Original Article

Presence of Fragmented QRS Complexes in Patients with Obstructive Sleep Apnea Syndrome

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Abstract

Background: Obstructive sleep apnea syndrome (OSAS) is a disease with increasing prevalence, which is mainly characterized by increased cardiopulmonary mortality and morbidity. It is well-known that OSAS patients have increased prevalence of cardiovascular diseases including coronary heart disease, heart failure, and arrhythmias. The aim of this study was to evaluate the presence of prolonged and fragmented QRS complexes, which have previously been associated with cardiovascular mortality, in OSAS patients.

Methods: Our study included 51 patients (mean age 41.6 ± 10.1 years) who were recently diagnosed with OSAS (apnea-hypopnea index [AHI] ≥5 events/h) and never received therapy. The control group consisted of 34 volunteers (mean age 43.1 ± 11.6 years) in whom OSAS was excluded (AHI <5 events/h). The longest QRS complexes was measured in the 12-lead electrocardiogram (ECG) and the presence of fragmentation in QRS complexes was investigated.

Results: Fragmented QRS frequency was significantly higher in patients with OSAS (n = 31 [61%] vs. n = 12 [35%], P = 0.021). QRS and QTc durations were also significantly longer in OSAS patients than controls (99.8 ± 13.9 ms vs. 84.7 ± 14.3 ms, P < 0.001; 411.4 ± 26.9 ms vs. 390.1 ± 32.2 ms, P = 0.001, respectively). Analysis of the patient and controls groups combined revealed a weak-moderate correlation between AHI and QRS duration (r = 0.292, P = 0.070). OSAS group had no correlation between AHI and QRS duration (r = −0.231, P = 0.203).

Conclusions: In our study fragmented QRS frequency and QRS duration were found to increase in OSAS patients. Both parameters are related with increased cardiovascular mortality. Considering the prognostic importance of ECG parameters, it may be reasonable to recommend more detailed evaluation of OSAS patients with fragmented or prolonged QRS complexes with respect to presence of cardiovascular diseases.

Key words: Electrocardiogram; Fragmented QRS; Obstructive Sleep Apnea; QRS Duration; QT Duration

Introduction

Obstructive sleep apnea syndrome (OSAS) is a complex clinical syndrome characterized by apnea episodes, sleep fragmentation, oxygen desaturation, and increased daytime somnolence as a result of recurrent obstructive episodes in upper airways during sleep.[1] Previous studies have revealed that OSAS is related with many cardiovascular diseases including hypertension, coronary artery disease, arrhythmias, and congestive heart failure.[2] Basic hemodynamic mechanisms responsible from cardiovascular diseases are increased negative intrathoracic pressure, hypoxemia, and increased catecholamine release.[2] In OSAS both ventricles are subjected to hemodynamic stress that induces various structural changes.[3]

The electrocardiogram (ECG) represents the sum of electrical activity of all myocytes within the heart and hemodynamic changes produce various ECG changes. It is known that OSAS may cause ECG alterations.[4] QRS complexes mainly represent ventricular depolarization and morphological assessment of QRS complex may give important prognostic information. It has been shown in previous trials that QRS fragmentation is a predictor of sudden cardiac death and total mortality.[5] In addition, a prolonged QRS duration has been implicated in cardiovascular events, sudden death, and total mortality.[6,7]

In this study, our object was to investigate QRS fragmentation and QRS duration in OSAS patients.

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Methods

Study design

This was a case-controlled observational study.

Study population

In our study, we took 51 consecutive patients who applied to "Zonguldak Uzun Mehmet Göğüs Hastalıkları" hospital and admitted to sleep laboratory in order to undergo polysomnography test. Each of these patients were diagnosed with OSAS (apnea-hypopnea index [AHI] ≥5 events/h) and they had no previous treatment. Thirty-four consecutive participants who were shown to have no OSAS (AHI <5 events/h) following polysomnopgraphy test were included as our control group.

Patients with following conditions were excluded from the study: Chronic obstructive pulmonary disease on pulmonary function testing, previous history of continuous positive airway pressure treatment, stage 2–3 hypertension, a positive stress test, coronary artery disease and/or previous myocardial infarction, left ventricular (LV) dysfunction, echocardiographically proven LV hypertrophy, moderate-to-severe valve disease, renal or hepatic dysfunction, impairment of thyroid function tests, atrial fibrillation, history of dysrhythmia, patients with permanent pacemakers, bundle branch block or fascicular block, and electrolyte abnormalities, presence of infections or inflammations, hematologic disease or any known malignancy, individuals who have systemic and metabolic diseases that could adversely affect the cardiac or pulmonary structure and functions. None of the participants were taking antiarrhythmic drugs, digitalis, beta-blockers, nondihydropyridine calcium-channel blockers or any other QT prolonging medications.

In this study, all of the procedures that took place were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Declaration of Helsinki* (1975), as revised in 2000. All participants gave informed written consent.

Polysomnography

Overnight polysomnography was performed in all patients by a computerized system (Alice 5 Diagnostic Sleep System, 55 channels; Respironics, USA). The test included the following variables: Electrooculogram (two channels), electroencephalogram (four channels), electromyogram of submental muscles (two channels), electromyogram of the anterior tibialis muscle of both legs (two channels), thoracic and abdominal movements, pulse oximeter oxygen saturation, ECG, airflow (with a nasal cannula), body position detector, and tracheal sound. The recordings were conducted at a speed of 10 mm/s, and sleep stage was scored according to the standard criteria of Rechtschaffen and Kales.[8] Arousals were scored according to accepted definitions.[9] The AHI was obtained by dividing the total number of apneas and hypopneas by the total sleep time. Apneas were defined as complete cessation of airflow ≥10 s. Hypopneas were defined as a reduction of >50% in one of the three respiratory signals, airflow signal or either respiratory or abdominal signals of respiratory inductance plethysmography, with an associated decrease of ≥3% in oxygen saturation or an arousal. According to the recently updated International Classification of Sleep Disorders published by the American Academy of Sleep Medicine,[10] a diagnosis of OSAS is to be made if the AHI is ≥15 events/h, independent of occurrence of symptoms, or whenever an AHI >5 events/h is associated with any of the following: (1) Sleep attacks or excessive daytime sleepiness, unrefreshing sleep, fatigue or (2) insomnia, or (3) witnessed heavy snoring and/or breathing pauses referred by the partner.[11] The Epworth sleepiness scale is a questionnaire that especially evaluates daytime sleepiness. OSAS was excluded by a negative history of sleep-related symptoms (snoring, witnessed apneas, and excessive daytime sleepiness) and with an AHI <5 events/h at overnight polysomnopgraphy. Patients with sleep disorders – except OSAS – such as upper airway resistance syndrome, periodic leg movement syndrome, or narcolepsy were excluded.

Electrocardiographic assessment

All standard 12-lead ECGs were obtained simultaneously using a recorder set at a 25–50 mm/s paper speed and a voltage calibration of 1 mV/cm. All examinations were carried out in a quiet room during spontaneous breathing, following 10 min of rest in the supine position. The ECGs were each numbered and presented to the analyzing investigators who were blind both to patient name and group information. ECG measurements were taken by two medically qualified observers blind to the name and group of patients. ECGs were interpreted using standard criteria. ECG parameters were measured using a digital caliper (sensitivity: 1/100 mm) by magnifying lens. The highest value for each parameter was used. Presence of fragmented QRS was determined with consensus. Fragmented QRS comprises various morphologies of QRS wave with or without a Q wave.[12] Fragmented QRS was diagnosed with the presence of an additional R wave (R') or notching in the nadir of the R wave or the S wave, or the presence of more than one R' (fragmentation) in two consecutive leads, corresponding to a certain myocardial territory.[12]

Echocardiographic assessment

Echocardiographic examination was carried out with the patient resting in a supine left lateral decubitus position. LV dimensions and wall thickness were obtained from the parasternal long axis view with the M-mode cursor positioned just below the mitral leaflet tips, perpendicular to the long axis of the LV. LV end-diastolic diameter and end-systolic diameter, thickness of the interventricular septum, and posterior wall of the LV were all measured using a single operator by the standards of the American Society of Echocardiography.[13] LV ejection fraction was measured in accordance with Simpson's method.[14]

Statistical analysis

SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Quantitative data were

expressed as mean ± standard deviation (SD). Categorical data were presented as number and frequency (%). In order for the suitable analysis technique to be chosen, Kolmogorov–Smirnov and homogeneity of variance tests were undertaken. Independent samples *t*-test was used for the two-group comparison of the normally distributed variables and Mann–Whitney *U*-test for the two-group comparison of the variables without normal distribution. Categorical variables were compared using the Chi-square test. Spearman's correlation analysis was used to examine the relationship between variables. A regression analysis was also performed. A $P < 0.05$ was considered statistically significant.

Reproducibility

The reproducibility of the ECG analyses was assessed by the intermeasurement coefficient of variation. The coefficient of variation is calculated as the SD of the differences between the repeated measurements divided by the averages of the repeated measurements, and is expressed as a percentage. The intraobserver variabilities were 4.08% for PQ, 5.60% for QRS, and 4.26% for QTc. The interobserver variabilities were 4.74% for PQ, 6.65% for QRS, and 4.21% for QTc.

Results

Clinical and demographic features of both groups are given on Table 1. OSAS group had more male patients. Waist and neck circumference were significantly greater in the OSAS group. OSAS group had a worse blood lipid profile and a significantly higher smoking rate.

Table 2 shows ECG and echocardiographic parameters of both groups. Fragmented QRS frequency was significantly higher in patients with OSAS ($n = 31$ [61%] vs. $n = 12$ [35%], $P = 0.021$). fQRS frequency was 2.8 times higher in patients compared to controls after adjustment for gender [Table 3]. When OSAS patients were grouped according to presence of fragmented QRS, it was found that the fragmented QRS group had a longer QRS duration (95.0 ± 11.6 ms vs. 102.9 ± 14.5 ms, $P = 0.045$) [Table 4]. Furthermore, CRP level was also higher in the fragmented QRS group (0.26 ± 0.32 mg/dl vs. 0.39 ± 0.36 mg/dl, $P = 0.027$).

QRS and QTc durations were significantly longer in OSAS group compared to the control group (99.8 ± 13.9 ms vs. 84.7 ± 14.3 ms, $P < 0.0001$; 411.4 ± 26.9 ms vs. 390.1 ± 32.2 ms, $P = 0.001$, respectively) [Figures 1 and 2]. QRS and QTc durations were also longer in patients compared to controls after adjustment for gender (99.7 ± 14.4 ms vs. 84.8 ± 14.6 ms, $P < 0.001$; 413.3 ± 29.1 ms vs. 387.3 ± 29.4 ms, $P < 0.001$, respectively). Echocardiographic parameters were within normal limits in both groups, although OSAS group had increased LV thickness and diameters, increased left atrial diameter, and a lower ejection fraction.

Analysis of the patient and control groups combined revealed a weak-moderate correlation between AHI and QRS duration ($r = 0.292$, $P = 0.070$) and between AHI and QTc duration ($r = 0.338$, $P = 0.020$). However, there was no correlation between AHI and QRS duration ($r = -0.231$, $P = 0.203$) and between AHI and QTc duration ($r = 0.004$, $P = 0.980$) in OSAS group.

Table 1: Clinical and demographic features of both groups

Variables	Control group ($n=34$)	OSAS group ($n=51$)	*P*
Age (years)	43.1 ± 11.6	41.6 ± 10.1	0.541*
Sex (female/male) (*n* (%))	17 (50)/17 (50)	10 (20)/41 (80)	0.003‡
AHI (events/h)	2.1 ± 1.2	21.4 ± 19.3	<0.0001†
BMI (kg/m^2)	30.2 ± 5.5	32.4 ± 5.5	0.069*
WC (cm)	100.2 ± 6.7	105.9 ± 9.4	0.003*
NC (cm)	38.3 ± 2.8	42.2 ± 3.5	<0.0001*
HT (*n*)	1	2	0.810‡
DM (*n*)	2	3	1.000‡
Smoking (*n*)	6	26	0.002‡
HL (*n*)	5	18	0.036‡
Hemoglobin (g/dl)	13.7 ± 1.1	14.3 ± 1.5	0.159*
Creatinine (mg/dl)	0.69 ± 0.15	0.81 ± 0.15	0.013*
TSH (mU/ml)	1.99 ± 0.90	1.88 ± 1.14	0.742*
FBG (mg/dl)	104.1 ± 29.0	100.1 ± 20.5	0.473*
LDL-C (mg/dl)	113.4 ± 37.5	120.9 ± 31.3	0.328*
HDL-C (mg/dl)	45.6 ± 11.7	41.2 ± 10.3	0.074*
TC (mg/dl)	191.1 ± 38.9	206.8 ± 134.4	0.319*
TG (mg/dl)	147.4 ± 35.5	206.8 ± 134.4	0.036†

*Independent *t*-test; †Mann–Whitney *U*-test; ‡Chi-square test. AHI: Apnea-hypopnea index; BMI: Body mass index; CRP: C-reactive protein; DM: Diabetes mellitus; FBG: Fasting blood glucose; HDL-C: High-density lipoprotein cholesterol; HL: Hyperlipidemia; HT: Hypertension; LDL-C: Low-density lipoprotein cholesterol; NC: Neck circumference; TC: Total cholesterol; TG: Triglycerides; TSH: Thyroid stimulating hormone; WC: Waist circumference; OSAS: Obstructive sleep apnea syndrome.

Table 2: Comparison of the electrocardiographic and echocardiographic parameters

Variables	Control group ($n=34$)	OSAS group ($n=51$)	*P*
PQ (ms)	166.6 ± 19.9	172.8 ± 18.3	0.146*
QRS (ms)	84.7 ± 14.3	99.8 ± 13.9	<0.0001*
QTc (ms)	390.1 ± 32.2	411.4 ± 26.9	0.001*
SLI (mm)	15.1 ± 5.1	12.2 ± 4.8	0.011*
CI (mm)	10.0 ± 3.7	10.8 ± 4.1	0.332*
fQRS (*n* (%))	12 (35)	31 (61)	0.021*
LV-EDD (cm)	4.61 ± 0.26	4.79 ± 0.45	0.094†
LV-ESD (cm)	2.55 ± 0.35	2.82 ± 0.42	0.021*
IVS (cm)	0.92 ± 0.10	1.04 ± 0.11	<0.0001†
PW (cm)	0.91 ± 0.11	1.01 ± 0.10	0.002†
LA (cm)	3.31 ± 0.36	3.66 ± 0.24	0.001†
EF (%)	63.3 ± 3.1	60.6 ± 1.9	0.002†

*Independent *t*-test; †Mann–Whitney *U*-test. CI: Cornell index; EF: Ejection fraction; fQRS: Fragmented QRS; IVS: Interventricular septum; LA: Left atrium; LV-EDD: Left ventricular end-diastolic diameter; LV-ESD: Left ventricular end-systolic diameter; PQ: PQ interval duration; PW: Posterior wall; QRS: QRS duration; QTc: Corrected QT interval duration; SLI: Skolow-Lyon index; OSAS: Obstructive sleep apnea syndrome.

Table 3: A logistic regression model for fQRS

Variables	*B*	SE	Wald	df	*P*	Exp (B)	95% *CI*	
							Lower	Upper
Step 1								
Constant	–0.748	0.446	2.812	1	0.094	0.473		
OSAS	0.964	0.481	4.016	1	0.045	2.622	1.021	6.731
Gender	0.278	0.507	0.301	1	0.583	1.320	0.489	3.563
Step 2								
Constant	–0.606	0.359	2.853	1	0.091	0.545		
OSAS	1.044	0.459	5.168	1	0.023	2.842	1.155	6.992

fQRS: Fragmented QRS; SE: Standard error; df: Degree of freedom; *CI*: Confidence interval; OSAS: Obstructive sleep apnea syndrome.

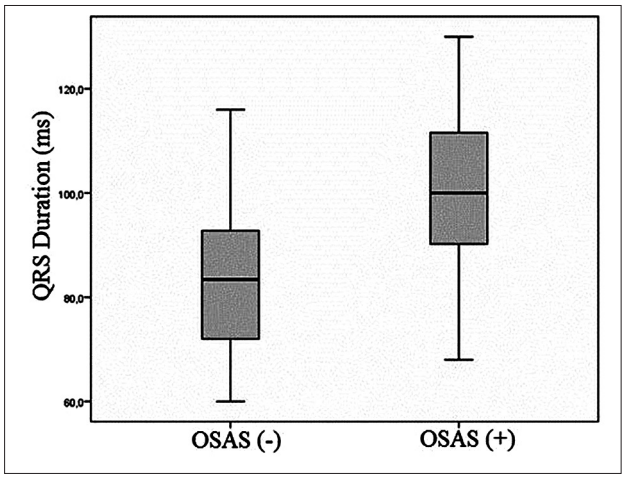

Figure 1: Obstructive sleep apnea syndrome and QRS duration.

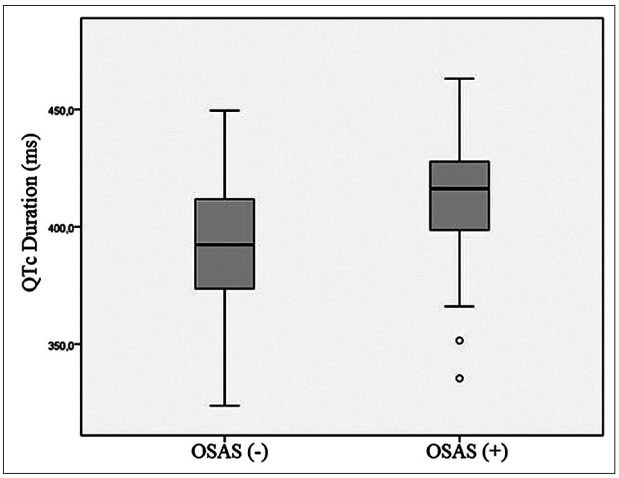

Figure 2: Obstructive sleep apnea syndrome and QTc duration.

Discussion

We found an increased fragmented QRS frequency, QRS duration and QTc duration in patients with OSAS compared to the control group. There was no correlation between AHI and QRS duration in OSAS patients.

Obstructive sleep apnea syndrome is an important public health problem since it is both prevalent and associated with disastrous outcomes including, but not limited to, cardiovascular morbidity and mortality.[15] So far, certain causative factors have been implicated in OSAS's deleterious effects on myocardial structure and function. Hypoxia and hypercapnia that are common during sleep; increased negative intrathoracic pressure during the arousal phase and excessive hemodynamic changes as a result of sympathetic stimulation; oxidative stress, systemic inflammation, endothelial dysfunction, increased myocardial oxygen supply-demand mismatch all lead to myocardial injury.[15,16] A study performed in rats demonstrated that chronic intermittent hypoxia as in OSAS was associated with LV damage in large scale and myocyte hypertrophy and cellular apoptosis at the cellular level.[17] Another study demonstrated an increased cardiomyocyte diameter and amount of interstitial fibrosis in LV myocardium partly as a result of oxidative stress in mice subjected to intermittent hypoxic stress.[18] Another study reported an increased amount of type III aminoterminal peptide, a peptide used as an indirect marker of myocardial fibrosis, and suggested that its amount is related with disease severity.[19] Myocardial scar or fibrosis does not necessarily lead to QRS prolongation, but rather they alter QRS shape without prolonging it by producing a previously absent R or a notch in either or both of R or S waves.[20] It has been shown in previous trials that QRS fragmentation is a predictor of sudden cardiac death and total mortality.[5] An increased fragmented QRS rate in OSAS patients in our study may have been related to cellular apoptosis and interstitial fibrosis in cardiac structure, which may be secondary to chronic hypoxia and other hemodynamic changes. Cetin *et al*.,[21] in a study in patients with stable angina pectoris, showed that fragmented QRS and CRP levels were inter-related. We also found that OSAS patients with fragmented QRS had higher CRP levels than those without. It has been previously established that OSAS causes inflammation.[22] A higher CRP level in OSAS patients with fragmented QRS may suggest that inflammation could also play a role in the alterations of the QRS morphology in OSAS patients.

Irrespective of its cause, LV hypertrophy is associated with increased cardiovascular morbidity and mortality. OSAS may induce LV hypertrophyin the absence of hypertension.[23] The causative factor of LV hypertrophy in OSAS is the increased afterload which may be due to increased negative intrathoracic pressure secondary to forceful breathing

Table 4: Clinical, demographic, electrocardiographic, and echocardiographic parameters for fragmented and non-fQRS

Parameters	fQRS (−) (*n*=20)	fQRS (+) (*n*=31)	*P*
Age (years)	41.0 ± 9.9	42.1 ± 10.4	0.702*
Sex (female/male) (*n* (%))	3 (15)/17 (85)	7 (23)/24 (77)	0.506‡
AHI (events/h)	28.1 ± 24.3	17.2 ± 14.0	0.017†
BMI (kg/m^2)	30.9 ± 4.9	33.4 ± 5.8	0.134*
WC (cm)	103.0 ± 9.3	107.6 ± 9.2	0.104*
NC (cm)	42.3 ± 2.9	42.0 ± 3.9	0.778*
HT (*n*)	0	2	0.247‡
DM (*n*)	1	2	0.830‡
Smoking (*n*)	13	13	0.108‡
HL (*n*)	7	11	0.972‡
Hemoglobin (g/dl)	14.6 ± 1.4	14.2 ± 1.5	0.415*
Creatinine (mg/dl)	0.83 ± 0.18	0.80 ± 0.14	0.577*
TSH (mU/ml)	1.73 ± 1.27	1.99 ± 1.06	0.552*
FBG (mg/dl)	104.2 ± 28.7	97.5 ± 12.7	0.266*
LDL-C (mg/dl)	122.1 ± 27.6	120.2 ± 34.0	0.834*
HDL-C (mg/dl)	41.3 ± 10.7	41.1 ± 10.2	0.171*
TC (mg/dl)	202.4 ± 32.2	197.2 ± 36.2	0.608*
TG (mg/dl)	207.6 ± 137.6	206.3 ± 134.6	0.915†
PQ (msn)	173.4 ± 18.7	172.3 ± 18.4	0.844*
QRS (msn)	95.0 ± 11.6	102.9 ± 14.5	0.045*
QTc (msn)	403.2 ± 26.6	416.8 ± 26.1	0.078*
SLI (mm)	11.7 ± 4.8	12.6 ± 4.9	0.562*
CI (mm)	10.2 ± 4.1	11.2 ± 4.1	0.388*
LV-EDD (cm)	4.81 ± 0.43	4.78 ± 0.47	0.898†
LV-ESD (cm)	2.82 ± 0.42	2.82 ± 0.43	0.961*
IVS (cm)	1.02 ± 0.15	1.05 ± 0.07	0.594†
PW (cm)	0.99 ± 0.13	1.01 ± 0.08	0.923†
LA (cm)	3.67 ± 0.25	3.65 ± 0.24	0.788†
EF (%)	60.7 ± 2.5	60.5 ± 1.4	0.761†

*Independent *t*-test; †Mann–Whitney *U*-test; ‡Chi-square test. AHI: apnea-hypopnea index; BMI: Body mass index; CI: Cornell index; DM: Diabetes mellitus; EF: Ejection fraction; fQRS: Fragmented QRS; FBG: Fasting blood glucose; HDL-C: High-density lipoprotein cholesterol; HL: Hyperlipidemia; HT: Hypertension; IVS: Interventricular septum; LA: Left atrium; LDL-C: Low-density lipoprotein cholesterol; LV-EDD: Left ventricular end-diastolic diameter; LV-ESD: Left ventricular end-systolic diameter; NC: Neck circumference; PQ: PQ interval duration; PW: Posterior wall; QRS: QRS duration; QTc: Corrected QT interval duration; SLI: Skolow-Lyon index; TC: Total cholesterol; TG: Triglycerides; TSH: Thyroid stimulating hormone; WC: Waist circumference.

attempts against a closed upper airway or to heightened blood pressure because of sympathetic activation, hypoxemia, and arousal from sleep.[16] In our study LV thickness was found to be increased in OSAS patients compared to controls despite the fact that there are a very low number of hypertensive patients and besides they had only mild hypertension. It is well-known that increased LV mural thickness may lead to prolonged QRS complexes.[24] In the LIFE trial QRS duration was independently predictive of cardiovascular and all-cause mortality.[25] Desai *et al*. reported that QRS duration was a significant and independent predictor of cardiovascular mortality in general medical population.[26] Similar to the previous one,[27] our study also found that OSAS patients had prolonged QRS duration. Another point to be considered was the higher numbers of male patients in the OSA group. Macfarlane *et al*. showed that, in the adults, the principal differences were an increased QRS duration in men compared with women both in the standard and signal-averaged ECG.[28] But QRS duration was also longer in patients compared to controls after adjustment for gender in our study. However, the OSAS group's QRS duration, which was within normal limits although it was prolonged as compared to the control group, may have altered secondary to above mentioned factors.

Our study also showed that, although in normal limits, QTc duration was longer in patients with OSAS. While OSA patients revealed longer QT durations similar to our study in literature,[29] in the study of Gupta *et al*. mentioned above, there was no significant lengthening in QRS duration.[27]

Study limitations

There are some limitations in this study. Firstly, the number of study subjects is not large. Secondly, in our patient group, we had more male patients than female patients. Because OSAS is diagnosed more frequently in male patients, and we have consecutively selected patients, we believe that our group study group supports the actual profile. Furthermore the results did not changed after adjustment for gender. Thirdly, we calculated measurements with electronic caliper by magnifying lens instead of computer-assisted calculations. However, our method has been used in previous studies.[30] Although we carefully assessed the patients for the presence of the coronary artery disease, we do not used invasive methods such as coronary angiography. Thus, it is possible that our cohort included patients with undetected coronary artery disease at entry. Furthermore, the sleep clinic population used here may not reflect the findings in the general community, and the results should be further confirmed with several longitudinal studies.

In conclusion, in our study fragmented QRS frequency and QRS duration were found to increase in OSAS patients. Both parameters are related with increased cardiovascular mortality. Considering the prognostic importance of ECG parameters, it may be reasonable to recommend more detailed evaluation of OSAS patients with fragmented or prolonged QRS complexes with respect to presence of cardiovascular diseases.

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