Özgün Çalışma / Original Article

Ankara Eğt. Arş. Hast. Derg., 2022 ; 55(1) : 28-33
DOI:10.20492/aeahtd.984531

YENİ TANI ALAN OBSTRÜKTİF UYKU APNE SENDROMLU HASTALARDA FRAGMENTE QRS VARLIĞI İLE VENTRİKÜLER ARİTMİLER ARASINDAKI İLİŞKİ

THE RELATIONSHIP BETWEEN THE PRESENCE OF FRAGMENTED QRS AND VENTRICULAR ARRHYTHMIAS IN PATIENTS WITH NEWLY DIAGNOSED OBSTRUCTIVE SLEEP APNEA SYNDROME

Hayati EREN[1], Muhammed Bahadır OMAR[2], Ülker KAYA[1], Denizhan Kıvanç YILMAZ[3], Lütfi ÖCAL[4], Macit KALÇIK[5]

ÖZET

Amaç: Obstrüktif uyku apne sendromu (OUAS) olan hastalarda kardiyak aritmiler sık görülür. Miyokardiyal fibrozis, OUAS'lı hastalarda kardiyak yeniden şekillenmenin bileşenlerinden biridir. Elektrokardiyografide (EKG) fragmente QRS'nin (fQRS) miyokardiyal fibrozisin bir belirteci olduğu gösterilmiştir. Bu çalışmada OUAS'lı hastalarda fQRS ile ventriküler aritmiler arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmaya yeni OUAS tanısı almış ardışık 92 hasta alındı. Daha sonra polisomnografi laboratuvarında OUAS tanısı almayan 96 hasta kontrol grubu olarak alındı. Başvuru sırasında tüm hastalara EKG çekildi ve fQRS, iki bitişik EKG derivasyonunda ek R' dalgası veya S dalgasının çentiklenmesi/ayrılması olarak tanımlandı. Tüm hastalara polisomnografi testi sırasında 24 saatlik Holter monitörizasyonu yapıldı ve tüm kardiyak aritmiler kaydedildi.

Bulgular: Kontrollere kıyasla OUAS'lı hastalarda fQRS (%64,1'e karşı %9,3, p<0,001) ve kompleks ventriküler aritmilerin (VA)(%15,2'ye karşı %1,0, p<0,001) prevalansı anlamlı derecede yüksekti. Ayrıca, fQRS olan OUAS hastalarında kompleks VA prevalansı (%18,6'ya karşı %9,0, p<0,001) anlamlı olarak daha yüksekti. OUAS hastalarında fQRS varlığının (OR: 3,262 95 %GA: 1,443-7,376; p=0,004) ve AHİ şiddetinin (OR: 1,510 95 %GA: 1,343-1,698; p<0,001) bağımsız olarak kompleks VA ile ilişkili olduğu gösterilmiştir.

Sonuç: OUAS'lı hastalarda fQRS varlığı kompleks VA'lar ile ilişkilidir. Bu nedenle, OUAS hastalarında yüksek aritmi riski taşıyan hastaları belirlemek için fQRS'nin varlığı kullanılabilir.

Anahtar sözcükler: Fragmente QRS, Obstrüktif Uyku Apne Sendromu, Ventriküler aritmi, Elektrokardiyografi, miyokardiyal fibrozis

ABSTRACT

Aim: Cardiac arrhythmias are frequent among patients with obstructive sleep apnea syndrome (OSAS). Myocardial fibrosis is one of the components of cardiac remodelling in patients with OSAS. Fragmented QRS (fQRS) on electrocardiography (ECG) has been shown to be a marker of myocardial fibrosis. In this study, we aimed to investigate the association between fQRS and ventricular arrhythmias in patients with OSAS.

Material and Method: 92 consecutive patients who were newly diagnosed with OSAS were enrolled into the study. Then 96 patients who were not diagnosed with OSAS on polysomnography laboratory were included as a control group. ECG were performed in all patients on admission and fQRS was defined as additional R' wave or notching/splitting of S wave in two contiguous ECG leads. All patients underwent 24-hour Holter monitoring during the polysomnography test and all cardiac arrhythmias were noted.

Results: Prevalence of fQRS (64.1% vs 9.3%, p<0.001) and complex VAs (15.2 vs 1.0%, p<0.001) were significantly higher in patients with OSAS as compared to the controls. Also, prevalence of complex ventricular arrhythmias (VAs) (18.6% vs 9.0%, p<0.001) was significantly higher in OSAS patients with fQRS. It was shown that presence of fQRS (OR: 3.262, 95 %CI: 1.443-7.376; p=0.004) and AHI severity (OR: 1.510, 95 %CI: 1.343-1.698; p<0.001) to be independently associated with complex VAs in OSAS patients.

Conclusion: The presence of fQRS is associated with complex VAs in patients with OSAS. Therefore, the presence of fQRS may be used to determine patients at high risk for arrhythmia in OSAS patients.

Keywords: Fragmented QRS, Obstructive Sleep Apnea Syndrome, Ventricular arrhythmia, Electrocardiography, Myocardial fibrosis

[1] Elbistan State Hospital, Department of Cardiology, Kahramanmaraş, Turkey,
[2] Fatih Sultan Mehmet Training and Research Hospital, Department of Cardiology, Istanbul, Turkey,
[1] Elbistan State Hospital, Department of Cardiology, Kahramanmaraş, Turkey,
[3] Elbistan State Hospital, Department of Pulmonary Diseases, Kahramanmaraş, Turkey,
[4] Kosuyolu Kartal Heart Training and Research Hospital, Department of Cardiology, Istanbul, Turkey,
[5] Hitit University Faculty of Medicine, Department of Cardiology, Çorum, Turkey,

Makale Geliş Tarihi / Submitted: Ağustos 2021 / August 2021

Makale Kabul Tarihi / Accepted: Ocak 2022 / January 2022

Sorumlu Yazar / Corresponding Author:
Hayati EREN
Address: Department of Cardiology, Elbistan State Hospital, Karaelbistan, Kahramanmaraş, Turkey
Tel: +90 344 413 8001, GSM: +90 554 584 8743
E-mail: drhayatieren@hotmail.com ORCID: 0000-0002-2159-064X

Yazar Bilgileri /Author Information:
Muhammed Bahadır OMAR: 0000-0002-7234-6321, bahadir266@hotmail.com
Ülker KAYA: 0000-0002-6802-5672, ulker0511@gmail.com
Denizhan Kıvanç YILMAZ: 0000-0001-5851-7828, denizhankivanc@hotmail.com
Lütfi ÖCAL: 0000-0003-4059-0861, lutfiocal@hotmail.com
Macit KALÇIK: 0000-0002-8791-4475, macitkalcik@yahoo.com

The study protocol was approved by Ümraniye Training and Research Hospital Ethical Review Board (decision number and date: 200-17.06.2021)

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of upper respiratory tract obstruction during sleep and decreased arterial oxygen saturation.[1] While OSAS is a common respiratory disease that affects about 5% of the population, its main importance lies in cardiovascular complications such as heart failure, stroke, coronary artery disease, and hypertension.[2-5] One of the most common complications of OSAS is cardiac arrhythmia, and in recent years OSAS has been especially strongly associated with cardiac arrhythmia.[2-6-7] The fundamental mechanisms of arrhythmia development in OSAS patients are increased sympathetic tone, ventricular changes due to negative thoracic pressure, and intermittent hypoxia.[8] All of these mechanisms contribute to formation of fibrosis in myocardial tissue over time and this developing fibrosis tissue causes structural and electrical deterioration in myocardium, forming substrate tissue for the development of cardiac arrhythmia.[9-11] Ventricular arrhythmias (VAs) are especially common among these arrhythmias.[12-14]

Definition of fragmented QRS (fQRS) includes only the narrow complexes with the presence of initial R wave followed by an S wave and a terminal positive deflection (R') on a resting 12-lead ECG15. Several studies report that presence of fQRS is indicative of fibrosis in the ventricles and predicts arrhythmias in various diseases.[16-21] The presence of fQRS indicates changes in the direction of ventricular activation with scar tissue that can be a substrate for reentrant arrhythmias.

Previously, the mechanism of VAs and various parameters in predicting the development of VAs in OSAS patients have been studied. However, to the best of our knowledge, association between the presence of fQRS and ventricular arrhythmias in OSAS patients has not been studied before. Therefore in this study, we aimed to determine the relationship between the presence of fQRS and ventricular arrhythmias in patients with OSAS.

MATERIAL AND METHOD

Study population

This study was designed retrospectively and the study consisted of 92 consecutive outpatients who were newly diagnosed with OSAS and admitted to the polysomnography laboratory between January 2016 and May 2019 retrospectively. Patients with angina pectoris or acute coronary syndrome, central sleep apnea, pregnancy, rheumatic heart disease, heart failure (ejection fraction <50% in echocardiography), systemic or metabolic disease, untreated or uncontrolled hypertension, thyroid dysfunction, electrolyte imbalance, renal or liver failure, cancer, or diagnosed arrhythmia were excluded from the study. ECGs with typical bundle branch block, pace rhythm, or any kind of significant conducting abnormalities were also excluded. Subsequently, 96 consecutive patients who were not diagnosed with OSAS in the polysomnography laboratory were determined as the control group. Also, all patients were not receiving CPAP or any OSAS treatment because they were newly diagnosed. The study protocol was approved by Ümraniye Training and Research Hospital Ethical Review Board (decision number and date: 200-17.06.2021) in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Polysomnography and Definition of OSAS

Sleep evaluations of all patients were conducted by a sleep specialist. Initial diagnostic polysomnograms, which included electroencephalogram, electrooculogram, electromyogram, electrocardiogram, thoracoabdominal excursions, pulse oximetry, and naso-oral airflow were reviewed. Apnea-hypopnea index (AHI) was calculated as the sum of apneas and hypopneas per hour of sleep. Awake oxygen saturation, mean nocturnal oxygen saturation, and lowest nocturnal oxygen saturation were also documented. According to American Academy of Sleep Medicine criteria, AHI ≥5 was diagnostic for OSAS22. Mild, moderate, and severe OSAS were defined as AHI between 5-15 events/h, 15-30 events/h, and >30 events/h respectively. In addition, patients with AHI <5 were defined as not OSAS22.

Laboratory Measurements

Venous blood samples were collected after 12-hours of fasting by a clean puncture of an antecubital vein blood samples taken on admission were used for laboratory assessment. The definitions of DM, HT, HL and other diseases were made according to appropriate guidelines (World Health Organization criteria). Each patient's height (cm) and weight (kg) were measured and body mass index (BMI) was calculated.

Electrocardiography and Definition of fQRS

Twelve-lead ECG was obtained at 25 mm/s paper speed, with a 0.16–100 Hz filter range and 10 mm/mV height from all patients in supine position. ECG was analyzed by two independent cardiologists (L.Ö, H.E) blinded to the patient characteristics. fQRS was defined as the presence of an additional R wave (R' prime) or notching of the R or S wave in two or more contiguous leads of those representing anterior (V1–V5), lateral (I, aVL, V6), or inferior (II, III, aVF) myocardial segments and QRS duration of <120 ms19 (Figure 1).

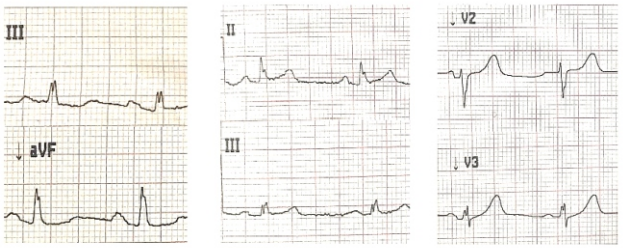

Figure 1: Examples of contiguous electrocardiography leads revealing the presence of QRS fragmentation in three different patients.

OSAS patients were divided into two groups according to the presence of fQRS.

Echocardiography

All patients underwent transthoracic echocardiography using a PHILIPS AFFINITI 50C system (Philips Medical Systems, Netherlands) with a 3.5 MHz transducer in the left lateral position. Quantitative echocardiography was performed following consensus guidelines from the European Association of Cardiovascular Imaging and American Society of Echocardiography23. Two-dimensional, pulsed, and continuous wave, tissue doppler and color Doppler echocardiography were performed. Left atrial diameter (LAD), interventricular septal thickness (IVST), posterior wall thickness (PWT), and left ventricular end-systolic (LVESD) and end-diastolic diameters (LVEDD) were measured by M-Mode on the parasternal long-axis view. The left ventricular ejection fraction (LVEF) was calculated using Biplane Simpson's method23. Left ventricular mass (LVM) was calculated based on Devereux formula [LVM = 0.8 (1.04 (IVST + LVEDD + PWT)3 – (LVEDD)3) + 0.6], and body surface area was estimated using Mosteller formula [body surface area = (height (cm) x body weight (kg)/3600)1/2]. LVM was divided by body surface area to estimate left ventricular mass index (LVMI). During apical four-chamber imaging, the diastolic transmitral flow waves (E and A velocities) were measured. Em and E/Em were calculated by tissue doppler echocardiography.

Detection and Classification of Ventricular Arrhythmias

Frequency of VAs was investigated using 24-hour-Holter monitoring device (Mortara H-scribe Compact Digital Holter, United States). All patients underwent 24-hour Holter monitoring during the polysomnography test. Results of Holter monitoring were examined by two experienced cardiologists. All ventricular ectopic beats, couplets, triplets, and ventricular tachycardia episodes were reviewed. Rate and duration of each episode were noted. VAs were classified according to a modified version of the Lown grading system24. VAs were classified as: Grade 0 as the absence of premature ventricular contractions (PVCs); Grade 1 as occasional and isolated and <30 PVCs in all given hours of monitoring; Grade 2 as isolated and frequent and >30 PVCs in any hour of monitoring; Grade 3 as multifocal PVCs; Grade 4a as the presence of couplets; and Grade 4b as ventricular tachycardia (VT) defined as three or more PVCs in succession with a frequency of over 100 beats/min. Lown class 3 or higher VAs were considered as complex VAs24,25.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows,

Version 22.0 (IBM Corp. Armonk, NY). Normality distribution of continuous variables was tested with the Kolmogorov-Smirnov test. Continuous variables with normal distribution were expressed as mean ± standard deviation while variables without normal distribution were expressed as median (25th–75th percentiles). Categorical variables were expressed as frequencies and percentages. Continuous variables were compared using Student's t-test or the Mann-Whitney U test when applicable. Chi-square or Fisher exact test was used for comparison of categorical variables. The inter-observer agreement was 94% and 96% for the diagnosis of fQRS and complex VAs respectively. A two-tailed p value <0.05 was considered statistically significant for all statistical analyses. Logistic regression analysis was performed to identify independent association between the presence of fQRS and complex VAs in OSAS patients. In multiple logistic regression analysis, effect size was adjusted for variables with a univariate significance level of ≤ 0.1. Adjusted odds ratios (OR), along with their 95% confidence intervals (CI) were presented.

RESULTS

A total of 92 OSAS patients (64.1% male; mean age: 55.9±7.5 years) and 96 control subjects (60.4% male; mean age: 55.2±7.2 years) were included in this study. fQRS was detected on ECG recordings of 59 (64.1%) OSAS patients and 9 (9.3%) controls (p<0.001). Demographic, laboratory, and echocardiographic characteristics of the study population are presented in Table 1. There was no significant difference between study groups in terms of age, gender, the prevalence of dyslipidemia, diabetes mellitus, coronary artery disease, smoking status, and laboratory parameters except for hemoglobin. However, the prevalence of hypertension (HT) (p=0.007), BMI (P<0.001), systolic blood pressure (SBP) (p=0.004) and diastolic blood pressure (DBP) (p=0.001) were significantly higher in the OSAS group as compared to the control group.

There was no significant difference between the groups regarding the echocardiographic parameters including LVEDD, LVESD, LAD, and LVEF values. However, IVST, PWT, LVMI, E/Em ratio, and A wave values were significantly higher in the OSAS group (all p value <0.001). E/A ratio (p<0.001) and E (p<0.001) wave was significantly lower in the OSAS group (Table 1).

Table 1. Baseline characteristics of the study groups

	OSAS (n=92)	Control (n=96)	p value
Demographic parameters			
Age (years)	55.9±7.5	55.2±7.2	0.313
Gender, male n (%)	59(64.1)	58(60.4)	0.264
Body mass index (kg/m²)	30.7±5.1	27.6±4.7	0.002
Hypertension n (%)	40(43.4)	27(28.1)	0.007
Current smoker n (%)	33(35.8)	33(34.3)	0.490
Diabetes Mellitus n (%)	12(13.1)	9(9.3)	0.018
Coronary artery disease n (%)	15(16.3)	14(14.5)	0.091
Systolic blood pressure (mmHg)	133±11	118±10	0.004
Diastolic blood pressure (mmHg)	99±8	85±7	0.001
Presence of fragmented QRS n (%)	59(64.1)	9(9.3)	<0.001
Beta blocker using	23(25.0)	22(22.9)	0.367
ACE inhibitors or ARBs	36(39.1)	25(26.1)	0.026
Calcium channel blocker using	17(18.4)	19(19.7)	0.216
Biochemical parameters			
Glucose (mg/dL)	96±22	94±14	0.324
Hemoglobin (mg/dL)	15.9±2.9	14.1±2.3	0.012
Creatinine (mg/dL)	0.90±0.16	0.89±0.14	0.332
Total cholesterol (mg/dL)	183±37	181±25	0.123
Triglyceride (mg/dL)	151±65	150±43	0.291
Low-density lipoprotein (mg/dL)	118±23	121±25	0.178
High-density lipoprotein (mg/dL)	37±5	37±9	0.412
Echocardiographic parameters			
LV ejection fraction (%)	59±4	59±5	0.293
LV end-diastolic diameter (cm)	4.9±0.5	4.9±0.5	0.633
LV end-systolic diameter (cm)	2.7±0.4	2.8±0.5	0.117
Interventricular septal thickness (mm	10.7±1.3	10.2±1.0	<0.001
Posterior wall thickness (mm)	10.6±1.2	10.0±0.9	<0.001
Left ventricular mass index (gr/m²)	97±16	82±15	<0.001
Left atrial diameter (cm)	3.9±0.5	3.7±0.4	0.212
E wave (m/s)	0.83±0.11	0.87±0.13	<0.001
A wave (m/s)	0.75±0.12	0.70±0.07	<0.001
E/A ratio	1.1±0.14	1.3±0.14	<0.001
E/Em ratio	9.7±1.3	8.9±1.0	<0.001

Abbreviations: LV: Left ventricle, OSAS: Obstructive Sleep Apnea Syndrome

The prevalence of complex VAs was significantly higher in OSAS patients as compared to the control group (15.2% vs 1.0%; p<0.001). Lown Grade 4 VAs, characterized by couplet ventricular beats and non-sustained ventricular tachycardia episodes, were observed in 5.4% of the OSAS patients while absent in the control group. (p<0.001) (Table 2). Furthermore, when Lown grade 2, 3, 4a and 4b VAs were evaluated separately, they were found significantly prevalent among OSAS patients (p <0.001 for all) (Table 2). All bradyarrhythmias were found to be higher in OSAS patients compared to the control group (p <0.05 for all) (Table 2).

Table 2. Prevalence of ventricular arrhythmias among study population

Lown Class	OSAS (n=92)	Control (n=96)	p value
Class 0, n (%)	33(35.8)	63(65.6)	<0.001
Class 1a, n (%)	34(36.9)	30(31.2)	0.105
Class 1b, n (%)	4(4.3)	2(2.0)	0.065
Class 2, n (%)	7(7.6)	0 (0)	<0.001
Class 3, n (%)	6(6.5)	0 (0)	<0.001
Class 4a, n (%)	5(5.4)	0 (0)	<0.001
Class 4b, n (%)	3(3.2)	0(0)	<0.001
Complex VA (≥ Lown Class 3), n (%)	14(15.2)	1(1.0)	<0.001
Bradyarrhythmias			
Sinus pause , n (%)	11(11.9)	6(6.2)	<0.001
First -degree atrioventricular block , n (%)	19(20.6)	7(7.2)	<0.001
Second -degree AV block type 1 , n (%)	2(2.1)	1(1.0)	0.039
Second -degree AV block type 2 , n (%)	3(3.2)	1(1.0)	0.027
Intraventricular conduction delay , n (%)	7(7.6)	4(4.1)	0.004

Abbreviations: AV: Atrioventricular, OSAS: Obstructive Sleep Apnea Syndrome, VA: ventricular arrhythmia

Comparison of baseline characteristics of OSAS patients with and without fQRS is summarized in Table 3. There was no significant difference between the two groups regarding age, sex, BMI, SBP, and nocturnal SaO2 values (mean SaO2, Percentage SaO2 < 90% and lowest nocturnal oxygen desaturation), and prevalence of dyslipidemia, hypertension, smoking, and diabetes mellitus (Table 3). However, DBP (p=0.002) and hemoglobin (p=0.003) values were significantly higher in the fQRS (+) group. There was no significant difference between the groups regarding the echocardiographic parameters including LVEDD, LVESD, LAD, and LVEF. However, the values of IVST, PWT, LVMI, E/Em ratio, and A wave was significantly higher in the Fqrs (+) group (p<0.001 for all) while E/A ratio (p<0.001) and E wave (p<0.001) was less prevalent in the fQRS (+) group (Table 3).

Table 3. Comparison of baseline characteristics of OSAS patients with and without fragmented QRS

	OSAS with fQRS (n=59)	OSAS without fQRS (n=33)	p value
Demographic parameters			
Age (years)	55.3±7.1	54.8±7.4	0.659
Gender, male, n (%)	36(64.5)	21(63.6)	0.490
Body mass index (kg/m²)	29.0±4.3	27.5±3.8	0.098
Hypertension, n(%)	26(44.1)	14(42.4)	0.486
Current smoker, n(%)	21(35.5)	12(36.3)	0.526
Diabetes Mellitus, n(%)	8(13.5)	4(12.1)	0.538
Coronary artery disease, n(%)	10(16.9)	5(15.1)	0.137
Systolic blood pressure (mmHg)	131±13	129±10	0.324
Diastolic blood pressure (mmHg)	95±11	91±6	0.002
Complex ventricular arrhythmias, n(%)	11(18.6)	3(9.0)	<0.001
AHI(events/h)	28.4±15.6	21.1±12.3	<0.001
Lowest nocturnal oxygen saturation, %	82±13	83±12	0.456
Biochemical parameters			
Glucose (mg/dL)	97±22	96±19	0.413
Hemoglobin (mg/dL)	15.3±2.8	13.4±3.1	0.003
Creatinine (mg/dL)	0.91±0.16	0.90±0.14	0.132
Total cholesterol (mg/dL)	182±36	183±27	0.345
Triglyceride (mg/dL)	149±67	146±45	0.365
Low-density lipoprotein (mg/dL)	122±23	120±20	0.201
High-density lipoprotein (mg/dL)	36±9	38±10	0.548
Echocardiographic parameters			
LV ejection fraction (%)	58±3	59±4	0.123
LV end-diastolic diameter (cm)	4.9±0.5	4.8±0.4	0.107
LV end-systolic diameter (cm)	2.7±0.4	2.8±0.3	0.213
Interventricular septal thickness(mm)	10.5±1.3	10.0±1.1	<0.001
Posterior wall thickness (mm)	10.4±1.3	9.8±0.8	<0.001
Left ventricular mass index (g/m²)	99±17	94±14	<0.001
Left atrial diameter (cm)	3.9±0.5	3.7±0.4	0.212
E wave (m/s)	0.79±0.11	0.83±0.13	<0.001
A wave (m/s)	0.72±0.10	0.67±0.07	<0.001
E/A ratio	1.1±0.13	1.3±0.15	<0.001
E/Em ratio	9.8±1.3	8.8±1.1	<0.001

Abbreviations: AHI: Apnea-hypopnea index, fQRS: Fragmented QRS complex, LV: Left ventricle, OSAS: Obstructiv Sleep Apnea Syndrome

AHI was significantly higher in the fQRS (+) group (28.4±15.6 vs 21.1± 12.3; p<0.001) (Table 3). Prevalence of complex VAs presence (Lown grade ≥ 3) was significantly high in the fQRS(+) group (18.6% vs 9.0%; p<0.001) (Table 4). Lown grade 4 VAs were significantly higher in OSAS patients with fQRS (10.1% vs 3.1%; p<0.001) (Table 4). Furthermore, prevalence of Lown grade 2, 3, 4a, and 4b VAs was significantly higher among fQRS (+) OSAS patients (p<0.001 for all) (Table 4). There was no significant difference between OSAS patients with and without fQRS in terms of bradyarrhythmias (Table 4).

Table 4. Prevalence of ventricular arrhythmias among OSAS patients with and without fragmented QRS complexes

Lown Class	OSAS with fQRS (n=59)	OSAS without fQRS (n=33)	p value
Class 0, n (%)	13(20.0)	14(42.4)	<0.001
Class 1a, n (%)	21(35.5)	13(39.3)	0.234
Class 1b, n (%)	3(5.1)	2(6.1)	0.123
Class 2, n (%)	11(18.6)	3(9.1)	<0.001
Class 3, n (%)	5(8.4)	2(6.1)	<0.001
Class 4a, n (%)	4(6.7)	1(3.1)	<0.001
Class 4b, n (%)	2(3.4)	0(0)	<0.001
Complex VAs (≥ Lown Class 3), n (%)	11(18.6)	3(9.0)	<0.001
Bradyarrhythmias			
Sinus pause	7(11.8)	3(9.1)	0.421
First -degree AV block , n (%)	14(23.7)	7(21.2)	0.135
Second -degree block type 1 , n (%)	2(3.4)	1(3.1)	0.341
Second -degree block type 2 , n (%)	2(3.4)	1(3.1)	0.341
Intraventricular conduction delay , n (%)	5(8.4)	2(6.1)	0.254

Abbreviations: AV: Atrioventricular, OSAS: Obstructive Sleep Apnea Syndrome, VA: ventricular arrhythmia

Multiple regression analyze showed that presence of fQRS (OR: 3.262, 95 %CI: 1.443-7.376; p=0.004) and AHI severity (OR: 1.510, 95 %CI: 1.343-1.698; p<0.001) to be independently associated with complex VAs in OSAS patients (Table 5).

Table 5. Multivariate regression analysis showing independent predictors of complex VAs

Variables	Univariate OR, (95% CI)	Univariate p value	Multivariate OR, (95% CI)	Multivariate p value
Presence of fQRS	5.850 (2.978-11.491)	<0.001	3.262 (1.443-7.376)	0.004
AHI	1.547 (1.381-1.732)	<0.001	1.510 (1.343-1.698)	<0.001
CAD	1.156 (1.142-1.287)	0.041		
SBP	1.123 (0.898-1.323)	0.095		
DBP	1.348 (0.987-2.657)	0.056		
Age	0.980 (0.938-1.023)	0.351		
Gender	1.333 (0.719-2.472)	0.362		
Smoking	1.447 (0.749-2.792)	0.271		
LVEF	0.966 (0.896-1.042)	0.370		
IVST	1.592 (1.156-5.214)	0.009		
PWT	1.412 (1.096-4.178)	0.022		
LVMI	1.845 (1.456-3.214)	0.003		
LVESD	1.534 (1.156-2.178)	0.017		
LVEDD	0.992 (0.962-1.023)	0.622		
E/Em	1.612 (1.219-2.133)	0.023		

Abbreviations: AHI: Apnea-hypopnea index, CAD: Coronary artery disease, CI: Confidence interval, DBP: Diastolic blood pressure, fQRS: Fragmented QRS complex, LVEF: Left ventricular ejection fraction, IVST: Interventricular septal thickness, LVEDD: Left ventricle end-diastolic diameter, LVESD: Left ventricle end-systolic diameter, LVMI: Left ventricle mass index, PWT: Posterior wall thickness, OR: Odd's ratio, SBP: Systolic blood pressure, VA: ventricular arrhythmia

DISCUSSION

This study investigated the association between the presence of fQRS and VAs in OSAS patients. Prevalence of fQRS and complex VAs were significantly higher in OSAS patients as compared to healthy controls. OSAS patients with fQRS had higher prevalence of complex VAs compared to those without fQRS. The presence of fQRS and AHI severity were found to be independently associated with the complex VAs in OSAS patients.

OSAS is a common global health problem that may cause severe complications1-7. Cardiovascular problems account for the main OSAS-related complications and top causes of mortality1-2. The main complications of OSAS are coronary artery disease, silent ischemia, myocardial infarction, hypertension, and stroke3-6. One of the most important complications of OSAS is the development of VAs6-9. Recent studies have especially been focusing on VAs and sudden cardiac death associated with OSAS6-9. According to the results of the current study, prevalence of complex VAs was significantly higher in OSAS patients as compared to the control group. Many studies have found that VAs and sudden cardiac death is more frequent among OSAS patients as compared to the normal population7-10. Mehra et al. found that complex VAs were more prevalent among OSAS patients than healthy individuals12. In another study, Gami et al. reported that OSAS was an independent risk factor for the formation of VAs, even after adjustments for conventional cardiovascular risk factors13. In another study, prevalence of complex VAs was reported between 27-74% in OSAS patients and 5-13% in healthy adults13,14. Our result was consistent with the literature. In a similar manner, in the Sleep Heart Health study, subgroup analyses after ruling out other risk factors showed that OSAS patients had 1.7 times increased risk of developing complex VAs compared to people without OSAS12.

Current studies have presented several hypotheses about mechanisms related to formation of VAs in OSAS patients6-8. While the details of these mechanisms are outside the focus of this study, various underlying mechanisms of arrhythmia include intermittent hypoxia, increased sympathetic tone, sympathovagal imbalance, and electrical abnormalities in the ventricular free wall due to negative intrathoracic pressure6-8, 26-30. In this study, high prevalence of VAs in OSAS patients can be explained with these mechanisms.

All of these processes cause fibrosis formation in the left ventricle31-33. Myocardial fibrosis is best revealed in magnetic resonance imaging and histological methods; however, these methods are expensive and difficult to apply. Contrarily, the simple and easily applicable method of assessing fQRS presence in ECG was found as an indicator of myocardial fibrosis19,20. fQRS is an ECG finding that indicates myocardial scarring and fibrosis in patients with ischemic or non-ischemic cardiac diseases19-21. Adar et al. found that prevalence of fQRS was significantly high in OSAS patients16. Sayın et al. also found high prevalence of fQRS presence in OSAS patients and associated it with poor outcomes17. In our study, the frequency of fQRS was found to be 64% in OSAS patients. This rate is similar to previous studies (58% to 82%)16-17. Another factor responsible for the formation of fibrosis tissue in OSAS patients is excessive collagen accumulation followed by remodeling which induces cardiac perivascular fibrosis33. When we evaluated the results of our study, we detected that fQRS positivity in OSAS patients was higher than the control group. In light of the information above, increased prevalence of fQRS may be an indicator of fibrosis in the OSAS group in the present study. Myocardial fibrosis formation causes inhomogeneity which leads to cardiac arrhythmias19,20. Miragoli et al. found that fibrosis tissue in the heart may be associated with increased risk of arrhythmia due to heart conduction abnormalities34.

According to our results, complex VAs had higher prevalence in OSAS patients with fQRS (+) patients compared to fQRS (-) patients. Similarly, fQRS presence has been associated with many ischemic and non-ischemic cardiac conditions15-20. Morita et al. conducted a study on patients with Brugada syndrome reported that prevalence of VAs was higher in patients with fQRS21. Similarly, Park et al. found that the prevalence of VAs was higher in fQRS (+) Ebstein anomaly patients15. Several mechanisms may be responsible for increased prevalence of complex VAs in OSAS patients and myocardial fibrosis has been reported to be a significant indicator of complex VAs in OSAS patients13,14,27. Myocardial fibrosis that occurs in OSAS may lead to micro-ischemia, promoting cardiac repolarization abnormalities followed by increased tendency to develop complex VAs35. We think that all structural and electrical abnormalities in the ventricles may explain the presence of arrhythmias in fQRS positive patients in our study.

In our study, it is an expected result that the IVST and PWT were higher in OSAS patients. In addition, the greater fibrous tissue development in OSAS patients with fQRS may explain the greater thickness of the ventricular walls and impaired ventricular relaxation in this group. Also, poor diastolic parameters in OSAS patients were not surprising. Review of all of these findings reveal increased ventricular hypertrophy and impaired diastolic function in the fQRS (+) group. This whole process may contribute to the increased prevalence of VAs in OSAS patients.

Results of our study showed that AHI scores were higher in the fQRS (+) group as compared to the fQRS (-) group in OSAS patients. At the same time, AHI severity was found to be independently associated with the complex VAs in OSAS patients. We believe that as AHI score increases, exposure to mechanisms responsible for fibrosis is more pronounced and myocardial fibrosis increases in a similar manner in OSAS patients. Aytemir et al. reported increased rate of cardiac arrhythmia with increased AHI score35. Considering that cardiac complications occur over a long period of time regarding the severity of hypoxia in the course of OSAS, increased arrhythmia prevalence associated with increased AHI scores was an expected result.

Limitations

This study had some limitations. First, our study was a cross-sectional and single center study with a relatively small number of patients. Further studies on larger populations are required to confirm the results of this study. The second limitation was that magnetic resonance imaging or histopathological tests which are more sensitive in showing myocardial fibrosis could not be performed due to difficulty in application and high cost. Third, only patients with QRS duration of <120 ms were included in the study. Also, 24-hour Holter records had limited ability in detecting VAs. Techniques which allow monitorization for longer periods of time will determine the frequency of arrhythmia more clearly in these patients. Furthermore, association between fQRS and mortality could not be clearly determined since patients were not followed up prospectively. For the same reason, future arrhythmic episodes could not be evaluated to clearly determine the association between fQRS and Vas.

CONCLUSION

In conclusion, OSAS is a common disease in the population and may have severe arrhythmic complications. In this study we showed that the presence of fQRS which is a simple ECG parameter was associated with prevalence of ventricular arrhythmias in OSAS patients. The presence of fQRS may be a guide in practice to determine the patients who are at risk of developing arrhythmia. Close follow up of fQRS (+) patients with more frequent Holter monitorization may be considered.

Author Contributions

HE: Substantial contributions to conception and design of the study and the article, data analysis and interpretation, drafting the article, final approval of the version to be published. MBO: Data analysis and interpretation, drafting the article. LÖ: Data analysis and interpretation. ÜK: Data analysis and interpretation. DKY: Data analysis and interpretation, drafting the article. All authors discussed the results and commented on the manuscript. MK: Data analysis and interpretation, drafting the article

Financial Support

This research received no specific grant from any funding agency in the public, commercial, or not-for profit sectors.

REFERENCES

1. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014;146(5):1387-1394.
2. Baranchuk A, Simpson CS, Redfearn DP. It's time to wake up! Sleep apnea and cardiac arrhythmias. Europace. 2008;10(6):666-667.
3. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research. Circulation. 2008;118(10):1080-1111.
4. Turan Y. Uyku apnesi, hipertansiyon ve kardiyovasküler hastaliklar. Bozok Tıp Dergisi. 2018;8(Uyku Hastalıkları Özel Sayı):1-8.
5. Atılgan ZA, Abakay A, Ülgen S. Tıkayıcı uyku apne sendromu ve kardiyovasküler sorunlar. Dicle Tıp Dergisi. 2011;38(2): 253-256.
6. Baranchuk A. Sleep apnea, cardiac arrhythmias, and conduction disorders. J Electrocardiol. 2012;45(5):508-512.
7. Hersi AS. Obstructive sleep apnea and cardiac arrhythmias. Ann Thorac Med. 2010;5(1):10-17.
8. Todd K, McIntyre WF, Baranchuk A. Obstructive sleep apnea and atrial fibrillation. Nat Sci Sleep. 2010;2(2):39-45.
9. Baguet JP, Barone-Rochette G, Tamisier R. Mechanisms of cardiac dysfunction in obstructive sleep apnea. Nat Rev Cardiol. 2012;9(12):679-688.
10. Zamarrón C, Valdés CL, Alvarez-Sala R. Pathophysiologic mechanisms of cardiovascular disease in obstructive sleep apnea syndrome. Pulm Med. 2013;2013:521087.
11. Evlice AT. Obstruktif Uyku Apne Sendromunda Otonomik Disfonksiyonun Değerlendirilmesi. Arşiv Kaynak Tarama Dergisi. 2012;21(2):109-121.
12. Mehra R, Benjamin EJ, Shahar E, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. Am J Respir Crit Care Med. 2006;173(8):910-916.
13. Gami AS, Olson EJ, Shen WK, et al. Obstructive sleep apnea and the risk of sudden cardiac death: a longitudinal study of 10,701 adults. J Am Coll Cardiol. 2013;62(7):610-616.
14. Mitra AK, Bhuiyan AR, Jones EA. Association and Risk Factors for Obstructive Sleep Apnea and Cardiovascular Diseases: A Systematic Review. Diseases. 2021;9(4):88.
15. Park SJ, Chung S, On YK, et al. Fragmented QRS complex in adult patients with Ebstein anomaly and its association with arrhythmic risk and the severity of the anomaly. Circ Arrhythm Electrophysiol. 2013;6(6):1148-1155.
16. Adar A, Kırış A, Bülbül Y, et al. Association of Fragmented QRS with Subclinical Left Ventricular Dysfunction in Patients with Obstructive Sleep Apnea. Med Princ Pract. 2015;24(4):376-381.
17. Sayin MR, Altuntas M, Aktop Z, et al. Presence of Fragmented QRS Complexes

in Patients with Obstructive Sleep Apnea Syndrome. Chin Med J (Engl). 2015;128(16):2141-2146.
18. Eren H, Kaya Ü, Öcal L, et al. Presence of fragmented QRS may be associated with complex ventricular arrhythmias in patients with type-2 diabetes mellitus. Acta Cardiol. 2021;76(1):67-75.
19. Das MK, Suradi H, Maskoun W, et al. Fragmented wide QRS on a 12-lead ECG: a sign of myocardial scar and poor prognosis. Circ Arrhythm Electrophysiol. 2008;1(4):258-268.
20. Homsi M, Alsayed L, Safadi B. Fragmented QRS complexes on 12-lead ECG: a marker of cardiac sarcoidosis as detected by gadolinium cardiac magnetic resonance imaging. Ann Noninvasive Electrocardiol. 2009;14(4):319-326.
21. Morita H, Watanabe A, Morimoto Y, et al. Distribution and Prognostic Significance of Fragmented QRS in Patients With Brugada Syndrome. Circ Arrhythm Electrophysiol. 2017;10(3):e004765.
22. Epstein LJ, Kristo D, Strollo PJ Jr, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med. 2009;5(3):263-276.
23. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.e14.
24. Balasundaram K, Masse S, Nair K. A classification scheme for ventricular arrhythmias using wavelets analysis. Med Biol Eng Comput. 2013;51(1-2):153-164.
25. Tempio D, Pruiti GP, Conti S, et al. Ventricular arrhythmias in aortic valve stenosis before and after transcatheter aortic valve implantation. Europace. 2015;17(7):1136-1140.
26. Jyothula SS, Ramachandran S. Reversible ventricular arrhythmia in REM sleep associated with hypoxic sleep-disordered breathing. Sleep Med. 2006;7(1):81-82.
27. Bayram NA, Diker E. Obstrüktif uyku apnesi sendromu ve kardiyak aritmi [Obstructive sleep apnea syndrome and cardiac arrhythmias]. Turk Kardiyol Dern Ars. 2008;36(1):44-50.
28. Yılmaz Y, Sarıkaya I, Eryol N. Obstrüktif Uyku Apne Sendromunda Sol Ventrikül Kitlesi ve Diyastolik Fonksiyonlar. Journal of Contemporary Medicine. 2020;10(3): 442-446.
29. Koshino Y, Villarraga HR, Orban M, et al. Changes in left and right ventricular mechanics during the Mueller maneuver in healthy adults: a possible mechanism for abnormal cardiac function in patients with obstructive sleep apnea. Circ Cardiovasc Imaging. 2010;3(3):282-289.
30. Chan KH, Wilcox I. Obstructive sleep apnea: novel trigger and potential therapeutic target for cardiac arrhythmias. Expert Rev Cardiovasc Ther. 2010;8(7):981-994.
31. Hayashi T, Yamashita C, Matsumoto C, et al. Role of gp91phox-containing NADPH oxidase in left ventricular remodeling induced by intermittent hypoxic stress. Am J Physiol Heart Circ Physiol. 2008;294(5):H2197-H2203.
32. Chen L, Zhang J, Gan TX, et al. Left ventricular dysfunction and associated cellular injury in rats exposed to chronic intermittent hypoxia. J Appl Physiol (1985). 2008;104(1):218-223.
33. Zhang GH, Yu FC, Li Y, et al. Prolyl 4-Hydroxylase Domain Protein 3 Overexpression Improved Obstructive Sleep Apnea-Induced Cardiac Perivascular Fibrosis Partially by Suppressing Endothelial-to-Mesenchymal Transition. J Am Heart Assoc. 2017;6(10):e006680.
34. Miragoli M, Gaudesius G, Rohr S. Electrotonic modulation of cardiac impulse conduction by myofibroblasts. Circ Res. 2006;98(6):801-810.
35. Aytemir K, Deniz A, Yavuz B, et al. Increased myocardial vulnerability and autonomic nervous system imbalance in obstructive sleep apnea syndrome. Respir Med. 2007;101(6):1277-1282

Ankara Eğt. Arş. Hast. Derg. (Med. J. Ankara Tr. Res. Hosp.) 2022 ; 55(1) : 28-33

The study protocol was approved by Ümraniye Training and Research Hospital Ethical Review Board (decision number and date: 200-17.06.2021)