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Original Article

Tp-e interval and Tp-e/qt ratio in patients with non alcoholic fatty liver disease

Nonalkolik yağlı karaciğer hastalığı olan bireylerde Tp-e intervali ve Tp-e/qt oranı

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Abstract

Aim: Ventricular repolarization is assessed using the Tp-e interval and QT interval corrected by the heart rate (QTc) via an electrocardiogram (ECG). Prolonged Tp-e/QTc is related with an increased risk of arrhythmias and cardiac mortality. As there have been few reports regarding the effects of NAFLD on ventricular repolarization, we aimed to appraise the assessment of Tp-e interval and Tp-e/QT ratio in patients with NAFLD.

Material and Methods: Totally 97 patients with NAFLD and 77 control subjects were enrolled in our study. Tp-e interval, Tp-e/QT and Tp-e/QTc ratios were measured from the 12-lead electrocardiogram.

Results: Heart rate was similar between groups (74.8 ± 10.1 vs. 75.7 ± 11.7; p=0.598). QT interval (396.0 ± 34.2 vs. 384.6 ± 30.7; p=0.023) and QTc interval (403.6 ± 34.8 vs. 399.9 ± 36.3; p=0.027), Tp-e interval (100.4 ± 13.6 vs. 91.4 ± 13.4; p<0.001) , Tp-e/QT ratio (0.25 ± 0.03 vs. 0.23 ± 0.03; p=0.003) and Tp-e/QTc ratio (0.23 ± 0.03 vs. 0.21 ± 0.03; p=0.002) were significantly different between groups. There was significant correlation between Tp-e interval (r= 0.328, p<0.001) and Tp-e/QTc ratio and hepatic steatosis grade (r= 0.237, p=0.002).

Conclusion: Tp-e interval, QT interval, QTc interval, Tp-e/QT and Tp-e/QTc ratios were prolonged in patients with NAFLD. NAFLD is found an independent factor for increased Tp-e/QT ratio. This is the first study that investigated the Tp-e interval and Tp-e/QT parameters in patients with NAFLD.

Keywords: NAFLD; Tp-e interval; Tp-e/QTc ratio; ventricular repolarization

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Öz

Amaç: Elektrokardiyografide (EKG) ventriküler repolarizasyon Tp-e intervali ve kalp hızına göre düzeltilmiş QT (QTc) aralığı kullanılarak değerlendirilir. Uzamış Tp-e/QTc oranı aritmiler ve kardiyak mortalite riskinde artışla ilişkilidir. NASH (nonalkolik steatohepatit)' in ventriküler repolarizasyon üzerine etkileriyle ilgili az sayıda çalışma olduğu için, NASH hastalarında Tp-e interval ölçümlerini ve Tp-e/QT oranını değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çalışmamıza toplam 97 NASH hastası ile 77 kişilik kontrol grubu dahil edildi. Tp-e intervali, Tp-e/QT ve Tp-e/QTc oranları 12-lead elektrokardiyogram ile ölçüldü.

Bulgular: Kalp hızı her iki grupta da benzerdi (74.8 ± 10.1 vs. 75.7 ± 11.7; p=0.598). QT interval (396.0 ± 34.2 vs. 384.6 ± 30.7; p=0.023) ve QTc interval (403.6 ± 34.8 vs. 399.9 ± 36.3; p=0.027), Tp-e interval (100.4 ± 13.6 vs. 91.4 ± 13.4; p<0.001) , Tp-e/QT oranı (0.25 ± 0.03 vs. 0.23 ± 0.03; p=0.003) ve Tp-e/QTc oranı (0.23 ± 0.03 vs. 0.21 ± 0.03; p=0.002), gruplararası anlamlı olarak farklı saptandı. Tp-e interval (r= 0.328, p<0.001) ve Tp-e/QTc oranı ile hepatik steatoz derecesi (r= 0.237, p=0.002) arasında anlamlı bir ilişki mevcuttu.

Sonuç: NASH hastalarında Tp-e interval, QT interval, QTc interval, Tp-e/QT ve Tp-e/QTc oranları uzamıştı. NASH 'in artmış Tp-e/QT oranı için bağımsız bir faktör olduğu bulundu. Bu çalışma NASH hastalarında Tp-e intervali ve Tp-e/QT parametrelerinin araştırıldığı ilk çalışmadır.

Anahtar kelimeler: NASH; Tp-e interval; Tp-e/QTc oranı; ventriküler repolarizasyon

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a pathologic condition frequently observed in clinical practice. The prevalence of NAFLD is approximately 25–30% among adults of the general population in Western countries but increases to approximately 70–75% among patients with type 2 diabetes mellitus[1]. It has become increasing clear that NAFLD is not only associated with an increased liver-related morbidity and mortality but that coronary heart disease is the primary cause of death in patients with NAFLD[2]. Recent studies have also demonstrated that patients with NAFLD have an increased risk of cardiac arrhythmias, including atrial fibrillation (AF), heart rate-corrected QT (QTc) interval prolongation and ventricular arrhythmias[3].

Ventricular repolarization is evaluated with QT interval corrected by heart rate (QTc) in electrocardiogram (ECG). A prolonged QTc is related to an increased risk of sudden cardiac death according to the arrhythmias. It is known that hypothyroidism was related with QTc prolongation [4, 5]. Besides, a study showed that hyperthyroidism was associated with QTc prolongation. Recently, the T-peak to T-end (Tp-e) interval on 12 lead electrocardiogram (ECG) has been shown to correlate with ventricular repolarization abnormalities. Both QT and the Tp-e intervals are heart rate dependent and this dependence has also been associated with risk of ventricular arrhythmias [6]. For this reason, it has been claimed that Tp-e/QT ratio might be an important and useful indicator of ventricular repolarization [7-9]. Currently, there is no study available on Tp-e interval and Tp-e/QT ratio in patients with hepatosteatosis. In this study, we aimed to appraise the assessment of Tp-e interval and Tp-e/QT ratio in patients with hepatosteatosis.

Material and Methods

Study design

This was a cross-sectional study that was conducted at a single center. Ninety-seven consecutive patients and 77 control subjects with January 2013 and March 2018, were enrolled to study. All subjects who investigated in this study were in sinus rhythm. All participants had no cardiac sign or symptom. Patients with coronary artery disease, chronic kidney disease, cirrhosis, viral hepatitis, drug induced liver disease or other chronic liver disease, left ventricular dysfunction, mild or severe valvular disorder, malignancy, advanced pulmonary disease, atrial fibrillation, any type of bundle branch block, cardiac device, those who were taking any drugs known to affect QT interval and those with excessive alcohol consumption (i.e. >30 g/day for men and >20 g/day for women) were excluded.

Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Patients were considered to have hypertension if their blood pressure was ≥140/90 mmHg or if they were taking any anti-hypertensive drugs[10]. Diabetes mellitus was defined as fasting blood

glucose of 126 mg/dL or greater and treatment with antidiabetic drugs. Peripheral venous blood was drawn from antecubital vein and was obtained in the morning after a 12-hour fast. All biochemical analyses were determined by Standard methods. All patients underwent two-dimensional transthoracic echocardiography with the Vivid 7 system (GE Healthcare, Wauwatosa, Wisconsin). Ejection fraction was calculated by using modified Simpson method. The Institutional Research Ethics Committee approved the study and informed consent was obtained from each patient.

Abdominal ultrasonography (Toshiba-SSA-250A) was performed by an independent radiologists for all of the study population. Right kidney echogenicity was referenced for the determination of liver parenchyma echogenicity. If the kidney cortex and liver parenchyma echogenicity were the same, it was assumed as normal, i.e., no hepatosteatosis was present (Grade 0). Fat infiltration in liver is described in three sonographic stages. Grade 1 is defined as minimal-diffuse increase in hepatic echogenicity wherein the diaphragm and intrahepatic vessel contours seem normal. Grade 2 is defined as moderate-diffuse increase in hepatic echogenicity in which mild deterioration in the image of the diaphragm and intrahepatic vessels is observed. Grade 3 is defined as apparent increase in echogenicity is observed [11]. This study was approved by the local ethics committee. Informed constents were collected from all patients.

Electrocardiography

The 12-lead ECG of the all participants were documented at amplitude of 20mm/mV and a velocity of 50mm/s (Hewlett Packard, Page-writer, USA) when the patients in supine position. The patients' ECG examples were scanned. After that, ECGs transferred to a personal computer to minimize the error measurements, and then used for x400% magnification by software. Two specialists who were blinded to the subjects' information evaluated the intervals. Patients with U waves were excluded. Mean value of three measurements was obtained for each lead. The QT interval was defined as from the origin of the QRS complex to the termination of the T wave. Bazett formula [QTc = QT$\sqrt{}$ (R-R interval] was used to assess corrected QT interval (QTc). Tp-e interval was defined as the interval between the peak and the end of T wave. Precordial leads were used to calculate Tp-e intervals [12]. The Tp-e/QT ratio was calculated after the result of these measurements.

Statistical Analysis

For statistical analysis, SPSS 20.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA) was used. In order to test normality of distribution Kolmogorov-Smirnov test was used. Quantitative variables with a normal distribution were specified as the mean ± standard deviation and variables with non-normal distribution were shown as median (interquartile range), categorical variables were shown as number and percentage values. Categorical variables were compared with Chi-square test. Spearman correlation analysis was performed to examine the relationship between Tp-e interval, Tp-e/QTc and hepatic steatosis grade. Multivariable linear regression analyses were performed to examine the relationship between Tp-e/QTc and predictors. The significant predictors were adjusted in the later multivariate logistic regression analyses and subsequent sensitivity analyses. A p value of <0.05 was accepted as statistically significant.

Results

A total of 97 with patients with NAFLD and 77 control subjects were enrolled in our study. Baseline characteristics of study population are shown in Table 1. The mean age of the study population was 55.2 ± 11.2 years and 43.7 % of participants were male and 36.5% of patients had hypertension and 23.7% of patients had diabetes mellitus. The mean age of NAFLD group was younger than control subjects (53.2 ± 11.3 vs. 57.6 ± 10.7; p=0.009). There were significant differences between groups in terms of albumin, alanine transaminase, aspartate aminotransferase, high-density lipoprotein cholesterol, and triglyceride values (p<0.05).

The electrocardiographic findings of the study groups were shown in Table 2. Heart rate was similar between groups (74.8 ± 10.1 vs. 75.7 ± 11.7; p=0.598). QT interval (396.0 ± 34.2 vs. 384.6 ± 30.7; p=0.023) and QTc interval (403.6 ± 34.8 vs. 399.9 ± 36.3; p=0.027), Tp-e interval (100.4 ± 13.6 vs. 91.4 ± 13.4; p<0.001) , Tp-e/QT ratio (0.25 ± 0.03 vs. 0.23 ± 0.03; p=0.003) and Tp-e/QTc ratio (0.23 ± 0.03 vs. 0.21 ± 0.03; p=0.002) were significantly different between groups. In correlation analysis, there was significant correlation between Tp-e interval (r= 0.328, p<0.001) and Tp-e/QTc ratio and hepatic steatosis grade (r= 0.237, p=0.002) (Table 3). In multivariate linear regression analysis, NAFLD is found an independent factor for increased Tp-e/QT ratio (Table 4).

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Table 1. Basal characteristics and laboratory parameters of the patients with NAFLD and control subjects.

Parameters	NAFLD (n=97)	Controls (n=77)	p value
Age, years	53.2 ± 11.3	57.6 ± 10.7	0.009
Male, n (%)	45 (46.3)	31 (40.2)	0.418
Hypertension, n (%)	42 (43.3)	28 (36.3)	0.354
Diabetes Mellitus, n (%)	20 (20.6)	19 (24.6)	0.524
Smoking, n (%)	25 (25.7)	13 (16.8)	0.159
LVEF, %	60 (58-61)	60 (58-60)	0.109
Body mass index, kg/m2	28.9 (26.3-30.7)	27.6 (25.7-29.9)	0.088
Hemoglobin, g/dl	14.4 ± 1.5	14.2 ± 1.6	0.384
Platelets, 109/L	266.9 ± 73.0	271.5 ± 60.1	0.659
White blood cell, 109/L	7.3 ± 1.7	7.5 ± 1.7	0.601
Total protein, g/dL	7.4 ± 0.5	7.3 ± 0.4	0.076
Albumin, g/dL	4.5 ± 0.3	4.4 ± 0.3	0.037
AST, U/L	22 (17-28)	18 (15-25)	0.005
ALT, U/L	26 (20-41)	17 (14-24)	<0.001
Creatinine, mg/dl	0.78 (0.67-0.90)	0.76 (0.69-0.87)	0.701
Glucose, mg/dl	101 (89-112)	98 (91-112)	0.743
Total cholesterol, mg/dl	196.0 ± 38.9	184.6 ± 39.8	0.061
LDL cholesterol, mg/dl	111.8 ± 31.0	109.9 ± 33.7	0.705
HDL cholesterol, mg/dl	45.3 ± 10.8	49.4 ± 12.6	0.025
Triglyceride, mg/dl	162.5 (114.7-220.0)	119.5 (91.2-162.5)	<0.001
Sodium, mmol/l	141.2 ± 2.4	142.0 ± 2.6	0.053
Potassium, mmol/l	4.44 ± 0.32	4.43 ± 0.36	0.920
TSH, µIU/mL	1.83 (1.32-2.59)	1.81 (1.31-3.27)	0.973
Hepatic steatosis grade, n (%)		-	-
Grade 1	39 (40.2)	-	-
Grade 2	45 (46.4)	-	-
Grade 3	13 (13.4)	-	-

Data are given as mean ± SD, median (interquartile range) or n (%).; ALT, alaninetransaminase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein. LVEF, Left ventricular ejection fraction

Table 2. Electrocardiographic and echocardiographic characteristics of the patients with NAFLD and control subjects.

Parameters	NAFLD (n=97)	Controls (n=77)	p value
Heart rate, bpm	74.8 ± 10.1	75.7 ± 11.7	0.598
Tp-e interval, ms	100.4 ± 13.6	91.4 ± 13.4	<0.001
QT interval, ms	396.0 ± 34.2	384.6 ± 30.7	0.023
QTc interval, ms	403.6 ± 34.8	399.9 ± 36.3	0.027
Tp-e/QT ratio	0.25 ± 0.03	0.23 ± 0.03	0.003
Tp-e/QTc ratio	0.23 ± 0.03	0.21 ± 0.03	0.002

Data are given as mean ± SD. QTc, corrected QT interval.

Table 3. Correlations between hepatic steatosis grade and Tp-e interval and Tp-e/QTc.

Parameters	r	p value
Tp-e interval	0.328	<0.001
Tp-e/QTc	0.237	0.002

Table 4. Association between Tp-e/QTc and Clinical Variables:Multivariable Linear Regression Model

	Univariable		Multivariable	
Variables	OR* (95 % CI)	p value	OR* (95 % CI)	p value
Age	0.809 (0.664-0.985)	0.758	-	-
Body mass index	0.929 (0.743-0.965)	0.721	-	-
Total protein	0.005 (-0.006-0.017)	0.347	-	-
Albumin	-0.010 (-0.025-0.006)	0.232	-	-
AST	0.002 (0.000-0.003)	0.287	-	-
ALT	0.001 (0.000-0.003)	0.169	-	-
Hepatic steatosis grade	0.007 (0.003-0.012)	0.003	0.007 (0.003-0.012)	0.003

ALT, alanine transaminase; AST, aspartate aminotransferase; CI, confidence interval;OR, odds ratio.

Discussion

In the present study, we demonstrated that Tp-e interval, QT interval, QTc interval, Tp-e/QT and Tp-e/QTc ratios were prolonged in patients with (NAFLD). This is the first study that investigated the Tp-e interval and Tp-e/QT parameters in patients with NAFLD.

Several studies showed the relationship between NAFLD

and QT interval. Hung et al. found the association of QTc prolongation and NAFLD [13]. They discussed that the potential mechanism that contributes to the association between NAFLD and the QTc interval can be inflammation. In their study, they observed association between high-sensitivity C-reactive protein and the QTc interval[13]. Also, they explained the association between NAFLD and the QTc interval with increased sympathetic activity according to the heart rate variability[13].

Targher et al. observed that the presence and severity of NAFLD on ultrasound was strongly associated with prolonged QTc interval in patients with type 2 diabetes, independently[14]. The pathophysiological mechanisms that link NAFLD to prolonged QTc interval are not clearly understood. According to the authors, NAFLD might be related with prolonged QTc interval simply as a consequence of shared cardiometabolic risk factors and co-morbidities or as a marker of coexisting ectopic fat accumulation in other organs. For instance, myocardial steatosis and increased pericardial fat volume might exert local adverse effects that result in functional and structural derangements of the myocardium[14]. Mantovani et al. examined the association between NAFLD and ventricular arrhythmias, defined as the presence of nonsustained ventricular tachycardia, 30 premature ventricular contractions/h, or both in a large sample of outpatients with type 2 diabetes referred for 24-h ambulatory Holter monitoring [15]. NAFLD is related with insulin resistance, lipid toxicity of myocardium, and the systemic release of a myriad of proinflammatory, procoagulant, pro-oxidant, and profibrogenic mediators that play major roles in the pathogenesis of the functional, structural, and arrhythmic abnormalities of the heart[15].

Prolonged ventricular repolarization parameters might cause mortality and sudden cardiac death by inducing malign arrhythmias[16]. QT dispersion and prolonged QT interval are important predictors of delayed heart repolarization on electrocardiography. In literature, there is inadequate data about electrocardiographic abnormalities and ventricular tachycardia in NAFLD.

Many studies have shown that increased dispersion of repolarization might predispose to ventricular arrhythmias. Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio may be used as electrocardiographic indexes of ventricular arrhythmogenesis and sudden cardiac death. Nowadays, the Tp-e interval and Tp-e/QT ratio have been studied as novel indicators of impaired ventricular repolarization dispersion [7, 8, 17]. Increased Tp-e interval was related higher mortality rate in the patients with long QT syndrome and Brugada syndrome[8]. The Heart rate does not affect the Tp-e/QT ratio that was accepted as more precise marker of the dispersion of ventricular repolarization, than QT dispersion, QTc dispersion and Tp-e intervals. [7, 18]. Tp-e/QT ratio is a potential significant index of arrhythmogenesis independent from the length of QT interval [8].

In our study, we showed that these markers were higher in patients with NAFLD. Also, we showed that NAFLD is an independent factor for increased Tp-e/QT ratio. However the mechanism which causes this condition is not clear. Liver fat and inflammation progresses and advanced fibrosis develops in NAFLD. Several modifications take place into the liver, such as increased in production of atherogenic lipoproteins and in an increased release into bloodstream of several pro-inflammatory (e.g., c-reactive protein, tumor necrosis factor-alpha, and interleukin-6), pro-fibrinogen (e.g., transforming growth factor-beta), pro-oxidant and thrombogenic (e.g., factor VIII, plasminogen activator inhibitor- 1, and endotelin-1) mediators[1-3, 19, 20]. These molecules and proinflammatory alterations might have a negative role on the risk of cardiac complications, including arrhythmias[21, 22]. Especially, instability of the myocardium might potentially present cellular and ultrastructural changes in myocardium as well as modifications of the action potential duration (e.g., modifications of ion current and reduction of connexins), resulting in an increament the risk of arrhythmia[1].

Cross-sectional design and low number of patients are the main limitations. The study is single-center study and the patients' follow-up data is absent. Ventricular arrhythmias of the patients were not evaluated according to the repolarization parameters. Large sample sized randomized studies are needed to establish exact role of Tp-e interval and Tp-e/QT ratio in patients with NAFLD who suffering from the arrhythmias.

Conclusion

In conclusion, this study demonstrated that Tp-e interval, Tp-e/QT and Tp-e/QTc ratios were prolonged in patients with NAFLD. Our study is considerable to display that NAFLD

may have a negative effect on cardiac conduction system, which potentially may induce formation of ventricular arrhythmias. Tp-e interval and Tp-e/QT ratio are simple, easily accessible, inexpensive and non-invasive methods that can be useful marker of predicting the ventricular arrhythmias in patients with NAFLD. Electrophysiological studies on human cardiomyocytes will be helpful in clarifying this issue.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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