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The Clinical Characteristics of Obstructive Sleep Apnea Patients with a Previous Cardiovascular Event

Kardiyovasküler Olay Öyküsü Olan Obstrüktif Uyku Apnesi Hastalarının Klinik Özellikleri

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Abstract

Objective: Obstructive sleep apnea (OSA) and cardiovascular diseases have some common pathophysiologic characteristics and effects on the outcomes of each other. This study is conducted to determine the characteristics of obstructive sleep apnea patients with a history of a cardiovascular event.

Materials and Methods: For this multicenter study, the patients with obstructive sleep apnea [apnea-hypopnea index (AHI) >5/hour] who had a history of coronary angioplasty, coronary bypass grafting, or cerebrovascular event after the onset of the symptoms related to OSA were recruited as the study group. The control group included patients without a history of a cardiovascular event. The weight, subjective sleep duration, smoking, and menopausal status, and the presence of comorbidities before and after the cardiovascular event were also questioned during the follow-up visits and by phone calls. This data was compared with the control group.

Results: This multicenter study comprised 281 patients (100 study group and 181 control group), 83% of whom had moderate/severe obstructive sleep apnea. Age, family history for cardiovascular event and, Epworth sleepiness scale score were statistically higher in the study group ($p<0.001$). Polysomnographic data showed that the study group had higher central AHI ($p=0.002$), non-supine AHI ($p=0.017$) and lower NREM3% ($p=0.001$), mean and minimum oxygen saturation ($p=0.002$). A subgroup analysis proved that polysomnographic data, which had statistically significant differences, can vary according to gender.

Conclusion: The results of this study guide for phenotyping obstructive sleep apnea patients with cardiovascular events. It has also been shown that cardiovascular events may have different effects on sleep parameters in women.

Keywords: Cardiovascular event, female OSA, obstructive sleep apnea syndrome, phenotype, polysomnography

Öz

Amaç: Obstrüktif uyku apnesi (OUA) ve kardiyovasküler hastalıkların bazı ortak patofizyolojik özellikleri ve birbirlerinin sonuçları üzerinde etkileri vardır. Bu çalışma, kardiyovasküler olay öyküsü olan OUA hastalarının özelliklerini belirlemek amacıyla yapılmıştır.

Gereç ve Yöntem: Bu çok merkezli çalışma için OUA ile ilgili semptomların başlamasından sonra koroner anjiyoplasti, koroner baypas greftleme veya serebrovasküler olay öyküsü olan OUA hastaları [apne-hipopne indeksi (AHİ)>5/saat] çalışmaya dahil edildi. Kardiyovasküler olay öyküsü olmayan hastalar kontrol grubuna, dahil edildi. Kardiyovasküler olay öncesi ve sonrası ağırlık, sübjektif uyku süresi, sigara, menopoz durumu ve komorbidite varlığı da takiplerde ve telefon görüşmelerinde sorgulandı. Bu veriler kontrol grubu ile karşılaştırıldı.

Bulgular: Bu çok merkezli çalışmaya, %83'ü orta/şiddetli OUA olan 281 hasta (100 çalışma grubu ve 181 kontrol grubu) dahil edildi. Yaş, ailede kardiyovasküler olay öyküsü ve Epworth uykululuk ölçeği puanı, hasta grubunda kontrol grubuna göre istatistiksel olarak anlamlı daha yüksek bulundu ($p<0,001$). Polisomnografik veriler, hasta grubunda kontrol grubuna kıyasla santral AHİ ($p=0,002$), non-supin AHİ ($p=0,017$) değerlerinin daha yüksek; NREM3 uyku yüzdesi ($p=0,001$), ortalama ve minimum oksijen satürasyonu ($p=0,002$) değerlerinin ise daha düşük olduğunu göstermiştir. Alt grup analizi ile istatistiksel açıdan anlamlı farklılıklar gösteren polisomnografik verilerin cinsiyete göre değişebildiği görülmüştür.

Sonuç: Bu çalışmanın sonuçları, kardiyovasküler olay öyküsü olan OUA hastalarının fenotipik özelliklerini ortaya koymaktadır. Ayrıca kardiyovasküler olayların kadınlarda uyku parametreleri üzerinde farklı etkileri olabileceğini de göstermektedir.

Anahtar Kelimeler: Kardiyovasküler olay, kadın OUA, obstrüktif uyku apne sendromu, fenotip, polisomnografi

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Introduction

Obstructive sleep apnea (OSA) accompanies 45-70% of ischemic heart diseases and is associated with increased mortality and morbidity in cardiovascular disease (CVD) (1,2). In OSA, intrathoracic pressure fluctuations, intermittent hypoxia, sleep fragmentations, and increased sympathetic activity are held responsible for CVD.

The physiological effects of OSA on the cardiovascular system are based on hypoxia and hypercapnia caused by repeated apneas and hypopneas during sleep which triggers pulmonary arterial vasoconstriction. The preload of the ventricles increases secondary to the negative intrathoracic pressure and left ventricular compliance decreases due to the interventricular septal shift toward the left ventricle. These changes result in left ventricular dysfunction and are also associated with increased sympathetic activity leading to adverse cardiac outcomes. Besides, endothelial dysfunction, systemic inflammation, oxidative stress, and metabolic dysregulation contribute to injury in coronary arteries (3,4).

It is noted that despite the same clinical properties, some patients who were admitted to sleep clinics had a history of cardiovascular events (CVE) while most of them do not. OSA and CVE share some common risk factors, such as male gender, advanced age, obesity, smoking, and use of alcohol. Hyperlipidemia (HL), diabetes mellitus, and hypertension (HT), which are comorbidities of OSA are also involved in the pathogenesis of CVEs. The effect of these confounding factors on cardiovascular outcomes in patients with OSA is not fully elucidated (5).

In the last decades, there have been some revolutionary changes in our understating of OSA. Recent studies focusing on the pathophysiologic and clinic phenotypes of OSA have represented valuable results improving prognostication, understanding of mechanisms, and treatment approaches. The clinical phenotypes that have been described so far can be listed as minimally symptomatic patients, patients with excessive daytime sleepiness (EDS), disturbed sleep/insomnia, and with obesity, cardiovascular or neurologic comorbidities (6,7). This approach has provided insight into the heterogeneity of OSA. Furthermore, the recognition of the sex-related differences in pathophysiology and presentation of OSA leads to the researches for the new screening and diagnostic tools of OSA in women. The new treatment algorithms for female OSA patients have also been a point of scientific interest (8).

The primary aim of this study is to determine the demographic, clinical, and polysomnographic characteristics of OSA patients with a history of a cardiovascular event. As a secondary end-point, it was planned to cover the characteristics of female OSA patients with CVE, separately.

Materials and Methods

Patients and study design

This multi-center study was designed in a cross-sectional, retrospective format. The study population consists of the patients diagnosed with OSA between June 2019 and June 2020. The patients were consecutively recruited from 7 sleep centers in Turkey. Those with an apnea-hypopnea index (AHI) greater than 5 in the full-night polysomnographic evaluation were accepted as OSA. The patients aged <18, working in shifts, using drugs that may affect sleep (antidepressants, antiepileptic, antipsychotics, hypnotics), those with net sleep time <180 minutes in the polysomnographic evaluation, those with neuromuscular diseases, thyroid dysfunction, malignancy, or chronic kidney disease were excluded. The patients with available data were divided into two groups: Those who had a history of CVE (coronary angioplasty, coronary bypass grafting, or cerebrovascular event) after the onset of the symptoms related to OSA (snoring, EDS, or witnessed apnea) were recruited as the study group and the patients without a history of CVE were included in the control group. The patients who had a history of CVE before the onset of OSA-related symptoms were excluded (Figure 1).

Height, weight, body mass index (BMI), neck-waist-hip circumferences, Epworth sleepiness scale (ESS) score, subjective sleep duration, comorbidities (HT, diabetes, HL, chronic obstructive pulmonary disease and asthma), smoking history, menopause status, family history for CVE and polysomnographic data were recorded from patients' files. EDS was defined when the total score was 10 or more on ESS that was validated in Turkish (9). The study parameters that were missing in the patients' files, if any, were completed during the control visits of the patients or by phone calls. The values regarding the status

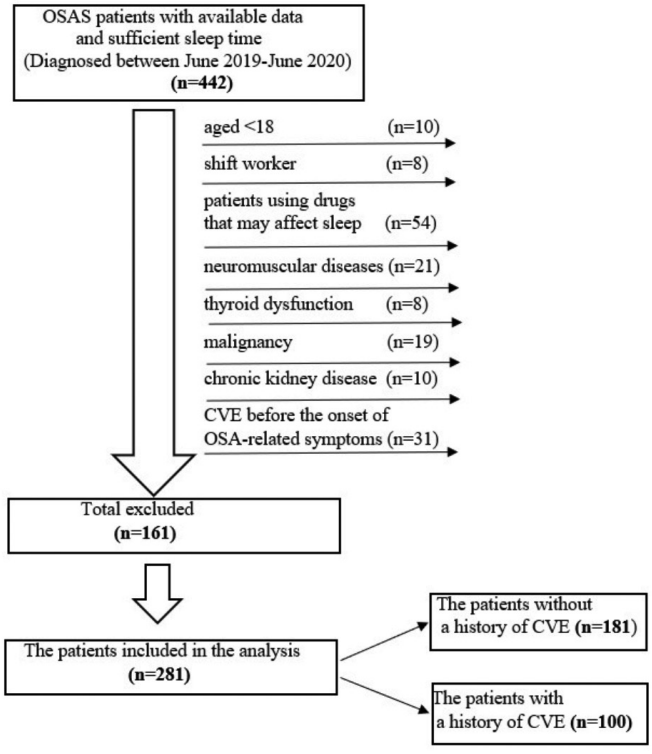

Figure 1. The flowchart of the study

CVE: Cardiovascular events, OSA: Obstructive sleep apnea

of the patient after the onset of CVE were referred to as post-CVE data.

The values before the onset of CVE (pre-CVE data) were also recorded for the parameters including weight, smoking status, subjective sleep time, and menopause status of those with a history of CVE. Also, the follow-up periods for comorbidities were questioned to determine the patients diagnosed before CVE (pre-CVE data). The post-CVE data was obtained during the first admission to the sleep clinic, the pre-CVE data were based on the patients' declarations. All data were analysed using only the values regarding the status of the patient after the onset of CVE (post- CVE data).

Measurements

The results of nocturnal polysomnography (NPSG) were analyzed manually by the criteria of the American Academy of Sleep Medicine (AASM) Scoring Manual Version 2.2 (10). All NPSGs were performed as full-night in-lab sleep study with a digital system which is in use in each center (Neuron-Spectrum EEG and EP neurophysiological system version 1.6.9.6, Neurosoft, Russia; Compumedics voyager digital ımaging E-series system Compumedics Ltd, Melbourne, Victoria, Australia; Grass comet-plus NATUS, system version 4.5.3.23, USA; Phillips Alice 6 NDXS, system version 3.9.4, USA; Embla N7000 device, Medicare, Iceland). All centers were using the standard sample rate and filtering for the signals that were recommended by AASM (10).

The conventional channels used for NPSG were as follows: Four channels of electroencephalography, two channels of electrooculography, one channel of chin electromyography, thermistor and nasal pressure transducer monitoring to measure airflow, thoracic and abdominal wall motion monitoring to measure respiratory effort, pulse oximetry to measure oxygen saturation, electrocardiography, and a microphone to record snoring.

The subjective sleep time was questioned into three categories: <6 hours/night, 6-8 hours/night, and >8 hours/night. The normal subjective sleep time was assumed as 6-8 hours/night.

Statistical Analysis

Statistical analyses were performed by using SPSS for Windows 21 software. The normality tests including using histograms, the ratio of the standard deviation to mean, and the Kolmogorov-Smirnov test were performed for all the variables. The normally distributed variables were presented as mean ± standard deviation. The randomly distributed variables were presented as median (25^{th}-75^{th} percentile). Nominal variables were presented as numbers and percentages. Mann-Whitney U test or Student's t-test was performed to compare the distribution of the two groups for numerical data. A chi-square test was used to examine the difference between groups for categorical variables. The proportions of comorbidities, active smoking, post-menopausal status, OSA-related major symptoms, and normal subjective sleep time (6-8 hours/night) were presented as percentages before CVE (pre- CVE data) and at the time of application to the sleep laboratory (post-CVE data). These proportions between pre and post-CVE data were compared by the McNemar test. For the multivariate analysis, the possible clinical parameters identified with univariate analysis were entered into the logistic regression analysis for phenotyping OSA with CVE. Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. P-value <0.05 was considered as statistically significant.

The study protocol was approved by the Ethical Committee at Afyonkarahisar University of Health Sciences (6/11/2020, 2011-KAEK-2). All procedures performed in this study were under the ethical standards of the institutional review board and with the 1964 Helsinki Declaration and its later amendments. Written and/or oral informed consent was obtained from all individual participants included in the study for the usage of their data.

Results

A total of 281 patients diagnosed with OSA following the criteria of the study were included in the study. Moderate-severe OSA was present in 83% of the patients. Among the subjects, 100 patients had a previous CVE history (study group), with only 2 being cerebrovascular events, and 181 had no history of CVE (control group). The gender distribution of the study group was similar to that of the control group. Age (58.1 vs 51.9, p<0.001), neck circumference (42.7 vs 41.2, p=0.006) and, the rate of family history for CVD (67% vs 31.3%, p<0.001) were higher in the study group. Among the anthropometric measurements, only neck circumference was statistically different between the groups at the time of admission. Follow-up times for the comorbidities were also statistically the same between study and control groups. The prevalence of HT (75% vs 42%, p<0.001) and HL (40% vs 16%, p<0.001) in the study group were statistically higher in ratio. Snoring was the most common symptom in both groups. Although the rate of sleep-related symptoms was statistically the same between the groups, the duration of these symptoms and the ESS score (11 vs 8) at the time of polysomnographic evaluation were higher in the study group (p<0.001) (Table 1).

However, multivariate analysis including possible characteristics for OSA with CVE revealed that the higher duration for sleep-related symptoms was dependent on the other factors included in the model. Age (p=0.006), ESS score (p=0.008) and, family history (p=0.006) preserved statistical significance in the multivariate analysis (Table 2).

Additionally, it was observed that the symptoms of EDS and witnessed apnea increased after CVE in the study group (p<0.001). In the study group, it was found that menopausal status and subjective sleep duration before and after CVE were similar, but after CVE almost half of the patients quit smoking and the rates of comorbidities increased significantly (Table 3).

Of the patients in the study group, 69 (69%) stated that there was no change in their weight after CVE, 20 (20%) gained more than 10% after the event, and 11 (11%) lost more than 10% weight.

Regarding the polysomnographic findings, compared to the control group, the percentage of deep sleep (p=0.001) and the mean and minimum oxygen saturation by pulse oximetry

(SpO_2) values (p=0.002 for both) were significantly lower in patients with a history of CVE, while non-supine AHI (p=0.017), and central apnea index (p=0.002) were significantly higher (Table 4).

Evaluation of PSG data for each gender revealed that minimum and mean SpO_2% levels were lower in study groups compared to the control groups in both genders. nREM1%, AHI, non-REM AHI, non-supine AHI, and hypopnea index were significantly higher in females with a history of CVE, whereas males with no history of CVE had a significantly lower percentage of deep sleep and higher central apnea index (p<0.05 for all) (Table 5).

Discussion

This study reveals the clinic and polysomnographic characteristic of a phenotype of OSA that consists of the patients with a prevalent CVE. Our results prove that the patients with this phenotype tend to delay in applying to sleep clinics. The sleep-related symptoms and other comorbidities seem to be more evident after CVE. The nocturnal polysomnographic data from this study clarifies the higher hypoxic burden of this group of patients with more non-positional and central respiratory events. Inclusion of the patients with pre-existing sleep-related symptoms does not prove, albeit favors the existence of OSA before CVE. Almost all the patients in the study group had the

Table 1. Demographic and clinical characteristics

	Study group (n=100)	**Control group (n=181)**	**p**
	n (%)	**n (%)**	
	Median (25^{th}-75^{th} percentile)	**Median (25^{th}-75^{th} percentile)**	
	Mean ± SD	**Mean ± SD**	
Age (years)	58.1±9.1	51.9±10.1	**<0.001**
Female gender	28 (28%)	66 (36.5%)	0.150
Postmenopausal status	24 (88.9%) n=27	46 (70.8%) n=65	0.064
Smoking status (active)	30 (30%)	36 (19.9%)	0.056
Family history of CVE	65 (67%)	55 (31.3%)	**<0.001**
BMI (kg/m^2)	31.7 (29.5-36.5)	31.6 (28.4-35.3)	0.310
Neck circumference (cm)	42.7±3.9 n=83	41.2±4.1 n=172	**0.006**
Waist circumference (cm)	112 (101-123) n=91	109 (100-118) n=178	0.118
Hip circumference (cm)	113 (109-120) n=91	113 (104.5-123) n=177	0.446
Waist/hip ratio	0.98±0.08	0.96±0.08	0.097
Hypertension	75 (75%)	76 (42%)	**<0.001**
Duration (years)	8 (5-15)	5 (3-10)	0.101
Diabetes mellitus	25 (25%)	33 (18.4%)	0.195
Duration (years)	10 (4.5-15)	10 (4-11)	0.623
Hyperlipidemia	40 (40%)	29 (16.0%)	**<0.001**
Duration (years)	5 (2-10)	5 (2-8)	0.203
Respiratory diseases	25 (25%)	34 (18.8%)	0.249
Duration (years)	10 (2.3-10)	8 (5-16.3)	0.308
Snoring	100 (100%)	178 (98.3%)	0.555
Duration (years)	15 (10-20)	10 (4-15)	**<0.001**
EDS	80 (80%)	134 (74%)	0.261
Duration (years)	6 (5-10)	3 (2-7)	**<0.001**
Witnessed apnea	84 (84%)	158 (87.3%)	0.445
Duration (years)	5 (4-10)	4 (2-8)	**<0.001**
ESS score	11 (6-17) n=99	8 (4.3-12) n=180	**<0.001**
Normal subjective sleep duration (6-8 hours)	61 (61%)	122 (67.8%)	0.215

BMI: Body-mass index, EDS: Excessive daytime sleepiness, ESS: Epworth sleepiness scale, SD: Standard deviation, CVE: Cardiovascular events

symptom of snoring which is claimed as the symptom with the higher sensitivity to predict the presence of OSA (11).

The results showed that although they are as symptomatic as the control group, the patients with CVE were admitted to sleep clinics at older ages. This means that the OSA patients with CVE are diagnosed and treated for OSA at older ages and after a longer period of symptoms. The results of the prospective observational cohort study of Baratta et al. (12) supported that the risk of cardiovascular and cerebrovascular events increases 3.5 folds more for patients with severe OSA. Increasing public awareness for the importance of OSA-related symptoms may provoke early detection of OSA and reduce the risk for CVE.

Our results clarified that the symptoms of EDS and witnessed apnea became more frequent after CVE. Despite higher ESS scores in the study group, the ratio of the patients with the complaint of EDS is statistically the same for both groups. The factors that make these patients ignore their sleep-related symptoms must be further investigated.

The comorbidities including diabetes, HT, HL, and respiratory diseases were mostly diagnosed after CVE and post-CVE percentages of HT and HL exceeded the control group. These results may point out that CVE may lead to the diagnosis of occult comorbidities and make OSA-related symptoms overt. The ratio of family history for CVE in the study group was more than two-folds of the control group. Despite the statistical similarity, the rate of active smoking was higher in the study group (30% vs 19.9%, p=0.056). It was also found that nearly half of the patients in the study group quited smoking after CVE. These results lead to a recommendation for determining the cardiovascular risk of OSA patients by using active smoking and family history instead of comorbidities and OSA-related symptoms. Gami et al. (13) showed that the family history of premature death from coronary artery disease is more prevalent in people with OSA independently of gender, BMI, and personal history of coronary artery disease. Our results obtained from multivariate analysis also indicated that the family history of CVDs, older age, and higher ESS score can be referred as the clinical characteristics of OSA patients with CVE.

It has been proven that both short and long sleep duration is associated with all-cause mortality and cardiovascular mortality, especially for men (14,15). In this study, subjective sleep duration or sleep time during polysomnography did not show a statistically significant difference between the groups. In a review about the relationship between subclinical CVDs and sleep duration and quality, results pointed out a strong association for which the mechanism should be clarified (16). Although the previous studies about the sub clinic CVD have some conflicting results due to heterogeneity in populations and methods, the non-significant results about the sleep duration in our population may be explained by the unknown ratio of sub clinic CVD in the control arm.

In this study, the differences in anthropometric measurements including neck, hip, waist circumferences, waist/hip ratio, and BMI were investigated. Neck circumference emerged as the only anthropometric measurement which was statistically higher in the study group. 20% of the study group declared a clinically important weight gain after CVE. This fact can be seen as a reason for increasing comorbidities and OSA-related symptoms after CVE.

A meta-analysis concluded a strong association between OSA and stroke, whereas its relationship with ischemic heart disease and cardiovascular mortality seemed to be significant in studies including mostly male patients (17). AHI is defined as one of the factors related to the incident risk of CVE among OSA patients. A large-scale study proved that hypopneas associated with at least 4% desaturations are independent risk factors for

Table 2. Multivariate analysis for the characteristics of OSA patients with a previous cardiovascular event

	OR (95% CI)	p
Gender	0.82 (0.25-2.71)	0.746
Age (years)	1.09 (1.02-1.15)	**0.006**
Neck circumference (cm)	1.16 (0.99-1.35)	0.061
Waist circumference (cm)	0.99 (0.96-1.04)	0.845
Family history of CVE	3.24 (1.33-7.88)	**0.010**
Smoking status (active)	2.44 (0.88-6.73)	0.085
Snoring duration (years)	1.01 (0.95-1.08)	0.743
EDS duration (years)	0.99 (0.90-1.09)	0.832
Witnessed apnea duration (years)	1.01 (0.90-1.13)	0.851
Diabetes mellitus (%)	1.09 (0.36-3.30)	0.885
Hypertension (%)	2.45 (0.84-7.10)	0.100
Hyperlipidaemia (%)	1.56 (0.60-4.02)	0.404
ESS score	1.12 (1.03-1.22)	**0.008**
AHI	0.99 (0.96-1.04)	0.400

CI: Confidence interval, EDS: Excessive daytime sleepiness, ESS: Epworth sleepiness scale, CVE: Cardiovascular events, OR: Odds ratio, AHI: Apnea-hypopnea index, OSA: Obstructive sleep apnea, p-value for Hosmer-Lemeshow test for this model is 0.140

Table 3. Comparisons of pre and post-CVE data for demographic and clinical variables

	Pre-CVE data[1]	Post-CVE data[2]	p
	n (%)	n (%)	
Postmenopausal status	21 (77.8%)	24 (88.9%)	0.250
Smoking status (active)	57 (57%)	30 (30%)	<**0.001**
Hypertension	46 (46.5%)	74 (74.7%)	<**0.001**
Diabetes mellitus	18 (18%)	25 (25%)	**0.016**
Hyperlipidemia	14 (14.3)	40 (40.8%)	<**0.001**
Respiratory diseases	9 (9.2%)	24 (24.5%)	<**0.001**
Snoring	97 (97%)	100 (100%)	-
EDS	51 (51%)	80 (80%)	<**0.001**
Witnessed apnea	53 (53%)	84 (84%)	<**0.001**
Normal subjective sleep duration (6-8 hours)	64 (64%)	61 (61%)	0.664

CVE: Cardiovascular event, EDS: Excessive daytime sleepiness [1]: Pre-CVE data represents the status of the study group before the onset of CVE. The data respresenting the status of the patients before CVE (pre-CVE data) was calculated via the symptom duration declared by the patient, [2]: Post-CVE data represents the status of the study group after the onset of CVE

CVDs (18). In contrast, our results did not show a difference in the index of 3% desaturations or hypopneas defined by 3% desaturations between groups. However, the levels of minimum and mean SpO_2 during sleep were found to be lower in the patients with a previous CVE.

Our study presents post-CVE polysomnographic characteristics that can be assumed as the consequences of CVE on sleep parameters. The large-scale study of Chami et al. (19) elucidated that total AHI, obstructive and central apnea indices show a greater increase in OSA patients with incident CVD than those without CVD according to a 5-year follow-up data with two PSGs. Likewise, our study showed that OSA patients with CVE had higher central apnea imdex. Additionally, analysis of our data ended up with higher non-supine AHI and lower mean and minimum SpO_2 in the study group. Non-positional OSA with nocturnal hypoxemia can be regarded as a common polysomnographic profile of OSA patients with prevalent CVE.

The large-scale study of Aurora et al. (20) in which the patients with REM-related OSA were included also compared the characteristics of the patients with and without prevalent CVD. Likewise, participants with prevalent CVD were found to be older and had a greater proportion of former smokers. They also provided strong evidence demonstrating that the patients who have prior CVD and severe REM-related OSA are more likely to have recurrent CVE (20). Contrary to these results, the proportion of REM-related OSA and REM AHI in our study group with prevalent CVE and control arm of our study were statistically the same. However, non-positional AHI was found to

Table 4. Polysomnographic characteristics			
	Study group n=100	**Control group n=181**	**p**
	n (%)	**n (%)**	
	Mean ± SD	**Mean ± SD**	
	Median (25^{th}-75^{th} percentile)	**Median (25^{th}-75^{th} percentile)**	
TST	381.3 (332-408.2)	388 (337.9-415)	0.828
WASO	56.9 (28.5-93.4) n=99	47.5 (25.6-69.6) n=167	0.062
Sleep efficiency (%)	83.6 (74.5-91.9)	85.7 (76.4-92.5)	0.337
Sleep latency (min)	8 (3-23.6)	11 (5-27.8)	0.084
REM latency (min)	115.5 (58.6-175.4)	130.5 (79.5-189)	0.236
NREM1 (%)	9.1 (4.3-14.9)	7.3 (4.1-12.1)	0.392
NREM2 (%)	57.8 (50.5-65.4)	56.5 (44.4-67.1)	0.227
NREM3 (%)	14.3 (6.8-22.0)	19.5 (11-29.4)	**0.001**
REM (%)	13.4 (9.8-18.2)	14.3 (9.2-19.7)	0.553
AHI	37.4 (21.9-59.9)	29.0 (15.8-50.7)	0.058
Mild OSA	15 (15%)	32 (17.7%)	0.564
Central apnea index	0.8 (0.2-3.6)	0.3 (0-1.7)	**0.002**
Obstructive apnea index	6.4 (1.5-22.2)	5.9 (1.1-16.9)	0.758
Hypopnea index	19.6 (11.7-31.9)	16.6 (9.7-25.4)	0.080
REM AHI	35.6 (19.5-58.9)	32.2 (13.6-56.2)	0.241
NREM AHI	36.7 (18.8-63.1)	27.7 (14.9-54.9)	0.108
Supine (%)	35.7 (14.8-87.8) n=86	42.2 (23.0-71.2) n=144	0.533
Supine AHI	50.5 (24.2-77.5) n=86	45.5 (21.1-71.6) n=144	0.365
Non-supine AHI	31.6 (13.5-56.1) n=86	19.5 (7.2-46.8) n=144	**0.017**
REM-related phenotype	17 (17%)	31 (17.1%)	0.992
ODI 3%	32.7 (15.6-51.5) n=95	26.4 (14.6-48.4) n=166	0.251
Mean SpO_2	90 (88-92)	91.9 (90-93.9)	**0.002**
Minimum SpO_2	76 (66-83.8)	80 (72.3-85)	**0.002**
Sleep-related hypoxemia	23 (23%)	25 (13.9%)	0.053

AHI: Apnea-hypopnea index, CVE: Cardiovascular event, ODI: Oxygen desaturation index, REM: Rapid eye movement, SD: Standard derivation, SpO_2: Arterial oxygen saturation by finger pulse oximetry, TST: Total sleep time, WASO: Wake after sleep onset, OSA: Obstructive sleep apnea

be higher in the study group. This result draws attention to the associations between prevalent CVE and non-positional OSA.
The prospective longitudinal the sleep heart health study demonstrated that middle-aged men with severe OSA are at risk for coronary heart disease (21,22). On the other hand, the female patients and older men with OSA are not reported as a risk group for coronary heart disease. A subgroup analysis evaluating the characteristics of the male/female OSA patients with a previous CVE revealed a gender effect on the polysomnographic parameters. AHI values for males in our study group were statistically the same as the control arm. The female OSA patients with previous CVE had higher AHI, hypopnea index, non-REM, and non-supine AHI than female controls who have similar anthropometric values and menopausal status. The hormonal status of women varies throughout the life span including pregnancy, reproductive, and postmenopausal periods. In addition to the hormonal changes, the fat distribution, upper airway anatomy, chemoreflex sensitivity, and respiratory plasticity in women are different than in men. These diversities of female OSA have clinical implications in terms of screening, diagnosis, and treatment (8). A recent study also showed that women with OSA were more likely to have CVD and diabetes (23). Our study reveals the polysomnographic characteristics of female OSA patients with cardiovascular comorbidity. Female OSA commonly presents with non-positional, REM-related hypopneas and respiratory effort-related arousals (8). In our study, the statistically significant differences in variables including AHI, hypopnea index, non-REM, and non-supine AHI in women suggest that CVE have different effects on sleep in women.

Study Limitations

As a limitation of this study, we did not perform cluster analysis. Univariate and multivariate statistical tests were used to show the differences of OSA patients with a prevalent CVE. The prognosis and treatment results of this group of patients must be further investigated to determine if it is a distinct phenotype of the OSA. The retrospective design of the study would not

Table 5. Polysomnographic characteristics (compared for each gender)

	Female study group n=28	Female control group n=66	p	Male study group n=72	Male control group n=115	p
	n (%)	n (%)		n (%)	n (%)	
	Median (25^{th}-75^{th} percentile)	Median (25^{th}-75^{th} percentile)		Median (25^{th}-75^{th} percentile)	Median (25^{th}-75^{th} percentile)	
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
TST	368.3 (328.5-402)	383.3 (334.2-409.4)	0.511	385 (337.2-410.5)	388 (339.3-419.5)	0.492
WASO	74.2 (33.6-105.3)	46.5 (20.3-70.5)	**0.051**	55.4 (24.7-85.5)	47.5 (28.1-69.6)	0.339
Sleep efficiency (%)	80.1 (70.8-89.5)	85 (75.8-92.8)	0.166	84.7 (74.5-93.1)	85.8 (76.9-92.5)	0.731
Sleep latency (min)	8 (4.5-22.1)	17 (4.5-35.5)	0.333	7.8 (2.5-23.6)	10 (5.5-23.4)	0.177
REM latency(min)	143.5 (72.5-196.3)	158.5 (108-239)	0.427	100.5 (57-161.8)	108.3 (70.3-162.8)	0.575
NREM1 (%)	9.1 (4.9-14.9)	5.1 (3.6-9.3)	**0.028**	9.1 (3-14.9)	8.9 (4.9-14.1)	0.603
NREM2 (%)	57.8 (48.5-66.7)	55.2 (45.1-62.7)	0.326	57.7 (50.8-65.3)	57.7 (42.8-67.9)	0.469
NREM3 (%)	14.8 (9.9-25.3)	21.4 (13.7-30.3)	0.072	13.8 (5.9-22.0)	17.8 (10.4-28)	**0.008**
REM (%)	11.7 (7.6-17.1)	13.3 (8.4-19.1)	0.232	14.6 (10.3-18.8)	15 (9.3-21)	0.877
AHI	39.5 (70.9-22.6)	21.8 (13.0-42.9)	**0.015**	35.4 (21.7-59.0)	31.4 (20.2-55.9)	0.730
Central apnea index	0.7 (0.03-1.9)	0.2 (0-1.2)	0.087	0.9 (0.2-6.2)	0.5 (0-2.5)	**0.021**
Obstructive apnea index	3.7 (0-25.5)	2.8 (0-5-13.2)	0.950	7.0 (2.4-19.1)	8.9 (1.8-18.8)	0.809
Hypopnea index	24.1 (15.0-37.1)	14.8 (9.5-22.9)	**0.011**	18.2 (10.7-30.1)	18.9 (9.7-26.9)	0.630
REM AHI	51.2 (29.3-64.8)	34.1 (14.1-58.6)	0.124	32.9 (18.3-55.1)	30.6 (13.4-55.6)	0.479
NREM AHI	36.2 (19.7-53.6)	19.9 (10.4-38.2)	**0.027**	37.2 (17-63.2)	31.7 (20.5-62.3)	0.891
Supine (%)	56 (15.6-90.5)	43.6 (12.5-39.7)	0.781	33.3 (14.1-84.6)	40.8 (23.7-70.2)	0.335
Supine AHI	42.1 (22.3-69.4)	20.7 (10.4-52.5)	0.137	61.7 (24.1-82.5)	61.1 (35.1-76.3)	0.955
Non-supine AHI	37.5 (23.9-55.5)	15.6 (5-33.2)	**0.010**	28.8 (12.8-57.2)	22.2 (7.9-59.8)	0.237
REM-related phenotype	4 (14.8%)	17 (25.8%)	0.252	13 (18.1%)	14 (12.2%)	0.265
ODI 3%	36.2 (15.9-50.6)	19.9 (10.6-52.6)	0.194	28.7 (15.5-51.8)	27.3 (15-45.8)	0.733
Mean SpO_2	90.5 (86-92)	91 (89-94)	**0.042**	90 (88-92)	92 (90-93.7)	**0.015**
Minimum SpO_2	75.5 (62.8-84)	82 (73-86)	**0.018**	76 (66.5-82.0)	80 (71.8-84)	**0.041**
Sleep-related hypoxemia	10 (35.7%)	13 (19.7%)	0.099	13 (18.1%)	12 (10.5%)	0.143

AHI: Apnea-hypopnea index, CVE: Cardiovascular event, ODI: Oxygen desaturation index REM: Rapid eye movement, SD: Standard derivation, SpO_2: Arterial oxygen saturation by finger pulse oximetry, TST: Total sleep time, WASO: Wake after sleep onset

let the determination of the independent risk factors for CVE in OSA population, either.

Conclusion

Despite the aforementioned limitations, this study showed that OSA patients with CVE have some diverse clinic and polysomnographic characteristics. The subgroup analysis of each gender also revealed the differences in female OSA patients with the previous CVE.

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Ethics

Ethics Committee Approval: The study protocol was approved by the Ethical Committee at Afyonkarahisar University of Health Sciences (6/11/2020, 2011-KAEK-2). All procedures performed in this study were under the ethical standards of the institutional review board and with the 1964 Helsinki Declaration and its later amendments.

Informed Consent: Written and/or oral informed consent was obtained from all individual participants included in the study for the usage of their data.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: S.Ş.D., F.A., Ş.Ç., A.C.P., N.S., Ö.E.D., Ö.Ö., A.A.G., S.B.S., H.A.Y., Design: S.Ş.D., F.A., Ş.Ç., A.C.P., N.S., Ö.E.D., Ö.Ö., A.A.G., S.B.S., H.A.Y., Data Collection or Processing: S.Ş.D., F.A., Ş.Ç., A.C.P., N.S., Ö.E.D., Ö.Ö., A.A.G., S.B.S., H.A.Y., Analysis or Interpretation: S.Ş.D., F.A., Writing: S.Ş.D.

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