EFFECT OF SLEEP APNEA SYNDROME ON QT DISPERSION AND QT CORRECTED INTERVAL IN PATIENTS WITH TYPE 2 DIABETES

Adriana Rusu [1,2]***, Cristina Nita*** [1,2]***, Cornelia Bala*** [1,2]***, Nicolae Hancu*** [1,3]

[1] Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[2] Clinical Center of Diabetes, Nutrition, Metabolic Diseases, Cluj-Napoca, Romania, Address: 2-4 Clinicilor Street, 4006 Cluj-Napoca, Romania
[3] Unirea Medical Center, Cluj-Napoca, Romania Address: 35 Motilor Street, 400006 Cluj-Napoca, Romania

Abstract

Objective. *Prolonged QT interval and increased QT interval dispersion (QTd) are well-characterized precursor of malignant ventricular arrhythmias. The aim of the present study was to assess QT interval corrected for heart rate (QTc) and QTd in patients with type 2 diabetes and sleep apnea syndrome (SAS) comparative with patients with type 2 diabetes without sleep apnea.* ***Methods.*** *52 subjects with type 2 diabetes were included in the study. According to apnea-hypopnea index (AHI) patients were divided into three groups: 1) control subjects (AHI < 5/hour of sleep); 2) patients with mild SAS (AHI=5-15/hour of sleep) and 3) patients with moderate–severe SAS (AHI≥15/hour of sleep). Bazett's formula (QTc=QT/√RR) was used to obtain heart rate corrected values of the QT intervals and dispersions.* ***Results.*** *Prevalence of increased QTc interval in the whole population was 19.2% (10.5% in control group and 26.1% in moderate/severe SAS group). The mean QTd was 52.7 ms in all patients, with values increasing from 40.0 ms in controls to 64.8 ms in group with moderate-severe SAS. Statistically significant positive association was found between QTd and oxygen desaturation index (ODI) (β=0.38, p=0.006) and between QTd and AHI (β=0.29, p=0.03). In addition, a statistically significant negative association was found between QTd and mean SaO_2 (β= -0.40, p=0.003) and between QTd and minimum SaO_2 (β= -0.43, p=0.001). After adjustment for confounding factors, AHI, ODI, mean SaO_2 and minimum SaO_2 remained statistically significant associated with QTd.* ***Conclusion.*** *Sleep apnea is associated with changes in QT interval variability in patients with type 2 diabetes. Increased severity of SAS, as determined by AHI, may result in inhomogeneity of repolarization, favoring ventricular tachyarrhytmias.*

keywords*: QT interval, type 2 diabetes, sleep apnea*

Background

Delayed cardiac repolarization leading to the prolongation of the QT interval is a well-characterized precursor of arrhythmias [1]. The variability in the QT interval duration between the different leads of a surface 12-lead ECG reflects local differences in recovery time of the myocardium [2,3]. Increased QTd may indicate non-uniform ventricular

repolarization, thus possibly providing a substrate for the development of malignant ventricular arrhythmias [1].

Patients with diabetes mellitus are at an increased risk of dying from cardiovascular diseases. Excess cardiovascular risk in this population persists even after normalization of other conventional cardiovascular risk factors (hypertension, dyslipidaemia, physical inactivity, smoking) suggesting that there are other incompletely understood mechanisms which increase cardiovascular risk in diabetic patients [4]. Ventricular instability, as manifested in QT abnormalities, might be an important additional mechanism [4]. Prevalence of prolonged QT interval and increased QTd is higher in people with type 1 and type 2 diabetes as compared to non-diabetic subjects [5,6], especially in the presence of autonomic neuropathy [7]. Prolonged QTc and increased QTd are independent markers for CHD in type 1 and type 2 diabetes [5,6] and have been demonstrated to be highly significant predictors of cardiac death [8] even in newly diagnosed type 2 diabetes [9].

Recently, there has been increasing recognition that sleep-disordered breathing is frequently associated with type 2 diabetes, and the observed association has important clinical and public health implications [10]. Sleep apnea syndrome (SAS) represents an ensemble of signs and symptoms caused by repetitive episodes of absence (apnea) or reduction (hypopnea) of the airflow at the nose/mouth during the sleep, associated with fall in oxygen saturation, arousals and awakenings [11]. It is now well established that SAS is associated with increased cardiovascular risk and is increasingly recognized as a potential target for the prevention of cardiovascular disease. Given that cardiovascular diseases are the main cause of death in patients with type 2 diabetes, this association could be particularly important in this group of patients.

The aim of the present study was to assess QTd in patients with type 2 diabetes and sleep apnea comparative with patients with type 2 diabetes without sleep apnea.

Methods

Study population

85 consecutive patients with type 2 diabetes presenting for routine visit in the outpatient clinic from Clinical Center of Diabetes, Nutrition and Metabolic Diseases Cluj-Napoca were invited to perform an in-hospital sleep study as a part of a research aiming to determine the prevalence of sleep apnea syndrome in patients with type 2 diabetes. Patients were invited to participate to the study regardless of age, gender, severity of obesity or presence or absence of SAS symptoms. All study participants had type 2 diabetes (defined according to World Health Organization criteria) [12] and were required to sign an informed consent before beginning the study procedures. Patients were excluded from the study if they had type 1 diabetes, other specific form of diabetes, current diagnosis of sleep apnea or refused to sign an informed consent form.

Of these patients, for current analysis were excluded those receiving medication that could affect their sleep (e.g. hypnotics, sedatives etc), having diseases that may change QT interval or make the measurement difficult (bundle branch block, atrial

fibrillation, any arrhythmias, hypothyroidism, chronic renal or hepatic diseases by both self-report and serum analysis, diabetic autonomic neuropathy) or serum electrolytes imbalances. None of the subjects were taking medications that could potentially prolong QT interval (antiarrhythmic drugs, antihistaminic, psychotropic, or antibiotics medications).

A physical examination was performed in all subjects. Systolic (SBP) and diastolic (DBP) blood pressures were measured in the sitting position using a sphygmomanometer after 5 min rest. Body weight and height were measured while the subjects were wearing light clothes and no shoes. Body mass index (BMI) was calculated as weight (kg)/[height (m)]^2.

A complete medical history, including diabetes duration, diabetes treatment and treatment for associated diseases was collected. Fasting blood samples were drawn from every individual in the morning after an 8 hours overnight fasting period in order to assess the levels of fasting plasma glucose, glycated hemoglobin, total cholesterol, HDL-cholesterol, triglycerides, creatinine and hepatic enzymes. LDL-cholesterol was calculated using Friedewald formula [13]. The Epworth Sleepiness Scale (which evaluates daytime sleepiness) [14] was administered to all patients.

The research was conducted in accordance with the guidelines in The Declaration of Helsinki and the medical ethical committee of the Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca approved the study protocol.

Measurement of QT interval and dispersion followed the protocol described by Dursunoglu et al. [1]. In the morning, after 5 min rest in the supine position, a 12- lead ECG was recorded at a paper speed of 25 mm/s on a six channel recorder. Two consecutive cycles were measured from each of the standard 12 leads and a mean QT was calculated from the two values. The QT intervals were manually measured from the onset of the QRS to the end of the T-wave, defined as the return to TP isoelectric baseline, by a tangential method [15]. Only monophasic well-defined T-waves were accepted for measurement. When U-waves were present, the QT was measured to the nadir of the curve between the T and U waves, with the aid of a tangent. The lead was not included in the analysis if the end of the T-wave could not be reliably determined, or if T-waves were isoelectric or of very low amplitude. A minimum of six leads, at least three precordial, was required for inclusion in the study. The measurements were performed manually. The QTd was defined as the difference between the maximum and minimum mean QT values calculated from two consecutive cycles in the same lead. Bazett's formula ($QTc=QT/\sqrt{RR}$) was used to obtain heart rate corrected values of the QT intervals (QTc) and dispersions [16]. A QTc > 440 ms was considered abnormally prolonged.

Sleep study

All the patients had undergone a complete in-hospital sleep study. The sleep study performed with ApneaLink^{TM} device (ResMed Corporation, Poway, Calif) consisted of the following: (1) nasal pressure detection using a nasal cannulae/pressure transducer system; (2) finger pulse oximeter and (3) breathing sound. Apnea was defined as the decrease in airflow by 90% of baseline for at least 10 seconds; and hypopnea was defined as decrease in

respiratory flow by 30% of baseline with ≥ 4% oxygen desaturation [11,17]. The sleep data were downloaded by ApneaLink's host software, a Windows-based application and then manually scored. All the information gathered were used to calculate apnea/ hypopnea index (AHI) and oxygen desaturation index (ODI). AHI represents the mean number of apneas and hypopneas per hour of sleep. ODI was defined as number of 4% desaturation events per hour of sleep.

According to the AHI and symptoms (daytime sleepiness, loud snoring, etc), 52 subjects that presented no exclusion criteria were divided into three groups: 1) control subjects (AHI < 5/ hour of sleep and no symptoms; n=19); 2) patients with mild SAS (AHI=5-15/hour of sleep and symptoms, n=10) and 3) patients with moderate–severe OSAS (AHI ≥15/ hour of sleep, n=23).

Statistical analysis

Statistical analysis was carried out using SPSS-PC 15.0 (SPSS Inc., Chicago, IL, USA). Skewness and kurtosis were used to test the normal distribution of the variables. Data are reported as means and standard deviation for variables with normal distribution. **One-way ANOVA** analysis was used for comparative analysis. Association between sleep respiratory parameters, QTd and QTc was tested assuming a linear relationship. The level of significance was set at 0.05, and all tests were performed twice.

Results

A total of 30 men and 22 women were included in the study. Basic characteristics and QTd of the patients are shown in table 1. The mean ESS score of the study population was 9.7±5.3 (range 0–21). There were no significant differences between moderate–severe SAS patients, mild SAS and controls according to sex, age, mean A1c, SBP, DBP and HR ($p>0.05$). AHI and ODI were significantly higher in moderate–severe SAS patients than in mild SAS and controls ($p<0.0001$), and, these patients had the lowest average and minimum nocturnal saturation of arterial oxygen ($p<0.0001$).

Also, data were analyzed regarding the prevalence of arterial hypertension and ischemic heart disease. There was no statistically significant difference between the three groups regarding the prevalence of arterial hypertension and ischemic heart disease ($p>0.05$).

Prevalence of increased QTc interval in the whole population was 19.2% (10.5% in control group and 26.1% in moderate/severe SAS group). The mean (SD) QTd was 52.7 ms (25.1) in all patients, with values increasing from 40.0 ms in controls to 64.8 ms in group with moderate-severe SAS.

Univariate linear regression analysis was performed to evaluate the relationship between QTd and parameters evaluated during sleep study. Statistically significant positive association was found between QTd and ODI ($\beta=0.38$, $p=0.006$) and between QTd and AHI ($\beta=0.29$, $p=0.03$). In addition, a statistically significant negative association was found between QTd and mean SaO_2 ($\beta= -0.40$, $p=0.003$) and between QTd and minimum SaO_2 ($\beta= -0.43$, $p=0.001$).

In order to avoid effects of confounding factors such as age, BMI, HR, SBP, DBP, CHD and diabetes control, univariate linear regression analysis adjusted for these factors was performed. Multiple regression analysis

was not used in consideration of problems related to colinearity. After adjustment for confounding factors, AHI, ODI, mean SaO_2 and minimum SaO_2 remained statistically significant associated with QTd (table 2).

Table 1. Characteristics of patients according to the severity of sleep apnea

	Controls (n=19)	Mild SAS (n=10)	Moderate-severe SAS (n=23)	p-value
Men No (%)	11 (57.9)	4 (40.0)	15 (65.2)	NS
Age (years)	53.6±12.4	56.5±8.3	56.5±5.6	NS
BMI (kg/m^2)	34.7±5.3	34.9±1.9	38.3±5.6	NS
A1c (%)	7.4±1.4	8.7±1.7	8.5±1.6	0.04
SBP (mmHg)	147.3±20.3	149.4±26.7	148.4±21.4	NS
DBP(mmHg)	91.5±11.3	89.9±15.3	83.3±11.8	NS
Diabetes duration (years)	6.4±5.5	8.8±4.4	7.5±7.4	NS
CHD No (%)	9 (47.4)	4 (40.0)	9 (39.1)	NS
ESS score	5.7±3.5	11.4±3.5	12.5±4.9	<0.001
AHI (events /hour)	2.8±2.2	8.3±1.8	41.8±24.1	<0.001
ODI (events /hour)	3.8±2.7	11.3±3.5	40.9±27.5	<0.001
SaO_2 mean (%)	96.3±1.3	93.0±1.8	91.2±2.2	<0.001
SaO_2 min (%)	90.1±4.6	80.7±6.9	74.8±5.9	<0.001
HR (beats/min)	76.8±10.0	72.7±11.9	78.1±9.8	NS
QTc (ms)	412.3±32.2	407.2±16.9	431.7±33.9	NS
QTd (ms)	40.0±13.7	49.0±25.1	64.8±27.4	0.004

Data in table are presented as mean±SD; No – number; BMI - body mass index; A1c – glycosilated hemoglobin; AHI - apnea–hypopnea index; ODI – oxygen desaturation index; ESS - Epworth Sleepiness Scale; SaO_2 - mean O_2 saturation; SaO_2 min – minimum O_2 saturation; QTc – heart rate corrected QT interval; QTd – QT interval dispersion; CHD – coronary heart disease; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate

Table 2. Univariate linear regression analysis for QTd adjusted for age, BMI, HR, SBP, DBP, CHD and HbA1c

	QTd β p
AHI (events /hour)	0.32 0.03
ODI (events /hour)	0.43 0.006
SaO_2 mean (%)	-0.33 0.04
SaO_2 min (%)	-0.36 0.03

QTd – QT interval dispersion; BMI – body mass index; A1c – glycosilated hemoglobin; AHI – apnea-hypopnea index; ODI – oxygen desaturation index; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate

No relationship between QTc interval and sleep respiratory parameters was found (in unadjusted or adjusted linear regression).

Discussion

A single QT interval on the surface ECG does not give any information on dispersion of recovery time but QTd is said to reflect spatial

differences in myocardial recovery time [18]. In patients with type 2 diabetes, increased QTd seems to represent the sum of several adverse cardiac abnormalities such as fibrosis, hypertrophy, dilatation, ischaemia and autonomic dysfunction [9,19]. All these factors individually confer increased cardiovascular risk and QTd, as a summation, could be a global prognostic marker for cardiac mortality in patients with diabetes [4].

The main finding of this study was a strong association between QT interval dispersion and respiratory sleep parameters in patients with type 2 diabetes. This relationship was independent of BMI, systolic and diastolic blood pressure, HbA1c and presence of coronary heart disease. Patients with greater severity of OSA, as determined by a higher AHI, had greater fluctuations in QT interval duration. None of the sleep respiratory parameters were associated with the length of the QT interval corrected for heart rate. Another important finding of our study is that the prevalence of abnormally long QTc interval increases with severity of sleep apnea: from 10.5% in the control group, to 26.1% in patients with moderate-severe sleep apnea.

SAS patients are at higher risk of sudden cardiac death [20]. In contrast to the general population, death occurs more often at night in SAS patients [21], suggesting the involvement of a sleep related mechanism/event. Several previous studies have reported an association between SAS and QT interval dispersion [1,22,23]. Dorsunoglu et al. reported that in patients with SAS, but without other comorbidities, QT interval dispersion is increased and that its value is significantly correlated with parameters associated with SAS severity (AHI and ODI) [1]. In the present study we obtained similar results. To support these results, Dursunoglu demonstrated in 2007 that in SAS patients without hypertension, CPAP therapy improves the inhomogenity of repolarization via a significant decrease in QTd [24].

Increased QTd has been observed in chronic heart failure, peripheral vascular disease, hypertension, hypertrophic cardiomyopathy and in CHD and has been correlated with increased risk of cardiovascular death in these conditions and in healthy subjects [4]. Also, there are numerous evidences linking obesity and diabetes to increased QTd [4-6,8,25]. In order to eliminate the effect of these confounding factors on QTd, univariate linear regression analysis adjusted for these factors was performed. Multiple regression analysis was not used in consideration of problems related to colinearity. After adjustment for cofounding factors, AHI, ODI, mean SaO_2 and minimum SaO_2 remained statistically significant associated with QTd, demonstrating that increased AHI and ODI may result in inhomogeneity of repolarization, favoring ventricular tachyarrhytmias. To the best of our knowledge, this is the first research that aimed to investigate the effect of SAS on QT interval in patients with type 2 diabetes.

This study has several limitations. One of the limitations is that most of the patients included were obese. In addition, the relatively low number of our study population (n=52) and the use of ApneaLink instead of an overnight polysomnography, which is considered the "gold standard" for the diagnosis of sleep apnea would affect the results. And last, but not least, a group of healthy control subjects and a group of

patients with SAS but without diabetes would help us to clarify the interaction between SAS, diabetes and QTd.

In **conclusion**, sleep apnea is associated with changes in QT interval variability in patients with type 2 diabetes. Increased severity of SAS, as determined by AHI, may result in inhomogeneity of repolarization, favoring ventricular tachyarrhytmias.

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Correspondence Data:
Adriana Rusu
Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca,
Department of Diabetes, Nutrition, Metabolic Diseases
2-4 Clinicilor Street
400006 Cluj-Napoca, Romania
Phone: +40773081977; Fax: +40264594455
Email: adi.rusu@yahoo.com