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Original Article

Is there any relationship between the time spent in respiratory events and cardiovascular morbidity in obstructive sleep apnea patients?

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Abstract

Aim: The importance of the duration of respiratory events, in addition to the number, in the evaluation of obstructive sleep apnea (OSA) is gradually increasing. We aimed to investigate whether parameter including the number and duration of respiratory events predict cardiovascular mortality.

Material and Methods: A retrospective study included 200 patients with OSA (100 severe, 50 moderate, 50 mild). Time spent during respiratory events, including the number and duration of respiratory events, was calculated for each respiratory event. Obstructive apnea time (OAT), hypopnea time (HT), total apnea time (TAT), and total respiratory event time (TRET) were obtained. The relationship between cardiovascular diseases of the patients and the time spent during respiratory events was examined.

Results: There was no relationship between the cardiovascular diseases and the time spent during respiratory events in the mild, moderate and all OSA group; however, the prolonged OAT (p=0.024) and TAT (p=0.039) in the severe OSA group were associated with an increase in the cardiovascular diseases, independent of other variables. However, the relationship between apnea-hypopnea index (AHI) and cardiovascular diseases in mild, moderate, severe, and all OSA was not significant.

Conclusion: Using parameters including the duration of respiratory events in addition to AHI may be more useful to understand the comorbidities of OSA particularly cardiovascular diseases.

Keywords: Cardiovascular disease; duration; obstructive sleep apnea; respiratory event

INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep disorder characterized by the repetitive partial or complete collapse of the upper airway, leading to transient hypoxemia and arousals during sleep. It is a common disorder, with prevalence estimated at 10-17% for men and 3-9% for women; associated with excessive daytime sleepiness, increased overall morbidity, and mortality (1). Apnea-hypopnea index (AHI) has been used as the main parameter to diagnose and classify the severity of the disease; defined as the average number of respiratory events per hour of sleep, regardless of the duration of the event. In recent years, studies evaluating the contribution of the duration of respiratory events in addition to the number of respiratory events in OSA have been carried out (2-9).

Cardiovascular diseases are common in the general population worldwide. It was estimated to result in 17.3 million deaths worldwide in 2012 and 2013, a number that is expected to be 23.6 million by 2030 (10). OSA has been associated with many different forms of cardiovascular diseases including hypertension, stroke, heart failure, coronary artery disease, and atrial fibrillation (11). One of the reasons for differences in cardiovascular diseases, non-cardiovascular morbidities, mortality, and response to therapy could be various respiratory event durations in OSA patients with the same severity. However, the number of studies examining the relationship between duration of respiratory events and cardiovascular morbidity in OSA is limited (8,12-14).

We hypothesized that there may be a relationship between the time spent during respiratory events and cardiovascular morbidity in OSA patients. So in this study, we aimed to evaluate the parameter "time spent during respiratory events" (second/hour) which includes the number and duration together, separately for each respiratory event;

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evaluated with the polysomnographic sleep parameters and cardiovascular morbidity in OSA patients.

MATERIAL and METHODS

Patients and Study Design

A retrospective clinical study included 200 OSA patients (100 severe, 50 moderate, 50 mild) who were >18 years of age and who were followed up in the sleep center. The diagnosis of OSA by PSG was supported by the American Academy of Sleep Medicine (AASM). Demographic parameters were extracted from the patient medical records. The Ethics Committee approved the study protocol (2011-KAEK-25 2019/10-24).

Polysomnography

PSG in the sleep laboratory included continuous electroencephalographic (EEG) polygraphic recording using EEG leads, the use of right and left electro-oculographic leads, and chin electromyography for sleep staging. Electrocardiography (ECG) monitoring during sleep, airflow measurement at the nose and mouth, chest and abdominal respiratory movements were measured during sleep. Arterial oxygen saturation was measured with pulse oximetry. All sleep studies were interpreted according to the manual of the AASM for the Scoring of Sleep, by certified sleep physicians. Apnea was identified when the airflow amplitude in the nasal cannula was <10% of baseline and when no flow occurred on the oral airflow sensor (thermistor). Hypopneas was identified when the amplitude of the airflow was reduced by 30% from the baseline, the event was followed by 4% desaturation. The AHI was defined as the total number of apnea and hypopnea events per hour of sleep. Oxygen desaturation index (ODI) represents the average number of desaturation events (4%) per hour of sleep.

Time Spent in Respiratory Events

The mean obstructive apnea duration (MOAD), mean total apnea duration (MTAD), mean hypopnea duration (MHD), and the number of each respiratory event were multiplied for each respiratory event separately and divided by the total sleep time. So the time spent during each respiratory event (second/hour); obstructive apnea time (OAT), hypopnea time (HT), total apnea time (TAT), and total respiratory event time (TRET) were obtained.

Cardiovascular Diseases

Cardiovascular diseases of the patients were retrospectively screened from the medical record system. Hypertension, heart failure, cardiac arrhythmias, and ischemic heart diseases were included.

Statistical Analysis

Data were expressed as the mean ± standard deviation (SD) or the median (interquartile range). The relationship between times spent in respiratory events (OAT, TAT, HT, TRET) and independent predictive variables were analyzed using linear regression with the enter method. Data were analyzed using IBM SPSS statistics 22.0 (SPSS Inc., Chicago, IL, USA). The value of $p<0.05$ was considered statistically significant

RESULTS

This retrospective study included 200 OSA patients. The demographic characteristics of the study population were summarized (Table 1). Times spent in respiratory events with polysomnographic parameters and blood oxygenation parameters were evaluated (Table 2).

Time spent in respiratory events and presence of the cardiovascular diseases were evaluated (Table 3). There was no relationship between the cardiovascular diseases and the time spent during respiratory events in the mild, moderate and all OSA group; however, the prolonged OAT (p=0.024) and TAT (p=0.039) in the severe OSA group were associated with an increase in the cardiovascular diseases, independent of other variables. No association was found between AHI and cardiovascular diseases in mild, moderate, severe, and all OSA.

Table 1. Demographic characteristics of the study population

	Mild OSA	Moderate OSA	Severe OSA	Total	Test value	p
Age (mean±SD)	44.6±10.3	50.0±11.6	51.35±11.4	49.3±11.5	6.181*	0.002
Gender (M/F)	21/29	28/22	65/35	114/86	7.222**	0.027
Height cm	162.5 (150-195)	167.4±9.1	168.9±8.5	167.5 (148-195)	9.494#	0.009
Weight kg	80.5(55-155)	86.2±13.1	93.5(70-145)	86 (55-155)	26.086#	<0.001
BMI kg/m^2	28.7 (22-61)	30.0(23-42)	32.75(22-54)	30.5 (22-61)	13.324#	0.001
AHI	8.9(5.1-14.9)	21.1(15.5-29.8)	60.9 (33.3-131.6)	31.6 (5.1-131.6)	167.916#	<0.001
OAT (sec/hr)	25.6(0-162.0)	84(0-541.7)	756.8(4.4-2792.4)	180.9 (0-2792.4)	116.684#	<0.001
TAT (sec/hr)	33.4(0-162)	99.7(0-546.5)	847.5 (4.4-2792.4)	192.2 (0-2792.4)	117.404#	<0.001
HT (sec/hr)	207.7±129.5	434.7±164.2	360.6(0-1372.9)	327.9 (0-1372.9)	32.825#	<0.001
TRET (sec/hr)	219.6(99.8-517.5)	578.1±155.0	1304.2(457.4-2794.4)	719.1 (99.8-2794.4)	153.526#	<0.001

SD: standard deviation. BMI: body mass index, AHI: apnea hypopnea index, OAT: obstructive apnea time, TAT: total apnea time, HT: hypopnea time, TRET: total respiratory event time. Values represent median (min-max). *one-way ANOVA **Chi-Square test. . #Kruskal-Wallis test

Table 2. Multiple linear regression analysis models for OAT, TAT, HT and TRET as dependent variables and age, gender, BMI, polysomnographic parameters as independent variables

		OAT			TAT			HT			TRET		
	OSA severity	β coefficient	p value	95% CI	β coefficient	p value	95% CI	β coefficient	p value	95% CI	β coefficient	p value	95% CI
Age	Mild OSA	0.001	0.896	-0.014/0.016	-0.001	0.887	-0.015/0.013	2.904	**0.040**	0.135/5.674	0.006	**0.002**	0.002/0.009
	Mod.OSA	0.020	0.051	<0.001/0.040	0.015	0.082	-0.002/0.033	-1.055	0.721	-6.979/4.869	0.001	0.535	-0.002/0.005
	Severe OSA	0.001	0.816	-0.007/0.009	0.000	0.916	-0.008/0.007	2.629	0.367	-3.127/8.384	-0.001	0.418	-0.003/0.001
	All OSA	0.007	**0.041**	0.000/0.014	0.006	0.080	-0.001/0.012	3.060	0.070	-0.250/6.371	0.004	**0.002**	0.001/0.007
Gender	Mild OSA	0.423	**0.011**	0.102/0.743	0.346	**0.022**	0.052/0.640	-9.091	0.749	-66.131/47.949	0.036	0.307	-0.034/0.105
	Mod.OSA	0.515	0.050	<0.001/1.030	0.394	0.085	-0.057/0.845	-77.373	0.292	-223.87/69.131	0.021	0.630	-0.068/0.111
	Severe OSA	0.254	**0.012**	0.057/0.452	0.316	**0.001**	0.127/0.505	-112.083	0.137	-260.459/36.293	0.081	**0.004**	0.027/0.135
	All OSA	0.391	**<0.001**	0.220/0.562	0.364	**<0.001**	0.206/0.522	-20.884	0.610	-101.49/59.729	0.108	**0.001**	0.046/0.171
BMI kg/m²	Mild OSA	-0.035	**0.022**	-0.064/-0.005	-0.035	**0.001**	-0.056/-0.014	1.736	0.404	-2.421/5.892	0.001	0.728	-0.004/0.006
	Mod.OSA	-0.004	0.886	-0.055/0.047	-0.013	0.554	-0.058/0.031	4.984	0.441	-7.961/17.929	0.000	0.953	-0.008/0.008
	Severe OSA	-0.017	0.051	-0.033/0.000	-0.017	**0.034**	-0.033/-0.001	10.394	0.104	-2.195/22.983	0.001	0.828	-0.004/0.005
	All OSA	-0.020	**0.009**	-0.036/-0.005	-0.027	**<0.001**	-0.040/-0.014	10.857	**0.001**	4.267/17.447	0.001	0.733	-0.004/0.006
TST	Mild OSA	-0.001	0.561	-0.003/0.002	-0.001	0.629	-0.003/0.002	0.169	0.441	-0.269/0.607	0.000	0.500	0.000/0.001
	Mod.OSA	0.002	0.368	-0.002/0.005	0.002	0.275	-0.001/0.005	0.065	0.899	-0.965/1.095	0.000	0.578	0.000/0.001
	Severe OSA	0.001	0.277	-0.001/0.002	0.001	0.358	-0.001/0.002	0.136	0.779	-0.828/1.101	0.000	**0.016**	0.000/0.001
	All OSA	-0.001	0.891	-0.001/0.001	0.000	0.853	-0.001/0.001	0.336	0.256	-0.245/0.916	0.000	0.125	0.000/0.001
REM Sleep(%)	Mild OSA	-0.010	0.444	-0.037/0.017	-0.006	0.630	-0.032/0.019	-1.362	0.597	-6.523/3.798	-0.005	0.119	-0.011/0.001
	Mod.OSA	0.006	0.860	-0.067/0.080	-0.009	0.773	-0.074/0.055	-2.823	0.794	-24.554/18.908	-0.001	0.838	-0.015/0.012
	Severe OSA	0.016	0.070	-0.001/0.032	0.015	0.071	-0.001/0.031	-5.988	0.350	-18.645/6.668	0.005	0.056	0.001/0.010
	All OSA	0.004	0.568	-0.011/0.019	0.003	0.690	-0.011/0.017	-2.319	0.528	-9.553/4.915	0.003	0.292	-0.003/0.009
Stage 1 NREM Sleep(%)	Mild OSA	-0.017	0.150	-0.041/0.007	-0.017	0.143	-0.039/0.006	2.534	0.277	-2.108/7.176	<0.001	0.944	-0.005/0.006
	Mod.OSA	0.015	0.669	-0.054/0.084	0.001	0.970	-0.059/0.062	-1.772	0.860	-21.896/18.352	-0.001	0.994	-0.012/0.012
	Severe OSA	0.007	0.263	-0.005/0.019	0.006	0.282	-0.005/0.018	-5.752	0.216	-14.919/3.415	0.003	0.111	-0.001/0.006
	All OSA	0.001	0.807	-0.010/0.012	0.001	0.816	-0.009/0.012	0.894	0.743	-4.472/6.261	0.004	0.096	-0.001/0.008
Stage 2 NREM Sleep(%)	Mod.OSA	0.023	0.497	-0.045/0.092	0.008	0.782	-0.052/0.068	-5.239	0.602	-25.391/14.913	-0.001	0.931	-0.013/0.012
	Severe OSA	0.013	**0.023**	0.002/0.024	0.013	0.019	0.002/0.024	-8.329	0.052	-16.718/0.059	0.006	<0.001	0.003/0.009
	All OSA	0.011	**0.013**	0.002/0.020	0.010	0.014	0.002/0.018	-2.767	0.201	-7.020/1.485	0.006	<0.001	0.003/0.010
Stage 3 NREM Sleep(%)	Mild OSA	-0.007	0.295	-0.020/0.006	-0.005	0.417	-0.017/0.007	0.363	0.767	-2.096/2.823	-0.002	0.151	-0.005/0.001
	Mod.OSA	0.021	0.539	-0.048/0.091	0.005	0.867	-0.056/0.066	-5.497	0.586	-25.749/14.755	-0.002	0.788	-0.014/0.011
	Severe OSA	-0.002	0.273	-0.004/0.001	-0.002	0.238	-0.004/0.001	-0.017	0.987	-2.151/2.117	0.001	0.953	-0.001/0.001
	All OSA	-0.001	0.506	-0.005/0.002	-0.002	0.343	-0.005/0.002	0.640	0.465	-1.084/3.811	0.000	0.780	-0.001/0.002
MOD	Mild OSA	0.218	**0.039**	0.012/0.424	0.196	0.048	0.002/0.391	-24.077	0.235	-64.416/16.261	-0.017	0.486	-0.066/0.032
	Mod.OSA	0.218	0.123	-0.062/0.498	0.203	0.101	-0.042/0.448	-80.426	0.050	-160.866/0.013	-0.020	0.425	-0.069/0.030
	Severe OSA	0.031	**0.002**	0.012/0.050	0.033	<0.001	0.015/0.052	-19.664	**0.004**	-32.733/-6.595	0.014	**<0.001**	0.008/0.019
	All OSA	0.055	**<0.001**	0.032/0.077	0.059	<0.001	0.038/0.080	-18.715	**<0.001**	-28.283/-9.146	0.023	**<0.001**	0.014/0.032
ODI	Mild OSA	-0.031	0.244	-0.085/0.022	-0.030	0.239	-0.080/0.021	40.214	**<0.001**	29.799/50.630	0.063	**<0.001**	0.050/0.076
	Mod.OSA	0.052	**0.049**	0.000/0.105	0.037	0.110	-0.009/0.082	17.802	**0.022**	2.734/32.870	0.019	**<0.001**	0.010/0.028
	Severe OSA	0.012	**<0.001**	0.007/0.017	0.013	<0.001	0.008/0.017	-0.010	0.995	-3.450/3.430	0.006	**<0.001**	0.005/0.007
	All OSA	0.024	**<0.001**	0.020/0.028	0.025	<0.001	0.021/0.028	1.086	0.077	-0.199/3.811	0.011	**<0.001**	0.010/0.013

CI: confidence interval, BMI: body mass index, TST: total sleep time, MOD: mean oxygen desaturation, ODI: oxygen desaturation index, OAT: obstructive apnea time, TAT: total apnea time, HT: hypopnea time, TRET: total respiratory event time, p<0.05 is significant

Table 2. Multiple linear regression analysis models for OAT, TAT, HT and TRET as dependent variables and age, gender, BMI, polysomnographic parameters as independent variables

	OAT			TAT			HT			TRET			AHI		
OSA severity	β coefficient	p value	95% CI	β coefficient	p value	95% CI	β coefficient	p value	95% CI	β coefficient	p value	95% CI	β coefficient	p value	95% CI
Mild OSA	-0.135	0.317	-0.405/ 0.135	-0.135	0.317	-0.405/ 0.135	-9.768	0.811	-91.805/ 72.269	-0.051	0.399	-0.172/ 0.070	-0.959	0.346	-2.989/ 1.071
Moderate OSA	0.299	0.116	-0.077/ 0.674	0.230	0.156	-0.092/ 0.552	-20.875	0.680	-122.27/ 80.520	0.010	0.780	-0.064/ 0.085	1.928	0.190	-0.991/ 4.848
Severe OSA	0.267	**0.024**	0.036/ 0.498	0.242	**0.039**	0.012/ 0.471	-58.412	0.419	-201.23/ 84.409	0.072	0.098	-0.014/ 0.158	8.787	0.084	-1.199/ 18.773
All OSA	-0.126	0.263	-0.348/ 0.095	-0.126	0.254	-0.343/ 0.091	-65.296	0.096	-142.19/ 11.605	-0.116	0.194	-0.213/ -0.019	-6.920	0.099	-15.158/ 1.318

CI: confidence interval, OAT: obstructive apnea time, TAT: total apnea time, HT: hypopnea time, TRET: total respiratory event time, AHI: apnea hypopnea index, $p<0.05$ is significant

DISCUSSION

The current diagnosis and severity classification of OSA is based on the number of respiratory events. In recent years, however, it has been shown that, in addition to the number of respiratory events, the duration of respiratory events contributes to the assessment of the OSA, accompanying morbidities and mortality. OSA has been associated with increased morbidity and mortality related to cardiovascular disease. Therefore the relationship between time spent during the respiratory events (parameter combining the number and duration of respiratory events) and cardiovascular diseases evaluated in the present study.

Population-based studies have shown an association between OSA and cardiovascular diseases (15,16). Intermittent hypoxia, a major pathophysiological change caused by OSA, causes increasing sympathetic nerve activity, systemic inflammation, and endothelial cell injury, which may also aggravate cardiovascular diseases including hypertension, arrhythmia, and arteriosclerosis (17). The data about the relationship between cardiovascular diseases and duration of respiratory events or parameters including duration of respiratory events in OSA are limited (8,12-14). It is shown that OSA patients with longer MAD (mean apnea-hypopnea duration) have more and worse hypertension than patients with shorter MAD (8). The reason for poor blood pressure control could be low oxygen saturation associated with longer MAD in this study. Also in the rat model of OSA, it was found that longer apnea-hypopnea duration is related to more hypertension (12). One of the two studies examining the relationship between cardiovascular disease with the duration and number of respiratory events together; showed that non-fatal cardiovascular events and cardiovascular mortality are higher in severe OSA formed based on adjusted-AHI (13). In this study adjusted AHI was found to be an independent risk factor for non-fatal cardiovascular events. According to the second one, hypertensive women have lower apnea and apnea-hypopnea time and hypertensive men have higher hypopnea time (14). However, female patients were more obese and older than male patients in that study. In our study, cardiovascular diseases were related to OAT and TAT only in severe OSA patients, independent of other variables (age, gender, BMI). However, HT or TRET was not related to cardiovascular morbidity. Regarding oxygenation parameters, both MOD and ODI were associated with OAT and TAT; so cardiovascular diseases associated with OSA could be due to a higher number of deoxygenation attacks together with a continuous lower oxygen level. AHI alone is not capable of explaining cardiovascular morbidity in OSA, so the parameters including the duration of respiratory events are more useful in understanding OSA and its effects.

Mortality in OSA associated with low mean oxygen saturation, high ODI, and presence of comorbidities such as congestive heart failure, coronary artery disease, diabetes mellitus, and chronic obstructive pulmonary disease (COPD) (18). It is found that longer MAD was associated with lower oxygen saturation in patients with severe OSA (2). Also, longer MOAD, MMAD (mean mix apnea duration), MCAD (mean central apnea), MTAD, MHD were related to deeper mean oxygen desaturation in patients with severe OSA and this relationship was stronger, especially with MOAD and MTAD (5). Similarly longer OAT and TAT in mild, severe, and all OSA group and longer TRET in severe and all OSA group were associated with higher MOD in our study. So nocturnal hypoxemia is more related to time spent in apnea rather than hypopnea in severe and all OSA patients. Nocturnal hypoxia may be one of the reasons for the relation between OAT, TAT, and cardiovascular diseases in severe OSA patients.

Obesity is an important risk factor for the development of OSA. It was shown that as the degree of obesity increases the severity of OSA also increase (19). Also, the remission of OSA was found as 93.4% after gastric bypass surgery (20). However, BMI shortens the duration of apneas and hypopneas (5,6). This can be explained by the positive correlation between AHI and BMI. As AHI increases with

the same total sleep time, the duration of respiratory events decreases. In this study also higher BMI was associated with shorter OAT in mild and all OSA group and shorter mild, severe, and all OSA group.

CONCLUSION

In this study, the parameter, time spent in respiratory events, was evaluated, which include the number and duration of respiratory events together. Cardiovascular diseases were higher in severe OSA patients who have higher OAT and TAT. However, this relationship does not exist with AHI alone in the same group. Also, no relationship was found between the time spent during respiratory events and cardiovascular diseases in mild and moderate OSA patients. Therefore, to better understand the effects of OSA in terms of accompanying morbidities (cardiovascular diseases and others), it can be useful to use parameters including the duration of respiratory events in addition to AHI alone.

The limitations of this study were being retrospective, single-center study, and also having a small study population. Cardiovascular diseases of the patients were screened retrospectively only from the medical record system. There is still a need for further prospective, large scale, controlled studies to examine the relationship between the time spent during respiratory events and other parameters like comorbidities especially cardiovascular complications associated with OSA.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The study was approved by the Health Sciences University Bursa Higher Specialization Education and Research Ethics Committee (2011-KAEK-25 2019/10-24).

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