

EVALUATION OF T_{PEAK-TEND} INTERVAL AND T_{PEAK-END}/QT RATIO IN PATIENTS WITH SARCOIDOSIS

Fatma Ucsular¹, Gulistan Karadeniz², Cem Karadeniz³, Enver Yalnız¹, Melike Demir⁴

¹Dr Suat Seren Chest Disease and Surgery Training and Research Hospital, Department of Pulmonology, Izmir, Turkey; ²Sifa University School of Medicine, Department of Pulmonology, Izmir, Turkey; ³Dr Behcet Uz Children's Hospital, Department of Pediatric Cardiology, Izmir, Turkey; ⁴Dicle University School of Medicine, Department of Pulmonology, Diyarbakır, Turkey

ABSTRACT. *Background:* T_{p-e} interval which represents the interval between the peak and the end of the T-wave on electrocardiogram (ECG), can be used as a marker of transmural dispersion of repolarization. Also, T_{p-e}/QT and T_{p-e}/QTc ratios are used as an index of arrhythmogenesis. Prolonged T_{p-e} interval and T_{p-e}/QT ratio was found associated with sudden cardiac death in different clinical conditions. Novel ventricular repolarization parameters, T_{p-e} interval, T_{p-e}/QT and T_{p-e}/QTc ratios have not been evaluated in patients with sarcoidosis without cardiac symptoms previously. Therefore, we investigated T_{p-e} interval in patients with pulmonary sarcoidosis. *Methods:* Sixty-one consecutive patients diagnosed with biopsy-proven pulmonary sarcoidosis were retrospectively reviewed. The 12-lead ECG examinations were performed at speed of 25 mm/s while the patients were in supine position. QT dispersion, T_{p-e} intervals and T_{p-e}/QT ratio were measured. *Results:* Comparison of ECG parameters between two groups showed a significantly higher average heart rate ($p < 0.05$) in the patients with sarcoidosis than controls. QT dispersion was higher in patients group. T_{p-e} interval was significantly prolonged in the study group compared to the control group (92 ± 21 ms and 85 ± 14 ms, respectively; $p < 0.05$). T_{p-e}/QT and T_{p-e}/QTc ratios were significantly higher in patients with sarcoidosis compared to control subjects (all p values < 0.05). *Conclusions:* The novel repolarization parameters T_{p-e} interval, T_{p-e}/QT and T_{p-e}/QTc ratios are increased in patients with sarcoidosis without any cardiac symptoms. These parameters might be used as a marker for predicting the ventricular arrhythmias and sudden cardiac death in patients with sarcoidosis. (*Sarcoidosis Vasc Diffuse Lung Dis* 2016; 33: 151-156)

KEY WORDS: Electrocardiogram, sarcoidosis, T_{peak-Tend} interval, T_{p-e}/QT ratio

Abbreviations

SCD= Sudden cardiac death; QTd=QT dispersion; QTcd= corrected QT dispersion; ECG=electrocardiogram; TDR= transmural dispersion of repolarization; VT= ventricular tachycardia; PVCs= premature ventricular contractions; ACE=angiotensin-converting enzyme; DLCO=diffusing capacity of the lung for carbon monoxide; FEV1= Volume that has been exhaled at the end of the first second of forced expiration; FVC= Forced vital capacity

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Correspondence: Gulistan Karadeniz, MD

Department of Pulmonology

Sifa University School of Medicine

35540 Izmir, Turkey

Tel. +90 232 362 66 66

Fax +90 232 362 89 89

E-mail: drglstn35@gmail.com

INTRODUCTION

Sarcoidosis is a chronic granulomatous multi-system disease that effects the different organ systems. The lung, skin, and lymph node are the most commonly affected sides (1). Granulomatous inflammation of the cardiac tissue can lead to various manifestations such as involvement of cardiac valves, myocardial ischemia caused by granulomatous coronary artery disease, constructive pericarditis and arrhythmia secondary to involvement of cardiac conduction system (2-5). Also systemic inflammatory cytokines without cardiac granulomatous inflammation can also trigger cardiac arrhythmias. Although clinically evident cardiac involvement is seen approximately 3-5% of patients, on autopsy series cardiac involvement is observed in 20-30% of the patients (6). The prognosis is very poor when the cardiac tissue is involved and approximately 40% of the patients died in 5 years.(7) Ventricular arrhythmias and sudden cardiac death (SCD) are common initial presentation of myocardial involvement.(8,9)

Heterogeneity of ventricular repolarization can be evaluated with QT dispersion (QTd), corrected QT dispersion (QTcd) (10,11). Besides these parameters, Tp-e interval which represents the interval between the peak and the end of the T-wave on electrocardiogram (ECG), can be used as a marker of transmural dispersion of repolarization (TDR). Also, Tp-e/QT and Tp-e/QTc ratios are used as an index of arrhythmogenesis.(12-14) Prolonged Tp-e interval and Tp-e/QT ratio was found associated with SCD in different clinical conditions.(15,16) Although ventricular repolarization was assessed previously with QT and QTc dispersions, in patients with sarcoidosis(17), the Tp-e interval and Tp-e/QT ratio have not been evaluated in patients with sarcoidosis before.

In this study we aimed to assess ventricular repolarization by using the Tp-e interval and Tp-e/QT ratio in patients with sarcoidosis without any cardiac involvement.

MATERIALS AND METHODS

Patients

Sixty-one consecutive patients diagnosed with biopsy-proven pulmonary sarcoidosis were retro-

spectively reviewed. The patients who had lung disease other than sarcoidosis, structural and ischemic cardiac diseases, systemic hypertension, diabetes mellitus, alcoholism, any arrhythmia and conduction disturbances were excluded. All patients were free from any cardiac symptom, thus further evaluation were not needed for cardiac involvement. Fifty-three sex-and-age matched healthy volunteers who did not have any history of cardiovascular disease, risk factors and had normal clinical examination were recruited as a control group. Patients demographic and clinical characteristics were extracted from patients file. The study was approved by the ethical committee of our institution.

Electrocardiography

The 12-lead ECG examinations were performed at speed of 25 mm/s while the patients were in supine position. Standard ECG measurements of QTd, Tp-e intervals and Tp-e/QT ratio were performed by a blinded cardiologist who did not know any clinical information about patients. All ECG parameters were measured manually with caliper and magnifying glass.

The QT interval was measured from the beginning of the QRS and the end of the T wave with the isoelectric line. When the presence U wave the deep point with the isoelectric line between T and U wave was accepted as the end point of T wave. Heart rate- corrected QT (QTc) was calculated according to Bazett's Formula (18). QT dispersion were calculated as the difference between maximum and minimum QT intervals (17). The Tp-e interval was measured from the peak of the T wave and the end of the T wave. All Tp-e measurements were performed from precordial leads. The Tp-e/QT ratio was calculated from these measurements (19).

Statistical analysis

Statistical Package for the Social Sciences (SPSS Version 18, SPSS Inc., Chicago, IL, USA) for Windows program was used to perform the analysis. In addition to graphical methods, Shapiro-Wilk test was used to check the normality assumption. Values are expressed as mean±SD or median(interquartile range) as appropriate. The student's t-test was used for normally distributed data and the Mann-Whit-

ney U test for not normally distributed data. Relationships among the numeric variables are tested with Pearson or Spearman Rho correlation analyse where appropriate. Chi square analysis was used for comparison of categorical data. A p value < 0.05 was considered significant.

Results

Sarcoidosis group consisted of 61 patients (40 were females, 21 were males), and they were compared 51 age-matched healthy control subjects (26 were females, 25 were males). The mean age of the sarcoidosis and control groups were 43.5 ± 12.6 and 41.4 ± 10.1 years, respectively. The demographic and ECG characteristics of the groups are shown in Table 1. Comparison of ECG parameters between two groups showed a significantly higher average heart rate ($p < 0.05$) in the patients with sarcoidosis than controls. Although, the patients with sarcoidosis had greater QTmin duration and QTd than the healthy controls ($p < 0.05$), we did not any difference between groups in terms of the QTmax duration ($p > 0.05$). Tp-e interval was significantly prolonged in the study group compared to the control group (92 ± 21 ms and 85 ± 14 ms, respectively; $p < 0.05$). Tp-e/QT and Tp-e/QTc ratios were significantly higher in patients with sarcoidosis compared to control subjects (0.22 ± 0.04 and 0.19 ± 0.03 , 0.19 ± 0.03 and 0.17 ± 0.03 , respectively; $p < 0.05$). The differences in Tp-e/QT and Tp-e/QTc ratios between the groups are shown in figure 1 and figure 2 respectively.

In patients group, mean follow-up duration after diagnosis was 15.7 ± 15.9 months, FEV1 and FVC

Table 1. Demographic and ECG characteristics of the patients and controls^a

	Patients with Sarcoidosis (n=61)	Controls (n=51)	P value
Age (years)	43.5 ± 12.6	41.4 ± 10.1	>0.05
Gender (F/M)	40/21	26/25	>0.05
Heart rate (bpm)	79.8 ± 13.3	73.7 ± 9.9	<0.05
QTd (ms)	40(40)	20(20)	<0.05
Tp-e (ms)	92 ± 21	85 ± 14	<0.05
Tp-e/QT	0.22 ± 0.04	0.19 ± 0.03	<0.05
Tp-e/QTc	0.19 ± 0.03	0.17 ± 0.03	<0.05

^a Data are presented as mean \pm SD, number or median (IQR); bpm=beat per minute; F=female; M=male; ms=millisecond

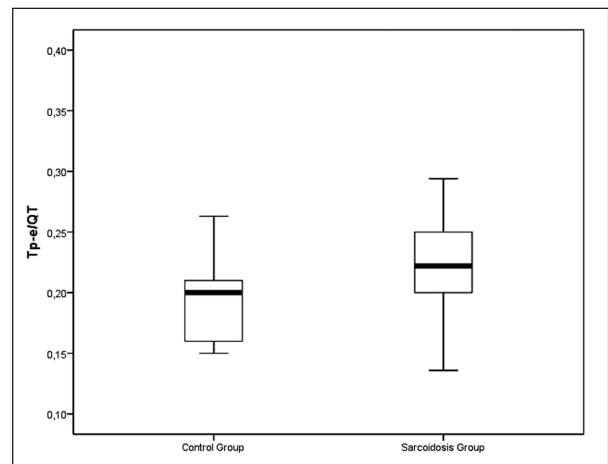


Fig. 1. Tp-e/QT ratio in controls and sarcoidosis groups

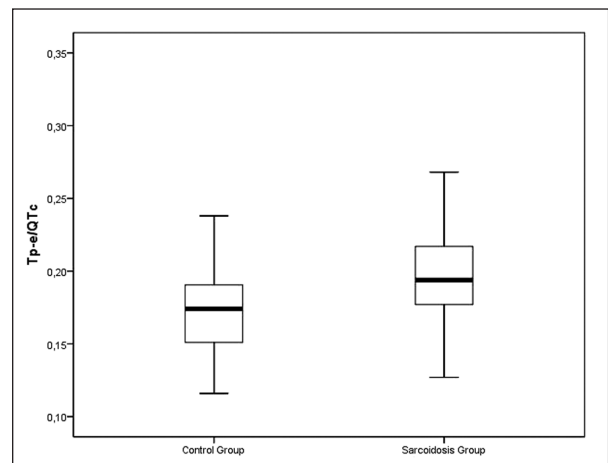


Fig. 2. Tp-e/QTc ratio in controls and sarcoidosis groups

values were 2.63 ± 1.0 and 3.03 ± 1.07 respectively. The mean ACE levels was 65 ± 43 U/L. While 46 of the patients had stage 2 disease, the remaining of the patients had stage 1 disease (Table 2). Also we did not find any correlation between follow-up duration after diagnosis and Tp-e interval and QTd ($r = -0.189$, $p = 0.14$ and $r = -0.12$, $p = 0.35$, respectively).

DISCUSSION

The present study showed that QT dispersion, Tp-e interval, Tp-e/QT and Tp-e/QTc ratios are increased in patients with sarcoidosis. Although, QT dispersion has been studied previously, to best our

Table 2. Pulmonary function test results, ACE levels, Follow-up duration, and stage of disease in patients with Sarcoidosis

	Patients with Sarcoidosis (n=61)
FEV ₁ (L) ^a	2.63±1.0
FVC (L) ^a	3.03±1.07
ACE (U/L) ^a	65±43
DLCO ^a	60.2±11.7
Follow-up duration (months) ^a	15.7±15.9
Stage (n)	
I	15
II	46
Pulmonary function test (n)	
Normal	36
Restrictive	18
Obstructive	7

^a =Data are presented as mean±SD; ACE=angiotensin-converting enzyme; DLCO=diffusing capacity of the lung for carbon monoxide; FEV₁=Volume that has been exhaled at the end of the first second of forced expiration; FVC=Forced vital capacity; L=liter; n=number of the patients

knowledge our study is the first to evaluate the parameters of transmural dispersion of repolarization including Tp-e interval, Tp-e/QT and Tp-e/QTc ratios and QT dispersion in a large group of patients with sarcoidosis.

Cardiac involvement still an important cause of morbidity and mortality in patients with sarcoidosis. Due to SCD can be the initial presentation of cardiac sarcoidosis early detection and treatment is crucial. (20) Advances in the cardiac imaging techniques especially in cardiac magnetic resonance imaging leads to increase in possibility of early detection of cardiac involvement (21,22). However, progressive nature of the disease and limited access of cardiac MRI make the extensive use of cardiac MRI impractical (4). Therefore, other non-invasive screening tools, such as routine 12-lead ECG becomes important for early detection of cardiac involvement (23). Although, some ECG findings including right bundle branch block, advanced atrioventricular block and ventricular arrhythmias are not specific for sarcoidosis, they represent the myocardial conduction abnormalities (23,24). With the myocardial inflammation and scarring, these areas are more prone to delayed myocardial activation and conduction abnormalities. Therefore, in the presence of mentioned above ECG findings in QT dispersion is accepted as an electrocardiographic marker related to tendency for potentially fatal ventricular arrhythmias and sudden cardiac

death (SCD). In a previously reported study that was conducted with larger number of patients, QTd was found to be a significant predictor of all cause of cardiovascular mortality (25). In another study, QTd was found higher in patients with inducible ventricular tachycardia (VT) compared to non-inducible patients (26). Although QT and QTc dispersions was evaluated in different inflammatory diseases, there is a only one study that was assessed these parameters in patients with sarcoidosis (4,27,28). In this study, Uyarel et al. (4) reported that QTd and QTcd was higher in cardiac sarcoidosis patients compared to non-cardiac sarcoidosis and healthy controls. Also these authors stated that the incidence of premature ventricular contractions (PVCs) were greater in cardiac sarcoidosis patients and that there were a significant correlation between QTd and PVCs. Though, Uyarel et al. (4) did not find any difference between non-cardiac sarcoidosis patients and healthy controls, we found significantly greater QTd values in non-cardiac sarcoidosis patients compared to healthy controls.

Electrically heterogenic structure of ventricular myocardium is well described. The ventricular myocardium contains three electro-physiologically different cell types such as epicardial, endocardial and midmyocardial M cells. (14). The M cells are located in endocardial layer and they have longer action potential than epicardial cells. This electrical heterogeneity results differences in the repolarization phases of ventricular myocardium and lead to TDR and malignant ventricular arrhythmia (14,29). Previously reported studies had shown that Tp-e interval, Tp-e dispersion, Tp-e/QT and Tp-e/QTc ratios are higher in long-and short-QT syndrome, Brugada syndrome, hypertrophic cardiomyopathy and myocardial infarction (16,29,30). In a study that was conducted with 353 cases with SCD showed that prolonged Tp-e interval and high Tp-e/QT ratio are strongly associated with SCD (15). In an another study Lubinski et al. (13) reported that patients with coronary artery disease who had prolonged Tp-e interval and greater Tp-e/QT ratio are more susceptible to development of ventricular arrhythmias. Akilli et al. (31) reported that Tp-e interval and Tp-e/QT ratio are greater in patients with carbon monoxide poisoning than control subjects and also they stated that prolonged Tp-e interval can be used as a marker of myocardial injury in these patients. Due to its independency from heart rate Tp-e/QT ratio was found as a more ac-

curate marker for ventricular arrhythmogenesis than T_{p-e} interval and QT_d (14,32). The association between cardiac sarcoidosis and ventricular arrhythmia is well known and VT is one of the most frequently seen arrhythmia in these patients and it is one of the presumed cause of SCD in patients with cardiac sarcoidosis (17,33). The inflammatory involvement of ventricular myocardium and sarcoid granuloma may cause heterogeneity of ventricular repolarization and increased risk of ventricular arrhythmia. To date, only one study have been investigated the ventricular repolarization heterogeneity in patients with cardiac sarcoidosis by using the QT and QT_c dispersions (17). However, novel ventricular repolarization parameters, T_{p-e} interval, T_{p-e}/QT and T_{p-e}/QT_c ratios have not been evaluated in patients with sarcoidosis without cardiac involvement yet. In our study, T_{p-e} interval, T_{p-e}/QT and T_{p-e}/QT_c ratios was found to be higher in patients with non-cardiac sarcoidosis compared to healthy controls. Because of the 25-30% of all patients with sarcoidosis have cardiac involvement in autopsy series, it is more likely that many patients with sarcoidosis are not clinically evident cardiac involvement.(6) Our results indicate that ventricular repolarization heterogeneity may increase in patients with non-cardiac sarcoidosis in the absence of obvious manifestations of myocardial involvement and they can be used as a marker for prompt further evaluation.

LIMITATIONS

The present study has some limitations that need to be considered. Retrospective design is the major limitation of this study. We did not evaluate the correlation between prolonged T_{p-e} interval, T_{p-e}/QT and T_{p-e}/QT_c ratios and PVCs. Also, we could not follow-up the study population prospectively for ventricular arrhythmias, thus we could not evaluate these parameters in terms of future arrhythmic events. Due to the absence of cardiac symptoms in our study population further diagnostic imaging tests such as echocardiography and cardiac MRI were not established, thus we could not evaluate the correlation between T_{p-e} interval, T_{p-e}/QT and T_{p-e}/QT_c ratios and the degree of cardiac involvement. Further prospective cardiac imaging studies are needed to demonstrate correlation between these

parameters and cardiac involvement. Finally, manual measurement of these parameters make the results less reliable than measurement with high-resolution digital systems.

CONCLUSIONS

The present study revealed that the novel parameters T_{p-e} interval, T_{p-e}/QT and T_{p-e}/QT_c ratios are increased in patients with sarcoidosis without any cardiac symptoms. These parameters might be used as a marker for predicting the ventricular arrhythmias and SCD in patients with sarcoidosis. Also, we want to draw attention to the importance of ECG as a simple, inexpensive and easily accessible toll as a part of risk stratification in sarcoidosis. Further prospective cardiac imaging and electrophysiological studies are needed to demonstrate correlation between these parameters and cardiac involvement in patients with sarcoidosis.

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