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Research Article

Evaluation of Ventricular Arrhythmia Markers in Obstructive Sleep Apnea Syndrome Patients

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Abstract

Aim: Obstructive sleep apnea syndrome (OSAS) is a prevalent sleep condition marked by recurrent upper airway blockages causing intermittent hypoxia, fragmented sleep, and autonomic nervous system issues. Significant emphasis has been paid to the connection between OSAS and the development of ventricular arrhythmias in recent years. The index of cardiac electrophysiological balance (ICEB) represents a new measure designed to predict the likelihood of ventricular arrhythmias.

Material and Methods: Forty OSAS patients and 40 healthy controls were enrolled in the research. Clinical and demographic variables of both groups were evaluated. Electrocardiogram was taken and routine blood values of the patients were studied. The ICEB is computed by dividing the QT interval by the QRS duration (QT/QRS). Apnea-hypopnea index was used to evaluate the severity of OSAS.

Results: The body-mass index value of OSAS patients was significantly higher than HCs (p=0.002). No significant smoking status difference between OSAS patients and HCs (p=0.822). As a result, QT, QTc, and ICEB were substantially greater in OSAS patients than in HCs (p<0.001, for all). According to Pearson correlation analysis, apnea-hypopnea index and body-mass index, QT, QTc, and ICEB were significantly correlated (p=0.020, p=0.009, p=0.010, and p=0.003, respectively). In linear regression analysis where the apnea-hypopnea index was taken as a dependent variable, ICEB predicted the apnea-hypopnea index significantly and positively (F(5.76)=18.451, R2=0.657, adjusted R2=0.715 and p<0.001).

Conclusion: In this study, a positive and significant relationship was found between the AHI value, which is used to evaluate the severity of OSAS, and ICEB. The fact that ICEB, which is used to evaluate the risk of ventricular arrhythmia, is higher in OSAS patients indicates that these patients should be followed more closely in the cardiologic outpatient clinic.

Keywords: Index of cardiac electrophysiological balance, obstructive sleep apnea syndrome, ventricular arrhythmia

INTRODUCTION

The common sleep disease known as obstructive sleep apnea syndrome (OSAS) is defined by recurrent episodes of partial or total upper airway obstruction while asleep, which can result in intermittent hypoxia and interrupted sleep cycles (1). Ventricular arrhythmias, on the other hand, are abnormal heart rhythms that originate in the heart's lower chambers, potentially leading to serious complications including sudden cardiac arrest (2). The relationship between OSAS and the risk of ventricular arrhythmias has garnered significant attention in recent years due to emerging evidence suggesting a complex interplay between these two conditions (3).

OSAS-related sleep fragmentation and intermittent hypoxia can lead to disruptions in the autonomic balance that regulates heart rate variability. A higher risk of abrupt cardiac events and ventricular arrhythmias is linked to decreased heart rate variability. These alterations can affect the heart's electrical conduction system, creating an environment that favors the emergence of arrhythmias (4).

The index of cardiac electrophysiological balance (ICEB) represents a new measure designed to predict the occurrence of ventricular arrhythmias. This index is computed by dividing the QT interval by the QRS duration (QT/QRS). It essentially encapsulates the equilibrium between the ventricular depolarization and repolarization phases of the cardiac cycle. What's noteworthy about ICEB is that it offers a non-invasive and readily quantifiable approach to evaluating this balance (5).

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ICEB carries several advantages over other electrocardiogram (ECG) parameters like QT interval or QT corrected (QTc) interval. By focusing on the ratio between two distinct phases of the cardiac cycle, ICEB captures more comprehensive information related to the prediction of ventricular arrhythmias (6). Remarkably, within the existing literature, there is a gap in employing ICEB to predict ventricular arrhythmias in patients with OSAS. No study has explored the application of ICEB specifically for this purpose. This brings us to the purpose of this study, which aims to fill this gap.

MATERIAL AND METHOD

Study Design

The study was conducted prospectively. Adıyaman University Ethics Committee approved the study protocol for Non-Interventional Clinical Trials (2022/2-7). Guidelines from the Helsinki Declaration were observed throughout the investigation. After exclusions, 40 out of 62 eligible OSAS patients participated. All participants provided informed consent for their participation.

Patients with OSAS who applied to the otorhinolaryngology outpatient clinic made up the study's patient population. The control group consisted of healthy volunteers who applied to the otorhinolaryngology outpatient clinic and had no obstructive pathology. Forty OSAS patients and 40 healthy controls were included in the study. Clinical and demographic characteristics of both groups were evaluated. ECG was taken and routine blood values of the patients were studied. Glucose, thyroid hormones, creatinine, complete blood count, electrolytes were studied from the blood samples taken. Demographic and clinical characteristics such as laboratory results, age, gender, smoking, body mass index (BMI), diastolic and systolic blood pressure measurement, and iCEB calculated by dividing the QT interval in the ECG, the QTc interval, the QT interval by the QRS duration (QT/QRS) group compared.

Those with left or right bundle branch block, extrasinus rhythm, atrioventricular conduction disorder on ECG were not included in the study. Those with a history of rheumatoid heart disease, valvular heart disease, thyroid dysfunction, chronic lung disease, chronic kidney disease, anemia, electrolyte disorder, chronic liver disease, chronic infection, systemic autoimmune disease, diabetes, hypertension, coronary heart disease, those using antidepressants, antipsychotics or antihistamines, were excluded from the study.

Electrocardiogram Examination

Measurements were conducted on the CardioFax S device (Nihon Kohden, Tokyo, Japan) 12-lead ECG. Resting heart rate was calculated as 300 divided by the number of large squares between consecutive R waves. QRS duration was gauged from onset to end. For QT interval, the interval between QRS onset and T wave end was measured. QTc interval was derived as heart-rate adjusted.

Laboratory Examination

During hospital admission, venous blood samples were subjected to comprehensive analysis. Utilizing the CELL-DYN Ruby device from Abbott Diagnostics, we quantified the white blood cell count, including neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts in x 103 cells/mm3. Moreover, measurements encompassed hemoglobin, hematocrit, and thrombocyte counts.

Abbott Diagnostics' biochemistry kits and the Architect c8000 Chemistry System were instrumental in assessing CRP, creatinine, thyroid hormones, and urea levels. Plasma concentrations of fasting blood glucose and electrolytes were determined through a meticulous enzymatic chemical clearing process executed via the Cobas 6000 system from Roche Diagnostics GmbH in Mannheim, Germany. These exhaustive analyses provided crucial insights into participants' physiological status, enhancing the depth and accuracy of the study's findings.

OSAS Severity Evaluation

The Apnea-Hypopnea Index (AHI) is a crucial parameter in sleep medicine, used to quantify the severity of obstructive sleep apnea (OSA) and assess its impact on an individual's sleep quality and overall health. It measures the frequency of respiratory events that occur during sleep, including apneas (complete pauses in breathing) and hypopneas (partial reductions in airflow). The total number of apneas and hypopneas recorded during a sleep study is divided by the total number of hours of sleep to arrive at the AHI. The result is typically expressed as the number of events per hour. The interpretation of AHI values categorizes the severity of OSA as follows. AHI less than 5 occurrences per hour is considered normal. AHI of 5 to 15 incidents per hour is considered mild. AHI that is moderate has 15 to 30 incidents per hour. AHI over 30 occurrences per hour is considered severe (7).

Statistical Analysis

Sample size determined as 40 via G*Power (3.1) (power: 0.8, alpha: 0.05, effect size: 0.58). SPSS 26.0 for Mac (SPSS Inc., Chicago, IL) facilitated the analysis. Numbers and percentages were used to present categorical data. The Kolmogorov-Smirnov test assessed data normality. Normally distributed parameters were presented as mean±standard deviation, while non-normally distributed parameters were shown as median [minimum-maximum]. Independent samples t-test, Mann-Whitney U test, and chi-square test compared ECG and lab data between patients and controls. Pearson correlation and linear regression explored inflammation-ECG links. Significance was set at $p<0.05$, enhancing the rigor and precision of the study's outcomes.

RESULTS

The study included 40 OSAS patients and 40 healthy controls. Age and gender distribution showed no significant differences ($p=0.886$, $p=0.501$, respectively) (Table 1). The BMI value of OSAS patients was significantly higher

than HCs (p=0.002). Smoking status showed no notable difference between OSAS patients and HCs (p=0.822). Table 2 displays the ECG data comparison, indicating significantly higher QT, QTc, and ICEB values in OSAS patients compared to HCs (p<0.001, all).

Table 3 outlines the lab data contrast between OSAS patients and HCs. OSAS patients exhibited notably higher glucose and TSH levels than HCs (p=0.024 and p=0.023, respectively). Additionally, T4 levels were significantly lower in OSAS patients compared to HCs (p=0.044).

According to Pearson correlation analysis, AHI and BMI, QT, QTc, and ICEB were significantly correlated (p=0.020, p=0.009, p=0.010, and p=0.003, respectively) (Table 4). In the linear regression, ICEB significantly and positively predicted AHI (F(5.76)=18.451, R2=0.657, Adjusted R2=0.715, p<0.001) as presented in Table 5.

Table 1. Sociodemographic features of the OSAS patients and HCs

	OSAS Patients n=40 (M+SD) or n (%)	HCs n=40 (M+SD) or n (%)	p value
Gender			
Male	17 (42.5)	20 (50)	0.501[a]
Female	23 (57.5)	20 (50)	
Age	47.98±8.77	46.90±9.67	0.886[b]
Smoking	18 (45)	17 (42.5)	0.822[a]
BMI, kg/m²	29.2±4.56	25.8±5.3	**0.002[b]**

OSAS: Obstructive sleep apnea syndrome, HCs: healthy controls, BMI: body mass index
a: p value based on chi-square analysis, b: p value based on Student's t-test. A significance level of p<0.05 was considered

Table 2. Comparison of electrocardiogram parameters of OSAS patients and HCs

	OSAS Patients n=40 (M+SD) or n (%)	HCs n=40 (M+SD) or n (%)	p value
Heart rate, bpm	82.58±13.64	81.25±14.03	0.729
QRS, msec	89.30±8.39	88.00±8.42	0.491
QT, msec	408.15±30.85	359.90±27.76	**<0.001**
QTc, msec	435.75±25.41	406.58±25.21	**<0.001**
ICEB	4.60±0.51	4.12±0.41	**<0.001**

OSAS: obstructive sleep apnea syndrome, HCs: healthy controls, ICEB: index of cardiac electrophysiological balance
[1]Student's t test was used. p<.05 was accepted as statistical significance value

Table 3. Comparison of lab parameters of OSAS patients and HCs

	OSAS Patients n=40 (M+SD) or n (%)	HCs n=40 (M+SD) or n (%)	p value
Glucose, mg/dL	86.46±10.24	78.21±8.56	**0.024**
Hemoglobin, mg/dL	14.65±1.66	14.39±2.12	0.178
TSH, mU/L	3.91±1.86	3.40±1.35	**0.023**
T4, ng/dL	0.70±0.190	0.82±0.22	**0.044**
Urea, mg/dL	18.11±8.37	16.56±6.77	0.242
Creatinin, mg/dL	0.92±0.32	0.85±0.36	0.356
Na, mEq/L	139±6.51	140±6.44	0.781
K, mEq/L	4.01±0.65	3.81±0.78	0.101
WBC, $10^3/\mu L$	7.56±1.62	6.21±2.27	0.186
Neutrophil, $10^6/\mu L$	4.78±1.66	4.45±1.46	0.174
Lymphocyte, $10^3/\mu L$	2.26±0.56	2.53±0.93	0.102
Monocyte, $10^3/\mu L$	0.52±0.16	0.51±0.15	0.628
Basophil, $10^3/\mu L$	0.08±0.09	0.09±0.10	0.446
Eosinophil, $10^3/\mu L$	0.18±0.17	0.16±0.18	0.166
Platelet, $10^3/\mu L$	255.77±66.73	244.53±53.82	0.229
CRP, mg/dL	0.22±0.06	0.20±0.10	0.648

OSAS: obstructive sleep apnea syndrome, HCs: healthy controls, TSH: thyroid stimulating hormone, T4: thyroxine, WBC: white blood cell, CRP: C-reactive protein
Student's t test was used. p<.05 was accepted as statistical significance value

Table 4. Pearson correlation analyzes of AHI with age, BMI and ECG parameters in OSAS patients

	AHI
Age	r=0.254
	p=0.021
BMI	**r=0.246**
	p=0.020
QT	**r=0.180**
	p=0.009
QTc	**r=0.216**
	p=0.010
ICEB	**r=0.315**
	p=0.003

OSAS: obstructive sleep apnea syndrome, AHI: Apnea-Hypopnea index, QTc: corrected QT interval, ICEB: index of cardiac electrophysiological balance
Pearson correlation test was used. p <.05 was accepted as statistically significant

Table 5. Linear regression analyzes of AHI in OSAS patients

					95% CI	
	B	Beta	t	p	Lower	Upper
Age	1.651	0.212	1.830	0.137	-0.040	4.160
BMI	3.314	0.120	1.142	0.214	-2.503	10.136
QT	1.400	0.132	1.352	0.150	-0.644	3.640
QTc	0.134	0.254	2.753	0.186	0.050	0.218
ICEB	1.712	0.860	2.412	**0.004**	-1.768	4.365
Constant	-22.670		-2.106	0.046		

OSAS: obstructive sleep apnea syndrome, AHI: Apnea-Hypopnea index, QTc: corrected QT interval, ICEB: index of cardiac electrophysiological balance, CI: confidence interval
Lineer regression analyses was used. p<0.05 was accepted as statically significance. F(5.76)=18.451, R2=0.657, Adjusted R2=0.715 and p<0.001

DISCUSSION

This study shows crucial results: i) ICEB, QT, QTc, and BMI values were higher in OSAS patients than HCs. ii.) AHI was positively and significantly correlated with BMI, QT, QTc, and ICEB in OSAS patients. iii.) ICEB was found to be closely related to disease severity in OSAS patients.

An major factor in the pathogenesis of OSAS is BMI. Excess adipose tissue, especially around the neck and upper airway, can lead to airway narrowing and obstruction during sleep. This contributes to the hallmark symptoms of OSAS, including loud snoring, recurrent awakenings, and daytime sleepiness. Research consistently demonstrates a positive correlation between higher BMI levels and an increased risk of developing OSAS. As BMI rises, the risk of OSAS also escalates, underscoring the importance of weight management in OSAS prevention and management (8). The way OSAS is managed and treated is greatly influenced by BMI. Lifestyle modifications, including weight loss through diet and exercise, have been shown to alleviate OSAS symptoms and even lead to resolution in some cases. For individuals with a higher BMI, these interventions can be particularly effective. However, weight loss can be challenging for individuals with OSAS due to the factors mentioned above, making a multidisciplinary approach essential (9).

Several studies have investigated the potential impact of OSAS on the QT interval duration (10). The intermittent hypoxia and sympathetic activation that occur during OSAS episodes can lead to autonomic nervous system dysregulation. This imbalance can affect the duration of the QT interval, potentially leading to QT interval prolongation (11). An increased risk of torsades de pointes, a particular kind of arrhythmia that can result in fatal ventricular arrhythmias, is linked to prolonged QT intervals (12). The underlying mechanisms connecting OSAS and QT interval prolongation are multifaceted. Sympathetic nervous system overactivity triggered by OSAS can alter cardiac repolarization processes, influencing the duration of the QT interval. Additionally, the oxidative stress and inflammation resulting from intermittent hypoxia and reoxygenation in OSAS episodes can impact ion channel function, further affecting the QT interval duration (13).

OSAS, with its physiological disruptions, can significantly influence cardiac electrophysiology, creating an environment conducive to arrhythmias. The underlying mechanisms are complex and multifaceted. OSAS is known to trigger sympathetic overactivity and parasympathetic withdrawal. This imbalance can disrupt the heart's normal rhythm and predispose individuals to arrhythmias. Intermittent hypoxia during OSAS episodes can lead to alterations in the duration of the QT interval, a key parameter reflecting ventricular repolarization (14). OSAS-induced oxidative stress and inflammation can impact ion channel function and cardiac conduction pathways, increasing arrhythmia susceptibility. The intricate relationship between OSAS and the risk of arrhythmias underscores the significance of recognizing and addressing both conditions. The physiological disruptions caused by OSAS create an environment conducive to arrhythmias, necessitating vigilant monitoring and comprehensive patient care. By understanding this intricate connection, healthcare providers can proactively manage both OSAS and arrhythmias, enhancing the cardiovascular well-being and quality of life for individuals affected by these conditions (15).

The connection between autonomic nervous system imbalance and ventricular arrhythmias is established. Sympathetic and parasympathetic dysfunction disrupts cardiac rhythms, affecting ventricular repolarization (16). Elevated ICEB values may result from increased catecholamines linked to rising intracranial pressure (17). Catecholamines, including adrenaline and noradrenaline are released by the adrenal glands in response to stressors, exerting significant effects on the cardiovascular system. In OSAS, the sympathetic nervous system is overactivated, resulting in elevated catecholamine levels (18). This autonomic imbalance contributes to increased

heart rate, blood pressure variability, and altered cardiac electrophysiology. One of the cardinal concerns stemming from heightened catecholamine levels in OSAS is their potential role in the genesis of ventricular arrhythmias. Sympathetic overactivity triggered by OSAS episodes can provoke cardiac electrical instabilities, leading to alterations in ventricular repolarization. These changes, as reflected in parameters like the QT interval, can heighten the risk of ventricular arrhythmias, including life-threatening conditions like ventricular tachycardia (19). However, the correlation between serum catecholamine levels and ECG alterations requires further elucidation.

Although within normal limits, TSH value was higher in OSAS patients and T4 values were lower in OSAS patients. The complex interplay between hypothyroidism, a disorder marked by insufficient thyroid hormone production, and OSAS reveals a fascinating terrain of potential connections that affect people's health and well-being. Investigating this interaction reveals the complex mechanisms that demand careful medical assessment. Sleep patterns can be greatly impacted by hypothyroidism. Individuals are more vulnerable to OSAS-related symptoms such loud snoring, disrupted sleep, and daytime weariness due to slowed metabolism and decreased sympathetic activity (20).

Expanding the research to involve more patients and considering additional ECG markers like Tp-e and Tp-e/QT could yield more comprehensive insights. Our study's drawback includes the lack of electrolyte data, like calcium and magnesium, which can influence QT interval and ventricular repolarization. Since the normal ranges of ICEB are unknown, prospective longitudinal axis studies are needed to predict the risk of ventricular arrhythmias in OSAS patients. The duration of illness in OSAS patients may influence the risk of ventricular arrhythmias. Not recording this information is a limitation.

CONCLUSION

In this study, a relationship between ICEB and the AHI value, which is used to assess the severity of OSAS, was discovered to be both positive and significant. The fact that ICEB, which is used to evaluate the risk of ventricular arrhythmia, is higher in OSAS patients indicates that these patients should be followed more closely in the cardiologic outpatient clinic.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *Adıyaman University Ethics Committee approved the study protocol for Non-Interventional Clinical Trials (2022/2-7).*

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