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Changes in the parameters of ventricular repolarization during preapnea, apnea, and postapnea periods in patients with obstructive sleep apnea

Erdoğan Sökmen MD[1] | Sinan Cemgil Özbek MD[1] | Mustafa Çelik MD[1] | Serkan Sivri MD[1] | Mehmet Metin MD[2] | Mustafa Avcu MD[2]

[1]Department of Cardiology, Ahi Evran University Training and Research Hospital, Kirsehir, Turkey

[2]Department Otorhinolaryngology, Ahi Evran University Training and Research Hospital, Kirsehir, Turkey

Correspondence
Erdoğan Sökmen, Ahi Evran Universitesi, 2019 Sokak, No: 1 Merkez-Kırşehir, Turkey 40100.
Email: erdoganmen@gmail.com

Abstract

Background: Ventricular arrhythmias are reported to be more common in patients with obstructive sleep apnea (OSA). Preliminary evidence showed such parameters regarding ventricular repolarization as Tp-e, Tp-e/QT, and Tp-e/QTc may be related with increased cardiac arrhythmias and even sudden cardiac death. The purpose of the present study was to evaluate ventricular repolarization during immediately preapnea period, apnea period, and postapnea hyperventilation period in patients with OSA.

Methods: A total of 59 patients who underwent polysomnography and were diagnosed with OSA between the years 2016–2017 in our hospital were included in our study. Of 59 patients (mean age: 52.51 ± 9.66), 28 were male and 31 were female. In all patients, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio, together with some other parameters, were calculated. Categorical variables were expressed as proportion and continuous variables were expressed as mean ± standard deviation. Electrocardiogram calculations of interest were compared through preapnea, apnea, and postapnea periods using Friedman's test.

Results: Tp-e interval (85.6 ms [78.3–95.6], 98 ms [88.5–107.7], 91.2 ms [81–98.8], respectively; $P < 0.001$), Tp-e/QT ratio (0.219 [0.202–0.237], 0.242 [0.224–0.269], 0.233 [0.212–0.246], respectively; $P < 0.001$), and Tp-e/QTc ratio (0.210 [0.190–0.222], 0.233 [0.209–0.247], 0.212 [0.193–0.229], respectively; $P < 0.001$) were significantly increased during apnea period compared to the preapnea period and significantly decreased during postapnea hyperventilation period compared to the apnea period.

Conclusion: Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were shown to be increased during apnea period and decreased during postapnea hyperventilation period. Our findings may help explain cardiac arrhythmias and sudden death in OSA patients.

KEYWORDS
obstructive sleep apnea, parameters of ventricular repolarization, ventricular arrhythmias

1 | INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep-related disease of high prevalence, characterized by recurrent collapse of upper respiratory ways during sleep that eventually results in apnea/hypopnea episodes, oxygen desaturation, increased effort to restore respiration, and increased daytime sleepiness.[1–3] A published epidemiological data from 1993 to 2013 revealed that 27% of women and 22% of men had OSA.[4] Obstructive apnea refers to a ≥10-second pause in respiration, along with ineffective respiratory effort.[5] The diagnosis of OSA can be ascertained by using polysomnography (PSG). According to the apnea-hypopnea index (AHI) which refers to the number of apneas or hypopneas recorded per hour of sleep, OSA is classified as mild, moderate, and severe.[6]

Concurrence of cardiovascular disease (CAD) and sleep-related disorders has long been known. Most of the patients with OSA also have other significant cardiovascular comorbid conditions.[5] Accordingly, the most common reason for mortality and morbidity in OSA

patients is cardiovascular events.[7] Moreover, OSA has been associated with cardiac arrhythmias, hypertension, coronary arterial disease, and left ventricular dysfunction.[8] Although the mechanism by which cardiac arrhythmias generate during OSA has still yet to be totally elucidated, such mechanisms as intrathoracic pressure changes, transient hypoxia, autonomic system activation, and excessive negative intrathoracic pressure were proposed.[9–11] Thereby, myocardial cells could be rendered more prone to electrical instability. Arousals are also reported to exert a strong effect on sympathetic activity in patients with OSA.[12] Gami et al. reported increased risk of sudden death at night in patients with OSA compared to the general population.[13] There are limited data regarding alterations in ventricular repolarization, which may potentially contribute to the generation of ventricular arrhythmias in patients with OSA.

Among the parameters that can be used to evaluate ventricular repolarization are QT interval (QT), corrected QT interval (QTc), QT dispersion, and transmural dispersion of repolarization. Moreover, the time interval from the peak to the end of the T wave electrocardiographically referred to as Tp-e appears as an index for transmural dispersion of ventricular repolarization.[14] Tp-e/QT and Tp-e/QTc ratios are among the other electrocardiographic indices representing ventricular arrhythmogenic potential.

In the present study, we aimed to evaluate the status of ventricular repolarization during the period just before onset of apnea, during the apnea, and during the postapnea hyperventilation period by using Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio.

2 | METHODS

2.1 | Study population

A total of 59 (28 male, 31 female) newly diagnosed adult patients older than 18 years of age with OSA who had undergone diagnostic overnight PSG between 2016 and 2017 were included in our study. The mean age (mean ± standard deviation [SD]) of the patients was 52.51 ± 9.66. The exclusion criteria were as follows: severe coronary arterial disease, atrial fibrillation, presence of cardiac pacemaker, moderate-to-severe cardiac valvular disease, cardiomyopathy, and severe pulmonary disease. Our study protocol was approved by the local ethics committee at our institution.

2.2 | PSG

All patients underwent an overnight PSG (Philips, Respironics, Inc. Murrysville, PA, USA) with standard polysomnographic techniques. Electrooculography, electrocardiography, electroencephalography, submental and anterior tibialis electromyography, oxygen saturation, oronasal airflow, thoracic and abdominal respiration movements, snoring, and video monitoring were recorded in all patients. All the data were collected retrospectively. The PSG data were scored by two experienced otolaryngologists, who are coauthors of our study, certified for the practice and evaluation of PSG by a national association named "TUTDER." The mean of the total sleep time (mean ± SD) was 447.03 ± 67.14 minutes. Apnea was defined as airflow cessation for duration of at least 10 seconds. Hypopnea was defined as deduction of ventilation at least 50% accompanied by ≥4% oxygen desaturation. The AHI was calculated as the number of apnea/hypopnea events in each hour of sleep. The severity of OSA was categorized as follows: mild if AHI ≥5, but <15; moderate if AHI ≥15, but <30; severe if AHI ≥30.

2.3 | Electrocardiography

Calculation of electrocardiographic parameters was achieved by using polysomnographic ECG lead II recordings at sampling frequency of 200 Hz. One episode of obstructive apnea with clear ECG recording where the ECG parameters of interest would be calculated precisely was selected randomly from the polysomnographic data of each patient. Following selection of an apnea episode, segments of 10-second duration just preceding the onset of apnea, during apnea, and postapnea hyperventilation period were defined. RR interval, QT interval, and Tp-e interval were measured manually. QTc intervals were obtained using Bazett's formula.[15] Then, Tp-e/QT and Tp-e/QTc ratios were calculated. ECG complexes within the predefined 10-second segments were measured and the means of the measurements for each segment were recorded. All the measurements were performed by a single experienced cardiologist blinded to the study so as to prevent interobserver variability. There are two commonly used methods of measuring Tp-e interval: tangent method and tail method.[16,17] We used in our study the tail method, which refers to the time interval between the peak of the T wave and the point where the T wave converges into isoelectric line.[17]

2.4 | Statistical analysis

All the statistical analyses were conducted by using IBM SPSS V22.0 (IBM Corp., Armonk, NY, USA) package program for Windows. Categorical variables were expressed as proportion, and continuous variables were expressed as mean ± SD. ECG calculations of interest were compared through preapnea, apnea, and postapnea periods using Friedman's test, and expressed as median (25^{th}–75^{th} percentile). P-value of ≤ 0.05 was accepted to be statistically significant.

3 | RESULTS

Baseline characteristics of the study population are depicted in Table 1. Of 59 patients included in the study, 28 (47.4%) were male and 31 (52.6%) were female. Number of the patients classified according to the severity of OSA was as follows: mild, seven patients (11.8%); moderate, eight patients (13.5%); and, severe, 44 patients (74.5%). Of all patients, 33 (56%) had history of tobacco use, eight (14%) had history of diabetes mellitus, and 23 (39%) had history of primary hypertension. Among the medications of the study patients with hypertension are beta-blocking agents (three patients, 5%); angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (11 patients, 19%), and dihydropyridine calcium channel blockers

TABLE 1 Baseline characteristics of the study populations

Variables	Mean	Standard deviation
Age (years)	52.51	9.66
Body height (cm)	168.71	15.71
Body weight (kg)	89.17	12.28
Body mass index	30.72	4.08
Apnea-Hypopnea index	47.19	27.78
Total sleep time (min)	447.03	67.14
Mean SpO2 (%)	92.07	5.32
Lowest SpO2 (%)	79.2	6.3
Arousal index	21.7	15.3

Note: Values are presented as mean ± standard deviation.

(nine patients, 15%). Baseline echocardiographic characteristics of the study population were presented in Table 2. Tp-e interval was observed to be significantly prolonged during the apnea period compared to the period immediately before the onset of apnea and to be significantly decreased during the postapnea hyperventilation period compared to the apnea period (85.6 ms [78.3–95.6], 98 ms [88.5–107.7], and 91.2 ms [81–98.8], respectively; $P < 0.001$) (Table 3). QT interval was also significantly prolonged during the apnea period and significantly shortened in the postapnea hyperventilation period (378 ms [367–406], 402 ms [375–411], and 397 ms [371–407], respectively; $P < 0.001$). However, QTc interval was observed to be further prolonged in the postapnea hyperventilation period compared to the preapnea and apnea periods (415 ms [399–439], 421 ms [404–441], and 427 ms [414–447], respectively; $P < 0.001$). Moreover, Tp-e/QT ratio increased significantly during the apnea period and decreased significantly in the postapnea hyperventilation period (0.219 [0.202–0.237], 0.242 [0.224–0.269], and 0.233 [0.212–0.246], respectively; $P < 0.001$). Tp-e/QTc ratio was also significantly increased during the preapnea period and decreased during the postapnea hyperventilation period [0.210 (0.190–0.222), 0.233 (0.209–0.247), and 0.212 (0.193–0.229), respectively; $P < 0.001$].

TABLE 2 Baseline echocardiographic characteristics of the patients

Variables	Mean	Standard deviation
LVEDD (mm)	47.95	2.31
LVESD (mm)	33.90	2.20
LV EF (%)	61.92	2.93
Left atrial diameter (mm)	36.52	4.94
IVSD (mm)	11.10	1.66
PWT (mm)	10.00	1.45
E/A ratio	1.04	0.28
IVRT (ms)	88.28	10.40
E-wave DT (ms)	192.66	15.89
E/E' ratio	10.05	1.66

Note: Values are presented as mean ± standard deviation. E-wave DT = E-wave deceleration time; IVRT = isovolumetric relaxation time; IVSD = interventricular septum diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; PWT = posterior wall thickness of the left ventricle.

4 | DISCUSSION

Our study results indicate that Tp-e and QT intervals, and Tp-e/QT and Tp-e/QTc ratios, significantly increased during the apnea period compared to the period immediately before the onset of apnea, and significantly decreased in the postapnea hyperventilation period compared to the apnea period. However, QTc interval was revealed to show a significant prolongation during the apnea period, and persisted to be prolonged in the postapnea hyperventilation period, which was also statistically significant (Table 3).

CADs, including sudden cardiac death,[13,18] have long been known to be common in patients with OSA. Prolongation of QT, QTc, and Tp-e intervals indicating ventricular repolarization are likely to cause lethal ventricular arrhythmias. Relevant and effective therapy, on the other hand, was reported to abate this arrhythmia potential.[19–21]

Former studies have already reported a positive correlation between prolonged QT and QTc intervals and ventricular arrhythmias and mortality.[22–25] Tp-e interval is a relatively new parameter of cardiac repolarization, and its prolongation was reported to be associated with ventricular arrhythmias and sudden cardiac death.[14,26–29] More recently, Tp-e/QT showed up as new index of ventricular repolarization and was proposed to be a more accurate predictor of ventricular arrhythmias due to its being more stable despite distinctions in body weight and dynamic heart rate changes within a given subject.[30,31] Moreover, it provides more accurate data regarding the status of ventricular repolarization compared to Tp-e interval or QT interval alone.[31]

In a study by Camen et al. investigating the effect of simulated obstructive apnea and hypopnea on arrhythmic potential on healthy group of individuals reported a prolongation in QTc and Tp-e_c intervals.[32] Kilicaslan et al. reported an increase in Tp-e interval, and Tp-e/QT and Tp-e/QT ratios in patients with moderate to severe OSA, compared to the healthy individuals.[33] Nakamura et al. reported prolongation of QT interval in OSA patients.[34] Gillis et al. investigated the changes in QT and QTc intervals just before the onset of apnea, at the end of apnea, and during the postapnea hyperventilation period within randomly selected OSA episodes in 12 OSA patients and reported prolongation of QT interval at the onset of apnea, followed by a further prolongation during OSA. Moreover, duration of QT interval decreased abruptly during the postapnea hyperventilation period.[35] Contrary to QT interval, however, QTc interval was reported to increase at the onset of apnea, followed by significant decrease during both the apnea and postapnea hyperventilation periods.[35] For the sake of clarity, in the study by Kilicaslan et al.,[33] they compared the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio between moderate-to-severe OSA patients and those with normal PSG. They calculated the mean of the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio obtained from every single ECG complex in a 10-second-long ECG segment from the beginning of the apnea period to the end of the apnea period in a randomly selected

TABLE 3 Electrocardiographic parameters regarding ventricular repolarization within an OSA episode

Variables	Immediately preapnea period	Apnea period	Postapnea hyperventilation period	P-value
Tp-e (ms)	85.6 (78.3–95.6)	98 (88.5–107.7)	91.2 (81–98.8)	<0.001
QT (ms)	378 (367–406)	402 (375–411)	397 (371–407)	
QTc (ms)	415 (399–439)	421 (404–441)	427 (414–447)	
Tp-e/QT ratio	0.219 (0.202–0.237)	0.242 (0.224–0.269)	0.233 (0.212–0.246)	
Tp-e/QTc ratio	0.210 (0.190–0.222)	0.233 (0.209–0.247)	0.212 (0.193–0.229)	

Note: Values are presented as median (25^{th}–75^{th} percentile). OSA = obstructive sleep apnea.

apnea episode, then compared these mean values between the two groups. In our study, however, we only included mild-to-severe OSA patients documented by PSG. Moreover, we selected an OSA episode randomly, one with a very clear ECG recording to let us make accurate calculations, and used respective 10-second-long ECG recordings just before the onset of apnea episode, within the apnea episode, and during the hyperventilation arousal period immediately after the selected apnea episode within the same patient. Our study resembles, in some ways, the study by Gillis et al.[35] In our study, QT interval was prolonged during the apnea period and decreased during the postapnea hyperventilation period. On the other hand, QTc persisted to be prolonged instead of shortening during both the apnea and postapnea hyperventilation periods, which was statistically significant. Although the exact mechanism by which persistent prolongation of the QTc even in the postapnea hyperventilation period remains unclear, increased sympathetic activation and rapid alterations in the intrathoracic pressure during this period may underlie the persistence of QTc prolongation. Tp-e/QT and Tp-e/QTc ratios were also found to be increased during the apnea period compared to the preapnea period, and decreased significantly in the postapnea hyperventilation period.

To the best of our knowledge, Tp-e interval, and Tp-e/QT and Tp-e/QTc ratios have not been assessed during the preapnea, apnea, and postapnea hyperventilation periods in patients with OSA. Accordingly, the findings of our study may contribute to the attempts to explain the mechanisms underlying increased sudden cardiac death by revealing the increase in the parameters of ventricular repolarization during sleep in patients with OSA.

Our current study has some limitations. Most of the patients included in our study had severe OSA. Further studies with more proportional inclusion of OSA patients with different severity may reveal different results. We also did not evaluate the association between AHI and the parameters of ventricular repolarization. Our study population is relatively small and larger studies are needed to yield more precise results.

5 | CONCLUSION

Our study showed that Tp-e interval, QT interval, and Tp-e/QT and Tp-e/QTc ratios were significantly increased during the apnea period and significantly decreased during the postapnea hyperventilation period. QTc interval was increased during the apnea period; however, it persisted to increase further during the postapnea hyperventilation period.

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ORCID

Erdoğan Sökmen MD http://orcid.org/0000-0002-8170-5912

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