be associated with a higher CVD risk. This is in line with previous studies that patients with sleepy OSA may have a higher probability of cardiovascular adverse outcomes.

Regarding time domain parameters, previous studies are inconsistent, and there is no significant difference between night-time indices (8). We also found significantly lower SDNN, SDNNI, and TI in the EDS group, which can be associated with a higher risk of CVD.

Our study must be interpreted in consideration of its limitations; an inadequate sample size may have contributed to our finding of no difference in some parameters. One limitation of this study was that we were unable to measure HRV during OSA events, which may provide more precise information about the relationship

between OSA and HRV. Future studies should consider measuring HRV during OSA events to better understand this relationship.

CONCLUSION

The study found that patients with obstructive sleep apnea (OSA) and excessive daytime sleepiness (EDS) had higher cardiovascular risk, as indicated by different HRV parameters, compared to non-sleepy OSA patients. A significant positive correlation was found between ODI and AHI with VLF, and significantly higher LF and VLF in EDS patients. Further studies are needed to better understand the relationship between HRV and daily sleepiness in patients with OSA.

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