ORIGINAL ARTICLE

Parameters of ventricular repolarization in patients with autoimmune hepatitis

Otoimmün hepatit olan hastalarda ventrikül repolarizasyonu parametreleri

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ABSTRACT

Objective: Autoimmune hepatitis (AIH) is a liver disorder that affects both children and adults. It is characterized by inflammatory liver histology, elevated transaminase level, circulating nonorgan-specific autoantibodies, and increased level of immunoglobulin G in the absence of known etiology. Ventricular repolarization has been evaluated using T wave and QT interval measurements in patients with hepatic cirrhosis. Ventricular repolarization may be defined using QT interval, QT dispersion, and T wave measurements. Recently, it has been demonstrated that peak and end of the T wave (Tp-e) interval, Tp-e/QT, and Tp-e/corrected QT interval (QTc) ratios can be novel indicators for prediction of ventricular arrhythmias and mortality. In this study, an investigation of ventricular repolarization using Tp-e interval and Tp-e/QT ratio in patients with AIH was performed.

Methods: Total of 31 patients with AIH and 31 controls were enrolled in the present study. Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios were measured on 12-lead electrocardiogram.

Results: QT interval (378.9±41.4 *vs.* 350.0±22.7; p=0.001), QTc interval (396.8±46.7 *vs.* 367.3±34.9; p=0.039), Tp-e interval (68.2±12.3 *vs.* 42.5±6.8; p<0.001), Tp-e/QT ratio (0.18±0.02 *vs.* 0.12±0.01; p<0.001) and Tp-e/QTc ratio (0.17±0.02 *vs.* 0.11±0.01; p<0.001) were significantly higher in patients with AIH than control patients.

Conclusion: The results of the present study indicated that Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios were greater in patients with AIH.

ÖZET

Amaç: Otoimmün hepatit (OİH) hem çocuklar hem yetişkinleri etkileyen bir karaciğer hastalığıdır. Tanımlanamamış bir etiyoloji ile birlikte enflamatuvar karaciğer histolojisi, artmış transaminaz düzeyleri, organa özgü olmayan otoantikorların ve immünoglobülin G seviyelerinin artışı ile karakterizedir. Ventriküler repolarizasyon önceden karaciğer sirozu olan hastalarda T dalgası ve QT aralığı ölçümleri kullanılarak değerlendirilmiştir. Ventriküler repolarizasyon QT aralığı, QT dispersiyonu ve T dalga ölçümleri kullanılarak tanımlanabilir. Son zamanlarda, Tp-e aralığı, Tp-e/QT ve Tp-e/QTc oranlarının ventrikül aritmisi ve mortaliteyi öngörmede yeni göstergeler olabilecekleri gösterilmiştir. Bu çalışmada, OİH'de Tp-e aralığı ve Tp-e/QT oranını kullanarak ventrikül repolarizasyonunu araştırmayı amaçladık.

Yöntemler: OİH'li 31 ve 31 sağlıklı kontrol olgusu çalışmaya alındı. Tp-e aralığı, Tp-e/QT ve Tp-e/QTc oranı 12 derivasyonlu elektrokardiyogram ile ölçüldü.

Bulgular: QT aralığı (378.9±41.4 ve 350.0±22.7; p=0.001), QTc aralığı (396.8±46.7 ve 367.3±34.9; p=0.039), Tp-e aralığı (68.2±12.3 ve 42.5±6.8; p<0.001), Tp-e/QT oranı (0.18±0.02 ve 0.12±0.01; p<0.001) ve Tp-e/QTc oranı (0.17±0.02 ve 0.11±0.01; p<0.001) OİH'li hastalarda kontrol grubuna göre anlamlı olarak daha yüksek bulundu.

Sonuç: Çalışmamız Tp-e aralığı, Tp-e/QT ve Tp-e/QTc oranlarının OİH'li hastalarda artmış olduğunu gösterdi.

Autoimmune hepatitis (AIH) is a liver disorder that affects both children and adults. It is characterized by inflammatory liver histology, elevated transaminase level, circulating nonorgan-specific autoantibodies, and increased level of immunoglobulin G in the absence of a known etiology.[1] AIH is mostly responsive to immunosuppressive treatment, with symptom-free long-term survival for the majority of

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patients.[2] Persistent failure to respond or lack of adherence to treatment result in end-stage liver disease.[2] Some patients may require liver transplantation.[1]

Myocardial repolarization has been assessed using various methods, including QT dispersion (QTd) and corrected QT dispersion (cQTd). The interval between the peak and the end of T wave (Tp-e) on electrocardiogram (ECG) can be used as an index of total (transmural, apicobasal, and global) dispersion of repolarization[3,4] and it is related to sudden cardiac death risk.[5,6] Increased Tp-e interval might predict ventricular tachyarrhythmias and cardiovascular mortality.[7,8] Tp-e interval is affected by variations of body weight and heart rate.[9] Therefore, Tp-e/corrected QT interval (QTc) ratio is another parameter used as an electrocardiographic index of ventricular arrhythmia.[9] Tp-e/QT is not affected by alterations in heart rate.[9,10]

Although ventricular repolarization was previously evaluated using T wave and QT interval measurements in patients with hepatic cirrhosis,[11] repolarization indexes Tp-e interval and Tp-e/QT ratio have not been studied in patients with autoimmune hepatitis. This case-control study was conducted to demonstrate Tp-e interval, Tp-e/ QT ratio, and Tp-e/QTc in patients with autoimmune hepatitis.

METHODS

Study population

This study was conducted by members of the gastroenterology and cardiology departments of tertiary hospital between January 2010 and June 2015. Files of patients with AIH were analyzed retrospectively, and 31 AIH patients were enrolled in the study. Clinical data, including serological and follow-up data, were obtained from hospital records for all cases. Thirty-one healthy patients who presented at gastroenterology department for routine physical examination were defined as control group.

AIH diagnosis was made based on clinical, laboratory, and histological findings. Autoantibodies (antinuclear antibodies, antismooth muscle antibodies, anti-liver-kidney microsome-1 antibodies, and/or anti-soluble liver antigen/liver-pancreas) were studied in patients with elevated transaminase and immunoglobulin G or gammaglobulin, and cutoff titers were 1:40. All patients were screened for viral hepatitis and patients positive for hepatitis B surface antigen or hepatitis C antibody were excluded. Percutaneous liver biopsy was done in all patients for whom there was suspicion of AIH. Final AIH diagnosis was made with previously defined simplified criteria.[12] Patients with early stages of cirrhosis were also excluded from the study.

Abbreviations:

AIH	*Autoimmune hepatitis*
cQTd	*Corrected QT dispersion*
ECG	*Electrocardiogram*
Tp-e	*Peak and end of T wave*
QTc	*Corrected QT interval*
QTd	*QT dispersion*

Patients with coronary artery disease, malignancy, hematological or renal disease, moderate to severe heart valve disease, segmental wall motion abnormality or left ventricular ejection fraction (LVEF) below 50% on echocardiography, complete or incomplete bundle branch block, pre-excitation syndromes, atrioventricular block, atrial fibrillation and pacemaker rhythm on electrocardiography were also excluded from the study. All patients were in sinus rhythm at admission. The study was performed in compliance with the principles outlined in the Declaration of Helsinki and approval for the study was obtained from the institutional review board and ethics committee of the hospital.

Electrocardiography

Twelve-lead ECG was performed at paper speed of 50 mm/second with the patient at rest in supine position. Resting heart rate was then measured from ECG data. ECG measurements of QT and Tp-e intervals were performed manually by 2 different cardiologists to decrease error measurements. All ECG data were scanned and transferred to personal computer and used for x400% magnification with Adobe Photoshop software (Adobe Systems, Inc., San Jose, CA, USA). ECG measurements of QTc and Tp-e intervals were performed by 2 cardiologists who were blinded to patient data. Subjects with U wave on their ECG were excluded from the study. Average value of 3 examinations was calculated for each lead. QT interval was measured from beginning of QRS complex to end of T wave, and corrected for heart rate, using Bazett's formula.[13–16] Tp-e interval was defined as interval from peak of T wave to end of T wave. Measurements of Tp-e interval were performed from precordial leads. Tp-e/QT ratio was calculated from these measurements.

Statistical analysis

Statistical analysis was performed with IBM SPSS

Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). In order to test normality of distribution, Kolmogorov-Smirnov test was applied. Quantitative variables with normal distribution were specified as mean±SD, otherwise, median (interquartile range) was used for non-normally distributed data. Categorical variables were reported as number and percentage values. Mean differences between groups were compared using Student's t-test, and Mann-Whitney U test was used for comparisons of non-normally distributed variables. Categorical data were analyzed with continuity-corrected chi-square test. P value of <0.05 was accepted as statistically significant.

RESULTS

Baseline clinical characteristics and laboratory parameters of the groups are provided in Table 1. Mean age of participants was 51.5±10.3 years, and 77.4% of patients were female. There was no statistically significant difference between groups in terms of age, gender, smoking, body mass index, or basal laboratory findings, except aspartate aminotransferase, total and low-density lipoprotein cholesterol, erythrocyte sedimentation rate, and C-reactive protein levels. Mean disease duration of patients with AIH was 4.8 years (range: 0.5–8.9 years). Antibody status of patients with AIH is also visible in Table 1.

ECG and echocardiographic findings of the study groups are provided in Table 2. Heart rate (76.4±12.3 *vs.* 79.2±13.6; p=0.397), left ventricular ejection fraction (61.5±2.4 *vs.* 61.4±3.2; p=0.557), left ventricular end diastolic diameter (46.3±3.1 *vs.* 47.5±3.3; p=0.467), left ventricular end systolic diameter (28.0±2.9 *vs.* 29.7±2.5; p=0.299) and left atrial diameter (34.0±2.9 *vs.* 33.6±3.0; p=0.382) were similar between 2 groups. QT interval (378.9±41.4 *vs.* 350.0±22.7; p=0.001), QTc interval (396.8±46.7 *vs.* 367.3±34.9; p=0.039), Tp-e interval (68.2±12.3 *vs.* 42.5±6.8; p<0.001), Tp-e/QT ratio (0.18±0.02 *vs.*

Table 1. Basal characteristics and laboratory parameters of the study population

Parameters	Patients (n=31)	Controls (n=31)	*p*
Age (years)	51.1±13.8	51.9±7.3	0.775
Female, n (%)	25 (80.7)	23 (74.1)	0.761
Smoking, n (%)	6 (19.3)	7 (22.5)	1.000
Body mass index (kg/m^2)	23.6±5.0	23.3±4.7	0.624
Hemoglobin (g/dL)	13.6±1.6	14.0±1.0	0.393
Creatinine (mg/dL)	0.76±0.15	0.79±0.12	0.533
Glucose (mg/dL)	103±33	99±18	0.489
Aspartate aminotransferase (IU/l)	41 (17–185)	26 (18–38)	0.024
Alanine aminotransferase (IU/l)	46 (9–385)	21 (15–48)	0.086
Total bilirubin (mg/dL)	0.90±0.22	0.78±0.15	0.598
International normalized ratio level	1.33±0.13	1.28±0.11	0.785
Total cholesterol	197.6±39.7	223.8±27.9	0.011
Low-density lipoprotein cholesterol (mg/dL)	117.7±29.0	140.9±22.6	0.006
High-density lipoprotein cholesterol (mg/dL)	60.7±18.4	55.7±11.6	0.267
Triglyceride (mg/dL)	103 (70.2–124.5)	124 (105–153)	0.092
Erythrocyte sedimentation rate (mm/h)	19 (13–37)	5 (3–10)	<0.001
C-reactive protein (mg/L)	1.7 (0.8–3.4)	1.0 (0.4–1.7)	0.019
Ig A	3.0 (1.2–6.7)	–	–
Ig G	14.5 (8.7–20.0)	–	–
Ig M	1.6 (0.4–6.5)	–	–
Disease duration, years	4.8 (0.5–8.9)	–	–

Data are given as mean±standard deviation or n (%) or Median (interquartile range).

Table 2. Electrocardiographic and echocardiographic characteristics of the study population

Parameters	Patients (n=31)	Controls (n=31)	*p*
	Mean±SD	Mean±SD	
Heart rate (bpm)	76.4±12.3	79.2±13.6	0.397
Tp-e interval (ms)	68.2±12.3	42.5±6.8	<0.001
QT interval (ms)	378.9±41.4	350.0±22.7	0.001
QTc interval (ms)	396.8±46.7	367.3±34.9	0.039
Tp-e/QT ratio	0.18±0.02	0.12±0.01	<0.001
Tp-e/QTc ratio	0.17±0.02	0.11±0.01	<0.001
Ejection fraction (%)	61.5±2.4	61.4±3.2	0.557
Left ventricular end diastolic diameter (mm)	46.3±3.1	47.5±3.3	0.467
Left ventricular end sistolic diameter (mm)	28.0±2.9	29.7±2.5	0.299
Left atrium (mm)	34.0±2.9	33.6±3.0	0.382

SD: Standard deviation; QTc: Corrected QT interval.

0.12±0.01; p<0.001) and Tp-e/QTc ratio (0.17±0.02 *vs*. 0.11±0.01; p<0.001) were significantly higher in patients with AIH than controls.

DISCUSSION

In this study, it was demonstrated that Tp-e interval and Tp-e/QTc ratio, as indices of ventricular arrhythmogenesis, were significantly higher in patients with AIH compared with healthy controls. Our results may contribute to the knowledge of pathophysiological mechanisms of increased prevalence of ventricular arrhythmias in patients with hepatitis.

Tp-e interval and Tp-e/QT ratio have emerged as novel ECG markers for increased dispersion of ventricular repolarization.[6,13,14,17,18] Furthermore, as Tp-e/QT ratio is not affected by changes in body weight or heart rate, it is thought to be a more sensitive index of arrhythmogenesis compared with single use of either the Tp-e or QT intervals.[9] Many studies have reported association between prolonged Tp-e interval and ventricular arrhythmogenesis and sudden cardiac death.[7,15] Moreover, electrophysiological studies have shown that prolonged Tp-e interval was associated with ventricular tachycardia induction and spontaneous occurrence of ventricular tachycardia.[8,16] Higher Tp-e/QT ratio has been associated with arrhythmic events in many clinical conditions, such as Brugada syndrome, long-QT syndromes, and hypertrophic cardiomyopathy.[9]

Cardiovascular autonomic dysfunction has been described in both chronic alcoholic and non-alcoholic liver disease, including primary biliary cirrhosis and chronic hepatitis C virus infection.[19,20] Autonomic dysfunction in a patient with chronic hepatitis B was found by Demir et al. using heart rate variability.[21] Some studies have reported that total mortality of patients with viral hepatitis, such as hepatitis C, was greater than that of healthy persons.[22] Although cause of increased incidence of cardiovascular disorders and mortality are not entirely understood in these patients, autoimmunity might be related factor.[22] Furthermore, increased cardiovascular death has been demonstrated in patients with viral hepatitis when compared with controls in previous studies.[22] The underlying mechanism for cardiovascular events may be due to arrhythmia incidence in these patients.

Recently, Akboga et al. reported that Tp-e interval and Tp-e/QT ratios were increased in parallel to severity of liver cirrhosis.[11] They suggested that Tp-e interval and Tp-e/QTc ratio may be novel and useful indicators for prediction of arrhythmia in liver cirrhosis.[11] Many factors may be responsible for prolongation of Q-T interval in acquired conditions, such as electrolyte abnormalities, myocardial ischemia, alcohol toxicity, and autonomic imbalance with sympathetic nervous system hyperactivity.[23,24] Elevated plasma concentration of bile salts might also cause cardiac function abnormalities.[25,26] Although this study did not included cirrhotic patients, QT dispersion parameters were disturbed, which can be cause ventricular

arrhythmia. Furthermore, our results may contribute to pathophysiological mechanisms of increased incidence of ventricular arrhythmia and cardiovascular mortality risk in patients with AIH.

Our study has some limitations. This study had relatively small sample size and is single-center study. Long-term follow-up and large-scale prospective studies are needed to investigate predictive value of the Tp-e interval and Tp-e/QT ratio in patients with AIH.

Our study has demonstrated that Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios were greater in patients with AIH. Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios are simple, easily accessible, inexpensive, and noninvasive methods that can be useful index for left ventricular dysfunction that causes arrhythmia in patients with AIH.

Conflict-of-interest: None.

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Keywords: Autoimmune hepatitis; peak and end of T wave interval; QT ratio.

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