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Assessment of Tp-E Interval, Tp-E/Qt, Tp-E/Qtc Ratios in Thalassemia Major Patients

Talasemi Major Hastalarında Tp-E Intervali ve Tp-E/Qt, Tp-E/Qtc Oranlarının Değerlendirilmesi

Zehra Erkal[1]*

1.Antalya Training and Research Hospital Cardiology Department, Antalya, Turkey

ABSTRACT

Aim: Thalassemia major (TM) is a genetic hemoglobinopathy that causes chronic hemolytic anemia. Repeated blood transfusions are needed for treatment. Iron accumulation is used to predict the risk of ventricular arrhythmia. We designed this study to compare the Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio, which are the novel and reliable predictors that show ventricular repolarization, between the TM patients and healthy control group.

Method: We included 97 TM patients who presented to our outpatient clinic for routine cardiac check-up from March 2019 to June 2020 and 90 healthy volunteers. In addition to the demographic and echocardiographic findings, patients' electrocardiograms (ECG) were retrospectively analyzed. Their serum ferritin, C reactive protein (CRP) levels and neutrophil to lymphocyte ratios were recorded and compared.

Result: The Tp-e interval was 80 msn (60.0-80.0) in the group of thalassemia major patients whereas it was 60 msn (50.0-70.0) (p<0.001) in the control group. The Tp-e/QT ratio was 0.200 (0.160-0.225) in the TM group while it was 0.175(0.150-0.210) in the control group (p=0.014). The Tp-e/QTc ratio was 0.180 (0.130-0.190) in the TM group while it was 0.150 (0.130-0.180) in the control group (p=0.035). No correlation was found between their serum ferritin levels and ECG parameters.

Conclusion: Prolonged Tp-e interval, Tp-e/QT ve Tp-e/QTc ratios on the ECG in TM patients are associated with impaired ventricular repolarization due to excessive cardiac iron deposition and ventricular arrhythmias. These simple but reliable parameters can be used to predict the risk of arrhythmia.

Key Words:Arrhythmia, electrocardiography, thalassemia

ÖZ

Amaç: Talasemi majör (TM), kronik hemolitik anemiye sebep olan genetik bir hemoglobinopatidir. Tedavisinde tekrarlayan kan transfüzyonları gereklidir. Transfüzyonlara bağlı miyokardda biriken demir, kardiyomiyopati ve ventriküler aritmi gelişimine neden olur. Özellikle hayatı tehdit edebilecek ventriküler aritmi gelişme riskini öngörmek klinik açıdan çok önemlidir ve bu amaçla birçok parametre kullanılmıştır. Biz ventriküler repolarizasyonu gösteren, yeni ve güvenilir prediktörler olan Tp-e intervali, Tp-e/QT ve Tp-e/QTc oranını TM hastalarında ve sağlıklı kontrol grubunda karşılaştırmak amacıyla bu çalışmayı planladık.

Yöntem: Çalışmamıza Mart 2019- Haziran 2020 yılları arasında polikliniğimize rutin kardiyak kontrol amacıyla gelen 97 TM hastası ve 90 tane sağlıklı gönüllü kontrol grubu dahil edildi. Demografik ve ekokardiyografik bulgularına ek olarak retrospektif olarak hastaların elektrokardiyografileri (EKG) incelendi. Serum ferritin, C reaktif protein (CRP)düzeyleri ve nötrofil lenfosit oranları kaydedildi ve karşılaştırıldı. Yine hastalar aldıkları şelasyon tedavilerine göre sınıflandırılarak EKG parametreleri arasındaki fark açısından karşılaştırıldı.

Bulgular: Talasemi majör hasta grubunda Tp-e intervali 80 msn (60.0-80.0) iken kontrol grubunda 60 msn (50.0-70.0) (p<0.001), Tp-e/QT oranı TM grubunda 0.200 (0.160-0.225) iken kontrol grubunda 0.175(0.150-0.210) (p:0.014), Tp-e/QTc oranı TM grubunda 0.180 (0.130-0.190) iken kontrol grubunda 0.150 (0.130-0.180) (p:0.035) tespit edildi. Serum ferritin düzeyi ile EKG parametreleri arasında korelasyon izlenmedi.

Sonuç: Talasemi majör hastalarında EKG de artmış Tp-e intervali, Tp-e/QT ve Tp-e/QTc oranları, artmış kardiyak demir depolanmasına bağlı oluşan ventriküler repolarizasyon bozuklukları ve ventriküler aritmiler ile ilişkilidir. Aritmi gelişme riskini öngörmede bu basit ama güvenilir parametreler kullanılabilir.

Anahtar Kelimeler: Aritmi, elektrokardiyografi, talasemi

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*Corresponding Author: Zehra ERKAL, Antalya Training and Research Hospital, Department of Cardiology, Antalya, Turkey, +905056715846, zehraerkalkard@hotmail.com

ORCİD: 0000-0003-3950-2502

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INTRODUCTION

Thalassemia Major (TM) is a genetic hemoglobin disorder characterized by the reduction or complete impairment of the synthesis of the globin chains, required for the hemoglobin structure. It leads to chronic hemolytic anemia due to ineffective erythropoiesis [1]. Long term and repeated blood transfusions are given for its treatment; as a result of these, iron accumulates in the heart, liver and endocrine glands due to hemolysis and increased intestinal absorption [2].

In addition to iron deposition, a combination of inflammatory and immunogenetic factors lead to the impairment of cardiac functions. Cardiomyopathy that develops due to iron overload and arrhythmia are the most important causes of mortality in these patients. Arrhythmias and sudden cardiac death can even be observed before the symptoms and signs of heart failure present [3].

Several parameters that can be used to predict the risk of ventricular arrhythmias, which may cause sudden cardiac death, can be checked through the use of surface electrocardiography (ECG). These parameters are called ventricular repolarization markers (VPM). They include QT interval, corrected QT interval (QTc), QT dispersion (QTd), Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio (4). Out of these parameters, Tp-e interval, Tp-e/QT and Tp-e/QTc ratios are the novel and reliable markers that best demonstrate ventricular repolarization [4].

The purpose of our study was to compare the new reliable predictors that show ventricular polarization between the TM patients and healthy control group, in contrast with the conventional parameter on the ECG, and to assess if they are significant to predict the risk of arrhythmia in TM patients.

MATERIALS and METHOD

We included 97 patients who presented to the cardiology department from March 2019 to June 2020 for routine cardiac examination and follow-up, who did not have any cardiac complaints and were followed up after they had been diagnosed with thalassemia major. The thalassemia major patients in our study received 2 to 6 blood transfusions per month, and cardiology consultation was requested twice a year. Ninety healthy volunteers were included in the control group. This was a retrospective study, thus the hospital records of the patients and control group were analyzed retrospectively. Their personal (age, sex) and medical histories (the chelation therapies they received), laboratory parameters (hemogram, neutrophil to lymphocyte ratio, liver enzymes, kidney function tests, serum ferritin and C reactive protein level), electrocardiographic (heart rate, QT, QTc, Tp-e interval, Tpe/QT ratio, Tp-e/QTc ratio) and echocardiographic findings, were all obtained from their records, recorded and compared with those of the healthy control group.

Approval was obtained from the local ethic committee. Patients who had a severe valvular disease, coronary artery disease and heart failure, atrial fibrillation, malignancies or severe pulmonary diseases, pacemaker, and those that took any medication that might affect the ECG, were excluded from the study.

ELECTROCARDIOGRAPHY

The AECG recorder (Nihon Kohden, Tokyo, Japan) was set at the speed of 50 mm/s paper and 10 mm/mV voltage was used. The maximum and minimum QT and Tp–e intervals were performed by two cardiologists who were blinded to the patient data. QT and Tp–e intervals were measured manually with calipers and magnifying glass to reduce the error rate. Subjects with U waves on their ECGs were excluded from the study. The QT interval was measured from the beginning of the QRS complex to the end of the T wave and corrected for heart rate using the Bazett formulation: $QTc=QT\sqrt{}$ (R–R interval) [5]. Maximum (QTmax) and minimum (QTmin) QT-wave durations were defined as the longest and shortest measurable QT-wave durations, respectively, in any lead. Accordingly, corrected QT dispersion (QTcd) was calculated as the difference between maximal and minimal QTc intervals. Tp–e interval was defined as the interval between the peak and the end of T wave. Measurements of Tp–e interval were performed from precordial leads [6]. The Tp–e/QT and Tp–e/QTc ratios were calculated from these measurements.

ECHOCARDIOGRAPHY

Echocardiographic measurements of the patients were analyzed by an experienced cardiologist in accordance with the American Society of Echocardiography (ASE) guidelines. A Vivid–7 (GE Vingmed, Horten, Norway) device was used for the examination and the left ventricular ejection fraction was calculated by using the modified Simpson's method.

STATISTICAL ANALYSIS

The data obtained from the study was recorded in the SPSS 24.0 (Armonk, NY: IBM Corp.) software. Among the continuous variables, those with normal distribution were presented as mean ± standard deviation, those with normal distribution were presented as median (quartiles), while categorical variables were expressed as numbers and percentages. Conformity of continuous variables with normal distribution was examined by Kolmogorov-Smirnov test. Student-t test was used for normally distributed parameters and Mann-Whitney U test was used for non-normally distributed parameters for comparisons between groups. The Chi-square test was used in the analysis of categorical variables. Correlation analyses for ferritin, CRP (mg/L), N/L ratio were performed using Pearson or spearman tests. P values of <0.05 were considered statistically significant.

RESULTS

The mean age of the patients in the thalassemia major group was 28.0 (24.0-37.0) while it was 32.0 (23.7-39) in the control group, which were similar (p=0.257). The hemoglobin level was 9.2 g/dl (8.6-9.6) in the TM group while it was 14.0g/dl (13.0-15.1) in the control group (p<0.001). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were 27.0 U/L (19.0-44.0) and 41.0 U/L (32.0-72.0), respectively, in the TM group while they were 29.2 U/L (20.9-46.0) and 44.0 U/L (31.0-76.0), respectively, in the control group (p=0.440 and p=0.226, respectively). Serum creatine level was 0.72 mg/dl (0.5-0.9) in the TM group while it was 0.78 mg/dl (0.6-0.9) in the control group (p:0.552). Left ventricular ejection fraction was 65.0 (65.0-65.0) in the TM group and 65.0 (65.0-65.0) in the control group (p=0.660). Intraventricular septum diameter was 10.0 mm (9.0-11.0) in TM group and 11.0 mm (9.0-11.0) in control group (p=0.234). Left ventricular diastolic dysfunction was 36% in TM group and 44.4% in control group (p=0.075). Prevalence of left ventricular hypertrophy was 12.4%in TM group and 22.2% in control group (p=0.083) (Table 1).

Table 1. Comparison of laboratory and echocardiographic findings between thalassemia major group ve control group

Variable	Thalassemia Group (n=97)	Control Group (n=90)	p value
Hemoglobin, g/dL	9.2 (8.6-9.6)	14.0 (13.0-15.1)	<0.001
ALT (U/L)	27.0 (19.0-44.0)	29.2 (20.9-46.0)	0.440
AST (U/L)	41.0 (32.0-72.0)	44.0 (31.0-76.0)	0.226
Creatinine, mg/dL	0.72 (0.5-0.9)	0.78 (0.6-0.9)	0.552
LVEF, %	65. 0 (65.0-65.0)	65.0 (65.0-65.0)	0.660
IVSD (mm)	10.0 (9.0-11.0)	11.0 (9.0-11.0)	0.234
LVDD, % (n)	36 (35)	44.4 (40)	0.075
LVH	12.4 (12)	22.2 (20)	0.083

(which show a normal distribution mean ± SD, not show a normal distribution median (25th and 75th percentile) and percentage for categorical variables), (ALT; Alanine aminotransferase, AST; Aspartate aminotransferase, IVSD ;Intraventricular septum diameter, LVDD ;left ventricular diastolic dysfunction, LVEF; left ventricular ejection fraction)

Table 2 shows the comparison between the ECG parameters of both groups. The heart rate was 83.0 (75.0-88.5) in the TM group while it was 77.5 (70.0-93.2) in the control group. No significant difference was found between two groups (p=0.152). QTc was 420.4+-24.9 ms in the TM group and 395.2+- 30.3 ms (p<0.001) in the control group; QT was 360.0 ms (340.0-380.0) in the TM group and 350.0 ms (320.0-360.0) in the control group (p<0.001). Tp-e interval was 80.0ms (60.0-80.0) in the TM group and 60.0 ms (50.0-70.0) in the control group (p<0.001); Tp-e/QT ratio was 0.200 (0.160-0.225) in the TM group and 0.175 (0.150-0.210) in the control group (p=0.014); Tp-e/QTc ratio was 0.180 (0.130-0.190) in the TM group and 0.150 (0.130-0.180) in the control group (p=0.035).

Figure 1 shows the significant prolongation of Tp-e, QT, QTc intervals in the TM group compared to the control group. Figure 2 demonstrates the significant increase in the Tp-e/ QT and Tp-e/QTc ratios in the TM group compared to the control group.

As shown in Table 3, no significant correlation was found between the electrocardiographic parameters (QTc, QT, Tp-e, Tp-e/QT, Tp-e/QTc) and serum ferritin, C reactive protein (CRP) and neutrophil to lymphocyte ratio (N/L).

Table 2. Comparison of age and electrocardiographic findings between the thalassemia major group and control group

Variable	Thalassemia Group(n=97)	Control Group (n=90)	p value
Age, years	28.0 (24.0-37.0)	32.0 (23.7-39.0)	0.257
Heart Rate, (beat/min)	83.0 (75.0-88.5)	77.5 (70.0-93.2)	0.152
QTc, ms	420.4 ± 24.9	395.2 ± 30.3	<0.001
QT, ms	360.0 (340.0-380.0)	350.0 (320.0-360.0)	<0.001
Tp-e	80.0 (60.0-80.0)	60.0 (50.0-70.0)	<0.001
Tp-e/QT	0.200 (0.160-0.225)	0.175 (0.150-0.210)	0.014
Tp-e/QTc	0.180 (0.130-0.190)	0.150 (0.130-0.180)	0.035

(which show a normal distribution mean ± SD, not show a normal distribution median (25th and 75th. percentile) and percentage for categorical variables), QT; QT interval, QTc; Corrected QT, Tp-e; Tp-e interval,

Table 3. The correlation between TnI, CRP, N/L ratio and ECG parameters (QTc, QT, Tp-e, Tp-e/QT, Tp-e/QTc)

	Ferritin	CRP, mg/L	N/L ratio
QTc, ms			
Correlation coefficient	0.012	-0.023	-0.071
P value	0.909	0.819	0.511
QT, ms			
Correlation coefficient	-0.119	-0.026	-0.063
P value	0.250	0.799	0.562
Tp-e			
Correlation coefficient	0.147	-0.068	0.041
P value	0.152	0.509	0.704
Tp-e/QT			
Correlation coefficient	0.173	-0.021	0.047
P value	0.092	0.838	0.665
Tp-e/QTc			
Correlation coefficient	0.127	-0.039	0.063
P value	0.217	0.707	0.561

CRP: C reactive protein, (N/L: Neutrophil to Lymphocyte ratio)
QT; QT interval, QTc; Corrected QT, Tp-e; Tp-e interval

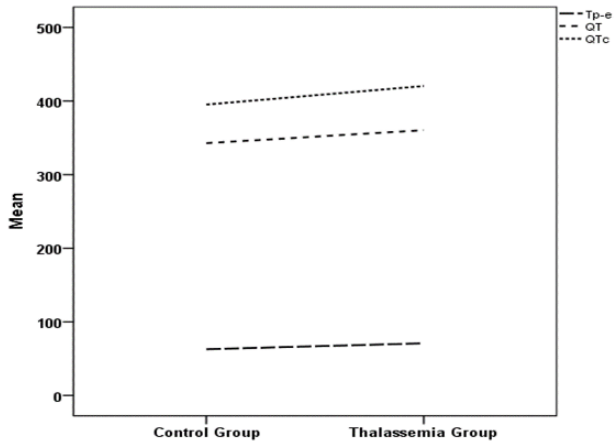

Figure 1. Tp e interval, QT and QTc increased significantly in the thalassemia major patients compared to the control group.

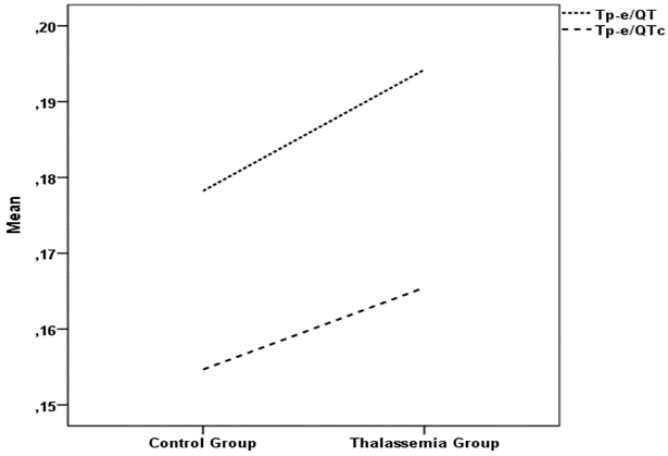

Figure 2. Tp e/QT and Tp e/QTc ratios were found to increase significantly in the thalassemia major group compared to the control group.

DISCUSSION

Our study revealed that the Tp-e interval, Tp-e/QT and Tp-e/QTc ratios increased in the TM patients compared to the healthy control group. These findings suggested that the TM patients had ventricular repolarization abnormalities. Moreover, no correlation was found between this increase and the serum ferritin, C reactive protein level and neutrophil to lymphocyte ratio. The patients were also compared as regards the ECG parameters according to the chelation therapies they received whereas no difference was found between the groups.

Continuous and repeated blood transfusion is essential for the treatment of TM patients. Repeated transfusion results in hemolysis and increased intestinal iron absorption, leading

to iron overload. Iron starts to accumulate in parenchymal tissues especially heart, liver and endocrine glands, within one year following the start of regular blood transfusion. If the iron binding capacity of transferrin is exceeded, a very toxic and free form of iron that is not bound on transferrin is formed. Free iron catalyzes the formation of hydroxyl radicals. These radicals attack proteins, lipids and DNA. As a result, cell death and fibrosis occur [7]. Moreover, iron causes a toxic effect on the endocrine glands and leads to the development of diabetes mellitus (DM). The calcium metabolism is impaired and the synthesis of the growth hormones and sex steroids is also impaired. Ultimately, all these events result in cardiac dysfunction [8].

Excessive iron accumulation in patients with thalassemia major inhibits sodium channels rapidly at cellular level, blocks the calcium releasing ryanodine channels and leads to modifications in sarcoplasmic reticulum, due to oxidative stress. All these events cause electrophysiological changes in cells and impairment of myocardial repolarization [9-10].

The most important causes of mortality and morbidity among patients with thalassemia major include cardiac involvement and associated heart failure as well as life-threatening severe ventricular arrhythmias [11-12]. Due to iron overload, first myocardial electrical conductivity is delayed or blocked and then myocardial contractility is impaired. This means that electrical activity is impaired in TM patients before heart failure develops [13]. Studies including TM patients showed that iron accumulation in the myocardium was not homogenous and it occurred earlier, especially in the free wall and interventricular septum. Such patch-like non-homogenous accumulation may be the reason for early involvement of the conduction system and higher incidence of arrhythmias among young patients [14]. Due to all these reasons, questions as to how the risk of arrhythmia can be distinguished among TM patients without any evidence of cardiac disease, and how these patients can be diagnosed early, are still important matters of debate.

Increased dispersion in ventricular repolarization is associated with life-threatening ventricular arrhythmias [13]. There are several parameters that show ventricular repolarization on the ECG. Several studies demonstrated that parameters such as QT interval, QTc interval, QT dispersion, JT dispersion increased in TM patients, which might be associated with serum ferritin level [15-17]. Similarly, increased QRS duration and presence of fragmented QRS in TM patients may be associated with increased arrhythmic events and mortality as shown in some studies [18-19]. Many ECG parameters have been used as the predictors of arrhythmia and supported by studies. There are no studies reported in the literature which used Tp-e interval, Tp-e/QT and Tp-e/QTc ratios that have been debated recently and show the transmural distribution of repolarization in TM patients.

Ventricular repolarization ends first in the epicardial cells. Action potential in the midmyocardial M cells is longer than the one in the other myocardial cells. The peak of the T wave shows the end of the epicardial action potential. The final point of the T wave shows the end of the midmyocardial action potential. In light of this information, the Tp-e interval, which is the distance between the peak point of the T wave and its last point, shows the transmural distribution of repolarization. Prolongation of this interval is associated with the risk of ventricular arrhythmia and sudden cardiac death [20]. As the Tp-e interval is affected by heart rate and body weight, Tp-e/QT and Tp-e/QTc ratios are the most precise indexes that show ventricular repolarization [21]. Several studies have demonstrated the association between these parameters and SCD and ventricular arrhythmia in different patient groups, however there is no data regarding TM patients.

In many cardiac and non-cardiac diseases, Tp-e interval, Tp-e/QT and Tp-e/QTc ratios are used as the predictors of arrhythmia. In some studies, the patient group that had aortic stenosis was found to have markedly prolonged Tp-e interval, Tp-e/QT and Tp-e/QTc ratios, compared to the control group, and these parameters increased in parallel to the increase in the severity of aortic stenosis [22]. MVP patients were found to have prolonged Tp-e interval, Tp-e/QT and Tp-e/QTc ratios, which correlated with the increased rate of mitral

regurgitation [23]. These indexes were found to increase in the hyperthrophic cardiomyopathy patients compared to the control group [24]. They were also found to increase in patients with slow coronary flow compared to the control group [25]. All these changes increase the risk of ventricular arrhythmia in these patient groups. In conclusion, these studies have demonstrated that the ECG parameters could be used to predict life-threatening arrhythmias in different patient groups.

In our study, the Tp-e interval, Tp-e/QT and Tp-e/QTc ratios in the TM patient group were markedly prolonged compared to the healthy control group. These patients are very prone to the development of ventricular arrhythmia and must be followed-up more closely for life-threatening arrhythmias.

Studies in the literature that were conducted on TM patients reported a correlation between ventricular repolarization parameters and high serum ferritin level, and concluded that elevated serum ferritin level indicated excessive iron accumulation in the heart [25]. In our study, however, no association with serum ferritin level was found. This may be explained by the fact that the spot measurement of serum ferritin level did not show cardiac iron accumulation [24]. As we highlighted above, due to the patch-like accumulation of iron in the myocardium, arrhythmias may develop without high ferritin level as the conductor system is affected.

The basic cause of cardiac problems in thalassemia major patients is iron overload and MRI is the golden standard to show the myocardial iron accumulation [25]. In particular, the T2* value of <10 that can be shown via MRI indicates a severe myocardial iron overload [21]. However, for technical and cost reasons, it may be difficult to access MRI in different centers. In our study, we did not compare the ECG parameters and the T2* value by using MRI, which constitutes one of its limitations.

Anemia is a condition that can affect ECG parameters. However, in our study, we think that iron accumulation in the myocardium due to recurrent blood transfusions was primarily responsible for the increased frequency of ventricular arrhythmias, in thalassemia patients.

Ajibare AO et al. support our finding in the article titled “Assessment of ventricular repolarization in sickle cell anemia patients: The role of QTc interval, Tp-e interval and Tp-e/QTc ration and its gender implication”. In this study recruiting patients with sickle cell anemia who were compared with the healthy control group, there was a significant difference in hemoglobin values between the groups. Here, too, the researchers associated changes in ECG parameters with myocardial iron load (26).

The findings of our study demonstrated that simple but reliable parameters that can be analyzed via non-invasive, cost-effective and easily accessible methods such as ECG, increased statistically significantly in the TM patients for whom ventricular arrhythmias were an important cause of mortality, compared to the control group.

Limitations

There were certain limitations in our study. We had a low number of patients and arrhythmias that could develop in the long term could not be demonstrated, as they were not followed up for a long term. Moreover, as mentioned above, MRI and T2* value were not used for technical reasons, availability and cost constraints. In our study, thalassemia patients and healthy control group were compared and a difference in hemoglobin values was detected between these groups. We know that anemia affects ECG parameters, but our primary hypothesis was the development of ventricular repolarization disorder due to myocardial iron deposition. The inability to make this distinction clearly was one of the limitations of our study.

Conclusion

Simple but reliable parameters such as Tp-e interval, Tp-e/QT and Tp-e/QTc ratios that could be found through electrocardiography, increased significantly among the TM patients compared to the control group. This was associated with impaired ventricular repolarization due to cardiac iron overload. The risk of arrhythmia can be predicted via the analysis of these parameters when patients do not present any cardiac manifestations, and patients who are found to have an increase in these parameters can be

examined and followed up for arrhythmias.

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