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Original Article

The influence of type 2 diabetes and gender on ventricular repolarization dispersion in patients with sub-clinic left ventricular diastolic dysfunction

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Abstract: Objective: To assess the influence of type 2 DM and gender, on the QT dispersion, Tpeak-Tend dispersion of ventricular repolarization, in patients with sub-clinic left ventricular diastolic dysfunction of the heart. Background: QT dispersion, that reflects spatial inhomogeneity in ventricular repolarization, Tpeak-Tend dispersion, this on the other hand reflects transmural inhomogeneity in ventricular repolarization, that is increased in an early stage of cardiomyopathy, and in patients with left ventricular diastolic dysfunction, as well. The left ventricular diastolic dysfunction, a basic characteristic of diabetic heart disease (diabetic cardiomyopathy), that developes earlier than systolic dysfunction, suggests that diastolic markers might be sensitive for early cardiac injury. It is also demonstrated that gender has complex influence on indices of myocardial repolarization abnormalities such as QT interval and QT dispersion. Material and methods: We performed an observational study including 300 diabetic patients with similar epidemiological-demographic characteristics recruited in our institution from May 2009 to July 2014, divided into two groups. Demographic and laboratory echocardiographic data were obtained, twelve lead resting electrocardiography, QT, QTc, Tpeak-Tend-intervals and dispersion, were determined manually, and were compared between various groups. For statistical analysis a t-test, X^2 test, and logistic regression are used according to the type of variables. A p value <0.05 was considered statistically significant for a confidence interval of 95%. Results: QTc max. interval, QTc dispersion and Tpeak-Tend dispersion, were significantly higher in diabetic group with subclinical LV (left ventricular) diastolic dysfunction, than in diabetic group with normal left ventricular diastolic function (445.24±14.7 ms vs. 433.55±14.4 ms, P<0.000; 44.98±18.78 ms vs. 32.05±17.9 ms, P<0.000; 32.60±1.6 ms vs. 17.46±2.0 ms, P<0.02. Prolonged QTc max. interval was found in 33% of patients, indiabetic group with subclinical left ventricular diastolic dysfunction vs. 13.3% of patients in diabetic group with normal left ventricular diastolic function, (Chi-square: 16.77, P<0.0001). A prolonged QTc dispersion, was found in 40.6% of patients, in diabetic group with subclinical left ventricular diastolic dysfunction vs. 20% of patients in diabetic group with normal left ventricular diastolic function Chi-square: 14.11, P<0.0002). A prolonged dispersion of Tpeak-Tend interval was found in 24% of patients in diabetic group with subclinical left ventricular diastolic dysfunction vs. 13.3% of patients in diabetic group with normal left ventricular diastolic function (Chi-square: 12.00, P<0.005). Females in diabetic group with subclinical left ventricular diastolic dysfunction in comparison with males in diabetic group with subclinical left ventricular diastolic dysfunction, have a significantly prolonged: mean QTc max. interval (23.3% vs. 10%, Chi-square: 12.0, P<0.005), mean QTc dispersion (27.3% vs. 13.3%, Chi-square: 10.24, P<0.001), mean Tpeak-Tend interval (10% vs. 3.3%, Chi-square: 5.77, P<0.01), mean Tpek-Tend dispersion (16.6% vs. 6.6%, Chi-square: 8.39, P<0.003). Conclusion: The present study has shown that influences of type 2 diabetes and gender in diabetics with sub-clinical left-ventricular diastolic dysfunction are reflected in a set of electrophysiological parameters that indicate a prolonged and more heterogeneous repolarization than in diabetic patients with normal diastolic function. In addition, it demonstrates that there exist differences between diabetic females with sub-clinic LV dysfunction and those with diabetes and normal LV function in the prevalence of increased set of electrophysiological parameters that indicate a prolonged and more heterogeneous repolarization.

Keywords: Type 2 diabetes, gender, dispersion of ventricular repolarization

Introduction

Prevalence of type 2 diabetes has been increasing worldwide in the last two decades, increasing fastin the female gender, and with them, the cardiovascular complications [1, 2].

Patients with diabetes mellitus have high cardiovascular morbidity and mortality. This risk remains elevated even after normalization of conventional cardiovascular risk factors (hypertension, dyslipidemia, physical inactivity, smoking habit, etc.), which suggests the existence of other mechanisms. The ventricular electrical instability, manifested in changes in the QT interval and QT dispersion, appears to be another important mechanism [3].

QT dispersion, that reflects spatial inhomogeneity in ventricular repolarization, Tpeak-Tend dispersion, that reflects transmural inhomogeneity in ventricular repolarization, are associated with increased risk of certain arrhythmias and sudden cardiac death in type 2 diabetic patients and general population [4-14]. Several studies, but not all, have found a significantly greater QT dispersion in diabetics [15-21].

QT dispersion has increased an early stage of cardiomyopathy, and also in patients with left ventricular diastolic dysfunction [7]. The repolarization abnormalities such as QT dispersion, has been reported that reflects left ventricular diastolic dysfunction [9]. The left ventricular diastolic dysfunction is an important underlying factor in the development of certain arrhythmias [6]. The left ventricular diastolic dysfunction a basic characteristic of diabetic heart disease (diabetic cardiomyopathy), appears before the development of systolic dysfunction, suggesting that diastolic markers might be sensitive for early cardiac injury [22]. Evidence is beginning to emerge that significant sex-related differences in the integrative neural control of the cardiovascular system exist. Prevalence of diastolic heart failure is greater in females with type 2 diabetes. Gender differences exist in cardiac electrophysiology, which significantly impacts the presentation, diagnosis and management of arrhythmias in women. Gender demonstrates a complex interaction on indices of myocardial repolarization abnormalities such as QT interval and QT dispersion [23-26].

The aim of this study was to assess the influence of type 2 DM and gender, on the QT dispersion, Tpeak-Tend dispersion of ventricular repolarization, in patients with sub-clinic left ventricular diastolic dysfunction of the heart.

Methods

We performed an observational study including 300 diabetic patients with similar epidemiological-demtographic characteristics recruited in our institution from May 2009 to July 2014, divided into two groups. One group comprised of 150 diabetics patients with sub-clinical left ventricular diastolic dysfunction and second group comprised of 150 with type 2 diabetes mellitus and normal left-ventricular diastolic function.

Inclusion criteria encompassed all individuals with type 2 diabetes mellitus between the ages of 45 and 55, diagnosed in accordance with the criteria of the American Diabetes Association [27].

We excluded all patients with: Age under 45 and over 55, arterial hypertension, ischemic heart disease(detected by anamnesis, surface electrocardiogram, exercise testing, left ventricular wall abnormalities in echocardiographic examination), cardiac arrhythmias, congenital or acquired valvular heart disease, left/right bundle branch block, pre-excitation syndromes, patients with pacemakers, and dialysis patients. We also excluded patients treated with drugs that prolong the QT interval, suggested by the European Society of Cardiology (ESC), [28], and patients with poor echocardiographic window.

Clinical evaluation: Detailed anamnesis data were taken from each patients and a physical examination was completed. The clinical data include: Age, sex, body weight and height, body mass index (BMI) [29], the duration and way of treatment of diabetes, the medication (hypoglycemia's). Measuring of blood pressure according to standard protocol [30]. All patients and healthy subjects underwent stress test ergometry examination in the period of less than a week from echocardiographic examination.

In the blood and urine samples the determined were the values of: Glycaemia, lipid profile (Total cholesterol, LDL-chol, HDL-chol, triglycer-

ides), and serum urea and creatinine were performed in all case and control subject. Routine biochemical measurements were performed. Echocardiographic measurements (M-mode, two-dimensional and Doppler echocardiography), were performed and/or reviewed by experienced staff cardiologists, compliant with the recommendation of the American Society of Echocardiography [31], stored in DICOM format and later reviewed by two experienced echocardiographers blinded to the ECG parameters.

Diastolic dysfunction was defined as an E/e' ratio >8, compliant with recommendation of the American Society of Echocardiography [32].

Throughout all echocardiographic findings, a consensus reading was again applied. Patients were excluded if they had poor echocardiographic image quality or poor quality tissue Doppler tracings, signs of left ventricular systolic dysfunction (EF <55 %), regional wall motion abnormalities, pericardial effusion, severe valvulopathies including relevant annular calcification and suspected or known familiar forms of hypertrophic and/or infiltrative cardiopathies due to secondary ECG changes (i.e. T wave inversions, bundle branch blocks, ST segment changes), which would have otherwise falsified the interpretation of the indices of interest. Echocardiographic examination were performed by operators unaware of presence of diabetes.

We conducted a simple 12-lead ECG in all diabetic patients. The ECG was always performed with the patient's supine, at rest, at a paper speed of 50 mm/s and voltage of 10 mm/mV. To make the ECGs we used the electrocardiograph Cardioline-Delta 1 Plus. For the control group we also conducted simple 12-lead electrocardiograms under the same conditions and measurements used for the diabetic patients. The subjects were required to have a normal ECG and with no pathologic processes that might affect ventricular repolarization. To this end, we conducted a consultation of the clinical process and only one ECG of the individuals that met the desired criteria. For the analysis of the ECG, we performed a manual measurement of the values using a digital caliper with measuring range of 0-150 mm, 0.01 mm resolution, and 0-100±0.02 mm accuracy. The value obtained was converted to milliseconds (ms).

Measurement of the QT interval (the interval from the start of the QRS complex to the end of the T-wave) was performed in all 12 leads, and the longest and the shortest intervals measured were selected. QT interval dispersion was obtained by the difference between the maximum and the minimum QT intervals found in the 12-lead electrocardiogram. The QT interval was corrected according to Bazett's formula which consists in dividing the measured QT by the square root of the RR interval ($QTc = QT/\sqrt{RR}$), thus providing the QT interval value adjusted for heart rate.

The QTc dispersion was obtained by the difference between the highest and the lowest values of QTc in the 12 leads of the ECG. [33].

According to internationally accepted guidelines, the QTc interval was considered prolonged when higher than 440 ms for male patientss, and higher than 460 ms for female patients [34]. The QT dispersion was considered prolonged when higher than 65 ms, according to other previously conducted studies [35]. Measurement of the Tpeak-Tend interval was conducted in DII, V2 and V5 leads. The Tpeak-Tend interval was obtained from the difference between QT interval and QTpeak interval. The Tpeak-Tend interval was considered prolonged when greater than 100 ms, and the Tpeak-Tend dispersion was considered prolonged when higher than 20 ms, as suggested by otherstudies [36]. The ECG was performed by the same operator, and the aforementioned measurements were made by two independent observers. In case of disagreement on the values obtained, the measurements were repeated by a third observer with expertise in electrocardiographic analysis.

The study is in compliance with the Declaration of Helsinki. All patients that participated in this study were informed in detail and were asked to provide written accordance for their voluntary participation in the study.

Statistical analysis

The collected data were entered in the software SPSS for Windows, version 19.0, which performed a statistical analysis. The distribution of variables was tested for normality using the Kolmogorov-Smirnov test, and the heterogeneity of variances was evaluated by Levene's test. A

Table 1. Basic demographic, clinical, echocardiographic and laboratory characteristics of study groups: diabetics with normal diastolic function (n-150) and diabetics with diastolic dysfunction (n-150)

Variables	Diabetics with normal diastolic function (n-150, of which 75 F and 75 M)		Diabetics with diastolic dysfunction (n-150, of which 75 F and 75 M)		*P*-value
	Mean	S.D.	Mean	S.D.	
Age (y)	50.33	±4.1	49.9	±3.9	0.38
BMI (kg/m)	25.7	±3.8	28.1	±5.2	0 .001
D.M.-duration (years)	3.3	±1.9	4.9	±1.2	0.01
SBP (mmHg)	117.8	±7.8	119.7	±6.5	0.95
DBP (mmHg)	79.5	±2.3	79.8	±2.9	0.49
Glic. (mmol/dl)	6.2	±0.6	6.5	±0.8	0.001
Ch.tot. (mmol/dl)	6.0	±0.8	6.1	±0.9	0.62
LDL-ch. (mmol/dl)	4.1	±0.8	4.3	±0.8	0.06
HDL-ch. (mmol/dl)	0.95	±0.1	0.96	±0.2	0.94
Trig. (mmol/dl)	2.3	±0.4	2.4	±0.8	0.09
LVM (gr)	103.6	±17.4	110.7	±20.7	0.001
E (cm)	0.76	±0.13	0.47	±0.11	0.000
A (cm)	0.50	±0.11	0.65	±0.10	0.000
E/A-rat	1.5	±0.02	0.72	±0.03	0.000
E/e'-rat	7.1	±0.58	9.0	±1.1	0.000

Valua are mean ± standard deviation; BMI = body mass index; D.M.-duration = diabetes mellitus duration; SBP = systolic blood pressure; DBP = diastolic blod presure; Disfun = disfunction; Glic. = glicemia; Ch-tot. = total holesterol; LDL-ch. = low density holesterol; HDL-ch. = hight density holesterol; Trig. = trigicerides. LVM = leftventricular mass E-peak velocity of early diastolic filling; A-peak of late diastolic filling; *P*-value <0.05 staistical significancy.

simple descriptive analysis was performed for the general characterization of the sample and distribution of variables. Continuous variables were presented as mean ± standard deviation, and categorical variables were presented as frequency (%). Differences between groups were analyzed using the Student t test for independent samples. Categorical data were analyzed using the chi-square (X^2) test. The association between variables were analyzed using logistic regression. A *p* value <0.05 was considered statistically significant for a confidence interval of 95%.

Results

The sample used for this study involved diabetic patientss n-300 (150 with normal diastolic function and 150 with sub-clinic left ventricular diastolic dysfunction).

Baseline demographic, clinical, echocardiographic and laboratory data are shown in **Table 1**. There were no statistically significant differences in age between the diabetic group with subclinic left ventricular diastolic dysfunction and diabetic group with normal left ventricular diastolic function (mean age 49.9±3.9 years versus 50.33±4.1, P=0.38). No significant changes were observed in relation to systolic and diastolic blood pressure, between the diabetic group with subclinic left ventricular diastolic dysfunction and diabetic group with normal left ventricular diastolic function (mean SBP of 119.7±6.5 mmHg vs. 117±7.8 mmHg, P>0.95; mean DBP of 79.8±2.9 mmHg vs. 79.5±2.3 mmHg, P>0.49). No significant changes were observed in relation to Tot. cholesterol, LDL-cholesterol, HDL-cholesterol, Triglicerides (6.1±0.9 vs. 6.0±0.8, P>0.62; 4.3±0.8 vs. 4.1±0.7, P>0.06; 0.95±0.1 vs. 0.95±0.4, P>0.09). Significant changes between groups were observed in relation to: BMI, was significantly higher in diabetic group with subclinic left ventricular diastolic dysfunction than the diabetic group with normal left ventricular diastolic function (28.1±5.2 mmol/dl vs. 25.7±3.8, P<0.01. D.M duration, was significantly higher in diabetic group with subclinic left ventricular diastolic dysfunction than the diabetic group with normal left ventricular diastolic function (4.9±1.2 year vs. 3.3±1.9 year, P<0.01. Glycaemia, was significantly higher in diabetic group with subclinic left ventricular diastolic dysfunction than the diabetic group

Table 2. ECG-characteristics of study groups: diabetics with normal diastolic function (150 patients) anddiabetics with diastolic dysfunction (n-150 patients)

Variables		Diabetics with normal diastol. funct. (n-150)	Diabetics with diast. dysfunct. (n-150)	*P*-values
QT interval (ms)	QT max	398.08±10.79	399.65±13.45	0.59
	QT mean	384.56±8.45	383.94±10.31	0.27
	QT min	370.98±10.18	369.88±11.24	0.21
QTc intrerval (ms)	QTc max	433.55±14.4	445.24±14.7	0.000
	QTc mean	418.60±6.61	419.24±11.52	0.55
	QTc min	393.58±13.46	393.78±12.23	0.89
QT dispersion (ms)		30.15±1.7	30.81±2.7	0.1
QTc dispersion (ms)		32.05±17.19	44.98±18.78	0.000
Tpeak-Tend intervals (ms)	Lead II	73.29±2.49	73.48±3.56	0.6
	Lead V2	72.25±3.33	72.86±3.92	0.1
	Lead V5	75.86±2.44	76.48±8.07	0.5
Tpeak-Tend dispersion		17.46±2.0	32.60±1.6	0.02

QTc max = QTc maximal duration in ms; QT min = minimal duration; QTc dispers = QTc dispersion in miliseconds; Tpeak-Tend = duration of Tpeak-Tend interval in miliseconds; Tpeak-Tend dispersion = duration of Tpeak-Tend dispersion in milliseconds. *P*-value <0.05 staistical significancy.

Table 3. Prevalence of increased QTc maximal interval duration,increased QTc dispersion and increased Tpeak-Tend interval duration ,increased Tpeak-Tend dispersion in the diabetics with normal diastolic function and in the diabetics with diastolic dysfunction

Variables	Diabetics with normal diastol. funct. (n-150)	Diabetics with diast. dysfunct. (n-150)	*P*-values
		Chi-square: 16.77	
Increased of QTc max duration (n; %)	20 (13.3%)	50 (33.3%)	0.0001
		Chi-square: 14.11	
Increased of QTc dispers duration (n; %)	30 (20%)	61 (40.6%)	0.0002
		Chi-square: 6.88	
Increased of Tp-Te duration (n; %)	7 (4.6%)	20 (13.3%)	0.0087
		Chi-square: 12.00	
Increased of Tpeak-Tend dispersion duration (n; %)	20 (13.3%)	36 (24%)	0.005

QTc max = QTc maximal duration in ms; QTc dispers = duration of QTc dispersion in ms; Tpeak-Tend = duration of Tpeak-Tend interval in ms; Tpeak-Tend dispersion = duration of Tpeak-Tend dispersion in ms. *P*-value <0.05 staistical significancy.

with normal left ventricular diastolic function (6.5±0.8 mmol/dl vs. 6.0±0.6 mmol/dl, P< 0.001). The majority of echocardiographic data did not show significant differences among patients between the groups. Significant differences among patients between the groups, were observed in relation to the data acquired with the pulsed-wave Doppler, on transmitral flow. The diabetic group with subclinic left ventricular diastolic dysfunction had significantly lower peak velocity of E-wave (0.47±0.11 vs. 0.76±0.13, P<0.000). The diabetic group with subclinic left ventricular diastolic dysfunction had significantly higher: peak velocity of A-wave (0.65±0.10. vs. 0.50±0.11. P<0.000); E/e'-rat. (9.0±1.1 ms vs. 7.1±0.58, P<0.000); IVR of (124.7±24.9 ms vs. 89.2 ±72, P<0.000); DCT of (267±38.4 ms vs. 186.8±12.8 ms, P<0.000). The diabetic group with subclinic left ventricular diastolic dysfunction had significantly higher LVM (110.7±20.7 gr vs. 103.6 ±17.4 gr, P<0.001).

We conducted a comparative analysis between diabetic group with subclinic left ventricular diastolic dysfunction and diabetic group with normal left ventricular diastolic function, of the following parameters: QT and QTc intervals, QT and QTc dispersions, Tpeak-Tend intervals, and Tpeak-Tend dispersions. Data are shown in **Tables 2**, **3** and **Figures 1**, **2**.

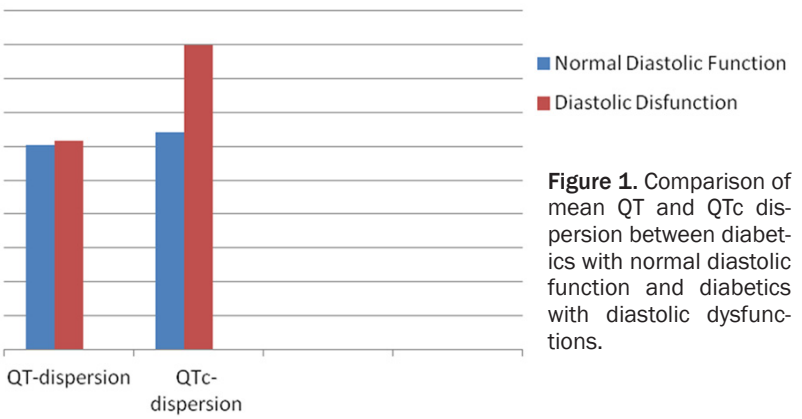

Figure 1. Comparison of mean QT and QTc dispersion between diabetics with normal diastolic function and diabetics with diastolic dysfunctions.

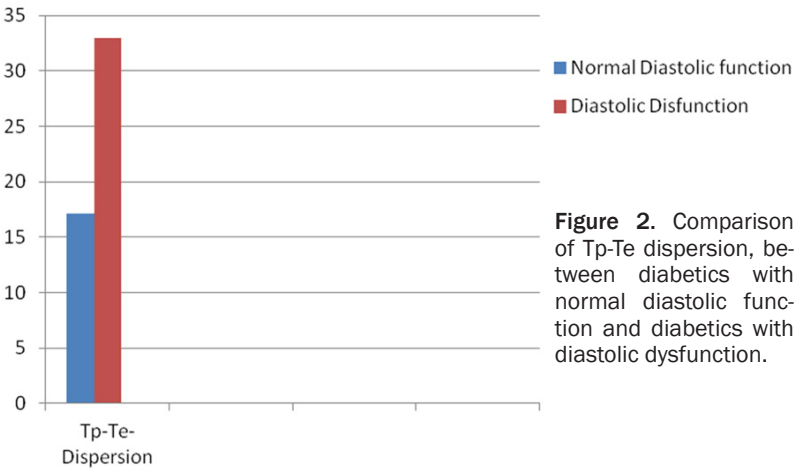

Figure 2. Comparison of Tp-Te dispersion, between diabetics with normal diastolic function and diabetics with diastolic dysfunction.

QT and QTc intervals

The result showed that, only mean of QTc max. interval, were significantly higher in diabetic group with subclinic left ventricular diastolic dysfunction, than in diabetic group with normal left ventricular diastolic function (445.24±14.7 ms vs. 433.55±14.4 ms, P<0.000). No significant differences were observed between groups in: others means QT intervals and means of corrected for Heart rate QT intervals. QT max (399.65±13.45 ms. 398.08±1079, P>0.59); QT mean. (383. 94±10.31 ms. vs. 384.56±8.45 ms, P>0.27); mean QT min. (369.88±11.24 ms. vs. 370.98±10.18, P>0.21), mean QTc mean. (419.24±11.52 ms. vs. 418.60±6.61 ms, P>0.55); mean QTc min. (393.78±12.23 vs. 393.58±13.46±13.46 ms, P>0.89).

QT and QTc dispersion

The results showed that diabetic group with subclinic left ventricular diastolic dysfunction have a significantly higher mean QTc dispersion than diabetic group with normal left ventricular diastolic function, (44.98 ±18.78 ms vs. 32.05±17.9 ms, P<0.000). No significant differences were observed between groups in QT dispersion (30.81±2.7 vs. 30.15±1.7 ms, P=0.1).

A prolonged QTc max. interval, was found in 33% of patients, indiabetic group with subclinic left ventricular diastolic dysfunction, and in 13.3% of patients in diabetic group with normal left ventricular diastolic function, the differences were statistically significant. (Chi-square: 16.77, P<0.0001).

A prolonged QTc dispersion, was found in 40.6% of patients, in diabetic group with subclinic left ventricular diastolic dysfunction and in 20% of patients in diabetic group with normal left ventricular diastolic function, the differences were statistically significant. (Chi-square: 14.11, P<0.0002).

Tpeak-Tend intervals

Regarding the comparison of Tpeak-Tend intervals, in diabetic group with subclinic left ventricular diastolic dysfunction and in diabetic group with normal left ventricular diastolic functionhere were no statistically significant differences in any of the comparisons made. Mean Tpeak-Tend intervals in: DII (73.48±3.56 ms vs. 73.29±2.49 ms, P>0.6; V2 (72.86±3.92 ms vs. 72.25±3.33 ms, P=0.1; V5 (76.48±8.07 ms vs. 75.86±2.44 ms, P>0.5.

Dispersion of Tpeak-Tend interval

Regarding the comparison of Dispersion of Tpeak-Tend intervals, in diabetic group with subclinic left ventricular diastolic dysfunction and in diabetic group with normal left ventricular diastolic function, the results showed that patients in diabetic group with subclinic left

Table 4. Relationship of gender and prevalence of increased QTc interval duration, QTc dispersion and Tpeak-Tend interval duration, Tpeak-Tend dispersion in the diabetics with normal diastolic function and in the diabetics with diastolic dysfunction

Variables	Diabetics with Normal Diastol. Funct. (75F and 75M)			Diabetics with Diast. Dysfunct. (75F and 75M)		*P*-values
	Females	Males	P	Females	Males	
Increased of QTc-max. duration (n; %)	11 (7.3)	9 (6.0)	0.63	35 (23.3)	15 (10)	0.005
	Chi-square: 0.23			Chisquare: 12.0		
Increased of QTc-dispers. duration (n; %)	14 (9.3)	16 (10.6)	0.7	41 (27.3)	20 (13.3)	0.001
	Chi-square: 0.15			Chisquare: 10.2		
Increased of Tp-Te duration (n; %)	3 (2.0)	4 (2.6)	0.7	15 (10)	5 (3.3)	0.01
	Chi-square: 0.14			Chi-square: 5.7		
Increased of Tp-Te Dispersion duration (n; %)	12 (8.0)	8 (5.3)	0.3	25 (16.6)	10 (6.6)	0.003
	Chi-square: 0.86			Chi-square: 8.39		

QTc max = QTc maximal duration in ms; QTc dispers = duration of QTc dispersion in ms; Tpeak-Tend = duration of Tpeak-Tend interval in ms; Tpeak-Tend dispersion = duration of Tpeak-Tend dispersion in ms. *P*-value <0.05 staistical significancy.

ventricular diastolic dysfunction have a significantly higher mean Tpeak-Tend dispersion than patients in diabetic group with normal left ventricular diastolic function. (32.60±1.6 ms vs. 17.46±2.0 ms, P<0.02).

Comparing the frequency of subjects with a prolonged Tpeak-Tend interval: (Above the cut-off limit determined for the study), the results showed that 13.3% of patients in diabetic group with subclinic left ventricular diastolic dysfunction had a prolonged Tpeak-Tend interval, and 4.6% of patients in diabetic group with normal left ventricular diastolic function had prolonged Tpeak-Tend interval. Difference were statistically significant. (Chi-square: 6.88 P<0.0087).

Comparing the frequency of subjects with a prolonged dispersion of Tpeak-Tend interval: (Above the cut-off limit determined for the study), the results showed that 24% of patients in diabetic group with subclinic left ventricular diastolic dysfunction had a prolonged Dispersion of Tpeak-Tend interval, and 13.3% of patients in diabetic group with normal left ventricular diastolic function had prolonged Dispersion of Tpeak-Tend interval. Difference were statistically significant. (Chi-square: 12.00, P<0.005).

Regarding the comparison the relationship of gender and prevalence of increased QTc interval duration, increased QTc dispersion duration and increased Tpeak-Tend interval duration, increased Tpeak-Tend dispersion duration, in diabetic group with diastolic dysfunction, and in the diabetic group with normal diastolic function, **Table 4** summarizes the results.

The results showed that females in diabetic group with subclinic left ventricular diastolic dysfunction in comparison with males with subclinic left ventricular diastolic dysfunction males, have a significantly prolonged: mean QTc max (23.3% vs. 10%, Chi-square: 12.0, P<0.005), mean QTc dispersion (27.3% vs. 13.3%, Chi-square: 10.24, P<0.001), mean Tpeak-Tend interval (10% vs. 3.3%, Chi-square: 5.77, P<0.01), mean Tpek-Tend dispersion (16.6% vs. 6.6%, Chi-square: 8.39, P<0.003).

There were no statistically significant differences in any of the comparisons made in diabetic group with normal diastolic function: mean QTc max (7.3% vs.6.0%, Chi-square: 0.23, P>0.63), mean QTC dispersion (9.3% vs. 10.6%, Chi-square: 0.15, P>0.7), mean Tpeak-Tend interval (2%% vs. 2.6%, Chi-square: 0.14, P>0.7), mean Tpek-Tend dispersion (8% vs. 5.3%, Chi-square: 0.86, P>0.35).

Discussion

The QT interval is the most used parameter in the electrocardiographic assessment of repolarization and its prolongation is associated with increased risk of arrhythmogenesis. The repolarization abnormalities such as QT dispersion, has been reported that reflects left ventricular diastolic dysfunction. The left ventricular diastolic dysfunction is an important underlying factor in the development of certain arrhythmias.

Therefore, in our study, we considered it important to assess this parameter in diabetic patients with sub-clinic left-ventricular diastolic dysfunction of the heart.

When comparing the QT intervals between diabetics with diastolic dysfunction and diabetics with normal diastolic function, no significant differences were found; however, the QT interval does not take into account the heart rate and, therefore, these results had no clinical relevance. However, after correcting the QT interval for heart rate using the formula of Bazzet, we found significant differences between diabetics with diastolic dysfunction and diabetics with normal diastolic function. QTc max. Interval and QTc dispersion, were significantly higher in diabetics with diastolic dysfunction. We found several studies that analyzed the QTc max. interval in diabetics with diastolic dysfunction. Most of these studies obtained results similar to those found in our study [9, 38, 39].

In our study, significant differences were observed in prevalence of prolonged values of QTc max. interval, and prolonged value of QTc dispersion, in diabetics with diastolic dysfunction when compared with diabetics with normal diastolic function, indicating that the repolarizationin diabetics with diastolic dysfunction was more heterogeneous than that observed in diabetics with normal diastolic function. Pathophysiologically, prolongation of the action potential duration may elicit manifest mechanical dysfunction through accumulation of intracellular calcium [41]. Others have found an also significantly prolonged values of QTc max. interval, QTc dispersion in diabetics with diastolic dysfunction [9, 38, 42, 43].

It is known a potential role of ECG indices, the Tpeak-Tend interval is a parameter that reflects the transmural dispersion of repolarization, for the recognition of patients with diastolic dysfunction [39]. It is known that diastolic function is more highly influenced by asynchronous motion than systolic function and dysfunction appears before the development of systolic dysfunction, suggesting that diastolic markers might be sensitive for early cardiac injury [44, 45]. In this study, when comparing the Tpeak-Tend intervals between diabetics with diastolic dysfunction and diabetics with normal diastolic function, no significant differences were found. One of thereasons for these results may have been the use of only three leads (DII, V2 and V5), which although providing a substantially orthogonal assessment (XYZ). In our study, significant differences were observed inprevalence of prolonged value of Tpeak-Tend dispersion, in diabetics with diastolic dysfunction when compared with diabetics with normal diastolic function. Results that are similar to previous studies of Tpeak-Tend dispersions in diabetic patientss [38, 39].

The majority of previous studies have shown that gender demonstrate a complex interaction onindices of myocardial repolarization with differen tmeasures behaving differently [18, 19]. In the present study, significant gender differences were observed inprevalence of prolonged values of QTc max. interval, Tpeak-Tend interval, QTc dispersion, Tpeak-Tend dispersion. The results showed that women in diabetic group with subclinic left ventricular diastolic dysfunction in comparison with in diabetic group with subclinic left ventricular diastolic dysfunction have a significantly prolonged values of QTc max. interval, Tpeak-Tend interval, QTc dispersion, Tpeak-Tend dispersion. Others have found similar results [46].

Obesity and BMI has been found to be a strong predictor of sudden cardiac death (SCD) in the Framingham heart study. It has been suggested that sudden deaths and/or ventricular arrhythmias may be linked to abnormalities in ventricular repolarization, maybe associated with early electrocardiographicand/or echocardiographic abnormalities even in the absence of clinical symptoms [47, 48]. In the present study, patients in diabetic group with subclinic left ventricular diastolic dysfunction in comparison with patients in diabetic group with normal ventricular diastolic function, have a significantly higher BMI. Others have found similar results [46].

Electrical repolarization abnormalities have been shown to be associated with increased cardiovascular complication in diabetic patients [49]. Since these complication are increased when the duration of diabetes is prolonged. This is consistent with results in the present study showing that patients in diabetic group with subclinic left ventricular diastolic dysfunction in comparison with patients in diabetic group with normal ventricular diastolic function, have a significantly prolonged QTc

dispersion, Tpeak-Tend dispersion and duration of diabetes.

In our study, poor glycemic control was associated with repolarization parameters. This result is in accordance with results of others studies [50].

Another fact of great importance is the influence of medication on several electrocardiographic parameters, because there are numerous drugs that cause prolongation and/or dispersion of repolarization. This study excluded individuals receiving medications that are more frequently associated with repolarization changes; however, there was no absolute guarantee that all other medications had no influence on repolarization. In fact, a study by Costa et al. [51], evaluated the influence of metformin (a drug commonly used in diabetics to control blood glucose) on QT interval and QT dispersion in diabetic rats. The results showed that, with low and moderate doses of metformin, there were significant changes in electrocardiographic parameters, but this did not happen when the dose was high. Treatment with drugs such B-blockers, antidepressant and cisapride may cause QTc prolongation: in this study, the proportion of patients treated with these drugs, was relatively small and the exclusion of this subgroup from the analysis, did not modify the relationship between prolonged QTc and diabetics patients.

This study was not without limitations

A larger sample would certainly increase the statistical power of the study, and probably some differences would therefore become more expressive. It was impossible to rule out coronary heart disease completely. Coronary angiography is not indicated in all asymptomatic patients and myocardial stress-scintigraphy is too expensive. Moreover, manual measurements of intervals without the support of any technology that could ensure a more precise measurement may also be an aspect to be taken into account. The accuracy and reproducibility of measurements of repolarization parameters problem encountered was the lack of a consensus on the values of several normal electrocardiographic parameters.

Despite some methodological limitations, this study clearly demonstrated a relationship between diabetes, subclinic left ventricular diastolic dysfunction, gender and changes in a set of electrophysiological parameters that indicate a prolonged and more heterogeneous repolarization in these patients, when compared with diabetics patients with normal ventricular diastolic function.

Conclusion

The present study has shown that interaction of type 2 diabetes and sex in diabetics with sub-clinicleft-ventricular diastolic dysfunction causes changes in a set of electrophysiological parameters that indicate a prolonged and more heterogeneous repolarization than in diabetics patients with normal diastolic function. Analyses by gender, showed that differences exist in the prevalence of increased set of electrophysiological parameters that indicate a prolonged and more heterogeneous repolarization in the relationship among, type 2 diabetic patients with sub-clinic left ventricular diastolic dysfunction. Prevalence of increased QTc interval duration, QTc dispersion duration, Tpeak-Tend dispersion duration, in diabetic patients a with sub-clinic left ventricular diastolic dysfunction is considerable high. These findings have both: Epidemiological and clinical relevance. This fact may be involved in the greater vulnerability of these patientss to cardiac arrhythmias, and excess mortality risk of type 2 diabetic patients with subclinic levt ventricular diastolic dysfunction. Therefore, the assessment of these markers for arrhythmogenic risk may be important for better risk stratification of diabetic patients, a conclusion that needs confirmation in larger prospective studies.

Disclosure of conflict of interest

None.

Abbreviations

AGE, Age; BMI, Body mass index; BP, Blood pressure; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; GLYC, Glycaemia; T2D, Diabetes type 2; TCH, Total cholesterol; LDL-chol, Low density cholesterol; HDC-chol, High density cholesterol; Trigl, Triglyceride; ESC, European Society of Cardiology; QTc, Corrected Heart Rate; DCT, Deceleration times of E-wave; IVRT, Isovolumetric relaxation times.

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