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Evaluation of the risk of sudden cardiac death in obstructive sleep apnea syndrome patients with Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio

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ABSTRACT

Aims: Obstructive sleep apnea syndrome (OSAS) is a disorder characterized by recurrent collapse of the upper airway during sleep. OSAS is associated with an increased risk of cardiovascular morbidity and mortality. Tpeak to Tend (Tp-e) interval, the Tp-e interval/QT interval (Tp-e/QT) ratio, and the Tp-e interval/corrected QT interval (Tp-e/QTc) ratio, are associated with ventricular arrhythmias and sudden cardiac death in various disease groups. We aimed to investigate the relationship between changes in the new arrhythmia markers Tp-e interval, Tp-e/QT and Tp-e/QTc ratios in OSAS patients.

Methods: The study looked at 45 people with OSAS (32 men) over the age of 18 and 43 healthy people (27 men) who were diagnosed with OSAS through polysomnography in a sleep lab. Tp-e interval, Tp-e/QT and Tp-e/QTc ratios were calculated on the ECG.

Results: The QT interval was shorter in the patient group than in the control group, in contrast to the QTc interval, which was comparable between groups ($p = 0.006$ and 0.810 in the patient and control groups, respectively). The Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were significantly higher in OSAS patients included in the patient group compared to those included in the control group ($p<0.01$ in total).

Conclusion: The Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios were prolonged in OSAS patients. These findings suggest that OSAS patients may be predisposed to severe ventricular arrhythmias.

Keywords: Obstructive sleep apnea syndrome, Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio, sudden cardiac death

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a disorder characterized by recurrent collapse of the upper airway during sleep. OSAS affects 2% of middle-aged women and 4% of men. Polysomnography is the gold standard diagnostic method using the number of apneas and hypopneas per hour of sleep, and the apnea-hypopnea index (AHI) is the way to measure this. The incidence increases with age and weight gain. OSAS is associated with an increased risk of cardiovascular morbidity and mortality.[1] It is also clearly associated with heart failure, atrial fibrillation (AF), coronary disease, and stroke.[2,3]

Arrhythmias such as sinus node dysfunction (sick sinus syndrome), atrioventricular block, AF, ventricular ectopy, and even ventricular tachycardia and sudden cardiac death have been reported in OSAS. The most common ventricular arrhythmia in OSAS is ventricular ectopic activity (VEA), and severe arrhythmias such as ventricular tachycardia are also seen.[4-6] The development of ventricular arrhythmias has also been claimed to be related to the severity of OSAS and oxygen desaturation.[4,7] Patients with ventricular arrhythmias are less likely to have respiratory system disease, and there is a close relationship between sudden cardiac death and AHI.[7]

Assessment of ventricular recovery and repolarization dispersion on the electrocardiogram (ECG) are useful markers for future ventricular arrhythmias. Certain markers of ventricular repolarization, such as the QT interval and T-wave alternans, have been shown to be useful in predicting arrhythmias.[8] Recent studies have shown that the ratio of new indices, such as the Tpeak to Trend (Tp-e) interval, the Tp-e interval/QT interval (Tp-e/QT) ratio, and the Tp-e interval/corrected QT interval (Tp-e/QTc) ratio, are associated with ventricular arrhythmias and sudden cardiac death in various disease groups.[9]

In this study, we aimed to investigate the relationship between changes in the new arrhythmia markers Tp-e interval, Tp-e/QT and Tp-e/QTc ratios in OSAS patients.

METHODS

The study was carried out with the permission of Ethical Committe of Kayseri City Training and Research Hospital (Date:12.12.2023, Decision No: 957). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study looked at 45 people with OSAS (32 men) over the age of 18 and 43 healthy people (27 men) who were diagnosed with OSAS through polysomnography in a sleep lab, had an Apnea-Hypopnea Index (AHI) >5, and had not been treated before. Medical history, laboratory results, and echocardiographic information were obtained from medical history records. The control group consisted of age- and gender-matched patients with no suspected respiratory system disease based on medical history, physical examination, and echocardiography findings.

The exclusion criteria were uninterpretable ECGs (left bundle branch block, presence of pacemaker, U waves and negative T waves on prewarning ECGs), hypertrophic cardiomyopathy, severe valvular disease, coronary artery disease, hypothyroidism and hyperthyroidism, hypokalemia and hyperkalemia, hypomagnesemia and hypermagnesemia, creatinine clearance (CrCl) <60 ml/min, and body mass index (BMI) >30 kg/m^2. None of the enrolled patients were taking any medication affecting the QT interval. Written informed consent and local ethics committee approval were obtained from all patients.

Sleep Test

Polysomnographic evaluation was performed in the sleep laboratory by continuous monitoring and analysis of ECG, electroencephalogram, electromyogram, pulse oximetry, electrooculogram, nasal airflow, snoring, leg movements, thoracic and abdominal movements, and body position. Polysomnographic records were evaluated by computer-assisted manual scoring according to the criteria of the American Academy of Sleep Medicine by physicians experienced in sleep disorders and polysomnography. OSAS was defined as the number of apneic and hypopneic events per hour during sleep.[10] Apnea was defined as the absence of airflow for at least 10 seconds. Hypopnea was defined as the reduction of airflow with 4% oxygen desaturation lasting at least 10 seconds with subsequent arousal.

Electrocardiogram Analysis

All standard 12-lead ECGs were performed in the supine position and at rest using an ECG device (Philips brand) standardized to 1 mV/cm and 25 mm/s paper speed. All ECGs were scanned and transferred to personal computers. ECGs were magnified 5-fold and measured using an electronic caliper (Cardio Calipers software version 3.3; Iconico.com, Philadelphia, PA, USA) for the necessary measurements. To reduce inaccurate measurements, two cardiologists performed ECG assessments while being blind to clinical information.

The Tp-e interval was defined as the distance between the peak of the T wave and the end of the T wave. All Tp-e intervals were measured using the best available T wave and generally using lead V5. When the V5 lead was not available for analysis, the V4 or V6 lead was used.

The QT interval was found by measuring the distance from the start of the QRS complex to the end of the T wave in lead V6, which is the best way to see the transmural axis of the left ventricle. Heart rate was then taken into account using the Bazett method. formula, i.e., QTc = QT/√R-R (R-R interval). Calculating Tp-e/QT and Tp-e/QTc ratios involved dividing Tp-e by QT and Tp-e by QTc, respectively. Intraobserver and interobserver coefficients of variation were less than 5%.

Echocardiography

Patients and healthy volunteers underwent conventional echocardiographic examination with an M4S-RS (1.5-3.6 MHz) cardiac transducer and Vingmed System 5 (General Electronic Horten, Norway) echocardiograph. Left ventricular diastolic (LVIDd) and systolic (LVIDs) diameters, interventricular septum (IVSWT), and posterior wall (LVPWT) diastolic thicknesses were measured in the parasternal long axis with M-mode echocardiography according to the standards set by the American Echocardiography Association. The ejection fraction was calculated using the Teichholz formula.

Statistical Analysis

Statistical analyses were performed using the SPSS Statistical software package for Windows version 21.0 (SPSS Inc., Chicago, IL, USA). The distributional characteristics of the data were determined using the Kolmogorov-Smirnov test. Independent samples t-test was used for parametric scale variables. Mann-Whitney U test was used for nonparametric scale variables. The $\chi 2$ (chi-square) test was used for the univariate analysis of categorical variables. Variables were expressed as mean ± SD (standard deviation); categorical variables were expressed as percentages. A probability value of $p < 0.05$ was considered to be significant, and two-tailed p values were used for all statistical analyses.

RESULTS

Baseline clinical and demographic characteristics of the study groups are presented in **Table 1**. There were no statistically significant differences between the patient and control groups in terms of gender, age, smoking status, diabetes, and hypertension (p>0.05). Systolic blood pressure was slightly elevated, and BMI was high in the patient group.

Table 1. Baseline characteristics of the study populations

	OSAS (n=45)	Control (n=43)	p
Age (years)	49±9	51±4	NS
Gender (male/female)	32/13	27/16	NS
Systolic blood pressure (mmHg)	120±12	110±6	<0.05
Diastolic blood pressure (mmHg)	80±7	70±8	NS
Stature (cm)	168±8	168±8	NS
Weight (kg)	84±15	70±7	<0.001
Body mass index (kg/m^2)	29±6	24±2	<0.001

OSAS; Obstructive Sleep Apnea Syndrome NS; not statistically significant
Independent samples t-test was used for parametric scale variables. Variables were expressed as mean ± SD (standard deviation); categorical variables were expressed as percentages.

The ECG parameters of the groups are shown in **Table 2**. Heart rate and QRS duration were similar between the groups (p = 0.344 and 0.220 in the patient and control groups, respectively). The QT interval was shorter in the patient group than in the control group, in contrast to the QTc interval, which was comparable between groups (p = 0.006 and 0.810 in the patient and control groups, respectively). The Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were significantly higher in OSAS patients included in the patient group compared to those included in the control group (p<0.01 in total).

Table 2. Electrocardiographic characteristics of the study population

Variables	Control group (45)	OSAS (43)	p
Heart rate (beat/min)	79.3±7.6	81.7±9.7	.017
QT (ms)	387.2±18.3	390.2±19.6	.280
QTc (ms)	424.1±12.9	403.6±10.8	**<0.001**
Tp-e (ms)	73.1±5.2	85.8±6.8	**<0.001**
TPe/QTc ratio (ms)	0.172±0.1	0.212±0.2	**<0.001**
TPe/QT ratio (ms_	0.188±0.2	0.219±0.2	**<0.001**

QTc; corrected QT interval, Tp-e; Tpeak to Tend interval, Tp-e/QT; Tp-e interval/QT interval ratio, Tp-e/QTc; Tp-e interval/corrected QT interval ratio

The $\chi 2$ (chi-square) test was used for the univariate analysis of categorical variables. Variables were expressed as mean ± SD (standard deviation); categorical variables were expressed as percentages.

DISCUSSION

The most important result of our study is that the Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios were prolonged in OSAS patients. These findings suggest that OSAS patients may be predisposed to severe ventricular arrhythmias.

The association between OSAS and cardiovascular disease has long been recognized and has been clearly demonstrated in hypertension as well as heart failure, atrial fibrillation (AF), coronary disease, and stroke.[7] The hypoxemia, hypercapnia, intrathoracic pressure fluctuations, reoxygenation, and arousals that occur in OSAS affect many tissues, including the cardiovascular system.[2,3,11] As a result, vasoconstriction, tachycardia, and acute blood pressure elevations due to sympathetic activation may occur. These mechanisms have direct cardiotoxic effects, including increased left ventricular wall stress, decreased cardiac variability, increased afterload, acute diastolic dysfunction, left atrial stress, left atrial enlargement, hypercoagulability, oxidative stress, and endothelial dysfunction.[7] Myocardial cells are overstimulated, and cardiac arrhythmias occur.

Three different cell types have been identified electrophysiologically in the ventricle: endocardial, epicardial, and myocardial M cells.[12,13] The peak of the T wave indicates epicardial repolarization, while the end of the T wave has been shown to overlap with repolarization of M cells; hence, the Tp-e interval is the duration of the transmural distribution of repolarization.[14] There is an association between Tp-e and life-threatening arrhythmic events, and therefore Tp-e helps to predict the risk of developing arrhythmias.[15-19] However, QT and Tp-e intervals vary greatly between individuals, and the Tp-e interval is affected by changes in heart rate. Therefore, regardless of Tp-e interval values, the Tp-e/QT ratio is thought to be more consistent across individuals and heart rates.[9]

Several studies have shown that OSAS is associated with an increased risk of ventricular arrhythmias and sudden cardiac death.[5,20,21] Gami et al.[22] 15-year follow-up study by Gami et al.[22]: SCD is a significant and increased risk among individuals suffering from sleep apnea. Barta et al.[23] reported that QT dispersion and QTc dispersion were not increased during the nocturnal period. Baumert et al.[24] showed that OSAS is associated with changes in QT interval variability during sleep. Sökmen et al.[25], Kilicarlan et al.[26], and Karacop et al.[27] found that Tp-e, Tpe/QT ratio, and Tp-e/QTc ratio were prolonged in OSAS patients. In our study, QT and QTc intervals were not different between the study and control groups. However, we found that other indicators of ventricular repolarization (i.e., Tp-e, Tpe/QT ratio, and Tp-e/QTc ratio) were increased in patients with OSAS. These results are consistent with the literature. However, we did not evaluate the clinical severity of our patients. Therefore, we could not evaluate the correlation with the severity of hypoxia or AHI. However, we still think that it predicts cardiac augmentations.

Limitations

The main limitations of our study are that the number of patients in our study group, prolonged Tpe, Tpe/QTc ratio were relatively small to see if OSAS patients develop ventricular arrhythmias and were not followed up by rhythm Holter and clinically for possible future ventricular arrhythmias. Our control group patients did not undergo sleep testing, which may have led to inaccurate results. OSAS patients were not grouped according to disease severity; further studies including OSAS patients more proportional to disease severity may reveal different results. We also did not evaluate the relationship between AHI and ventricular repolarization parameters.

CONCLUSION

Our results show that new ECG markers may provide more information about arrhythmic risk in OSAS patients than baseline ECGs. The pathologic state of OSAS in the cardiovascular system appears to have the potential to cause arrhythmogenic effects.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethical Committe of Kayseri City Training and Research Hospital (Date:12.12.2023, Decision No: 957). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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