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Original Article

Evaluation of the Relationship Between T2*CMR and Cardiac Depolarization and Repolarization Parameters in Beta-Thalassemia Patients

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Abstract

Background: Cardiac iron overload causes severe cardiac complications and is a leading cause of death in beta-thalassemia major (B-TM) patients. T2-weighted cardiovascular magnetic resonance (T2*CMR) can detect preclinical cardiac iron overload. We evaluated the ability of 12-lead electrocardiographic atrial and ventricular depolarization and repolarization parameters to predict cardiac iron loading in TM.

Methods: This cross-sectional study was conducted on patients with beta-thalassemia major; all participants underwent a standard 12-lead electrocardiogram during a single study visit, and the depolarization and repolarization parameters of ECG were measured and compared with the cardiac iron level detected by T2*CMR, with a detectable cardiac iron cutoff of T2* less than 20 ms.

Results: A total of 26 patients (mean age of 26.19 years, 34.62% male) were included. Mean T2*CMR values were 21.53 ms (46.15%<20 ms, 53.85%≥20 ms). Among ECG parameters, only Pwd, QTc, and QTcd (*P* values 0.026, 0.030, and 0.006, respectively) were significantly prolonged in patients with T2*<20 ms compared to patients with T2*≥20 ms. There was a statistically negative correlation between T2*CMR, Pwd, and QTcd (*P* values 0.028 and 0.021, respectively). Moreover, no correlation was found between Tp-e, Tp-e d, JTc, JTcd, Tp-e/QT, Tp-e/JT, Tp-e/JTc, and T2* values.

Conclusion: Pwd and QTcd can be used as alternatives to T2*CMR to predict cardiac iron load levels in patients with beta-thalassemia major.

Keywords: Beta-thalassemia major, Depolarization, ECG, Repolarization, T2*CMR

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Introduction

In thalassemia major (TM), iron overload is the joint result of multiple blood transfusions and a disproportionately increased iron absorption associated with inefficient erythropoiesis. It is the leading cause of morbidity and mortality in TM patients. Deposition of iron in the heart leads to severe cardiac complications, including heart failure and malignant arrhythmias. T2-weighted cardiovascular magnetic resonance (T2*CMR) is the gold standard technique for the evaluation of myocardial iron levels. However, it has some disadvantages, including high cost, time consumption, unavailability in most medical centers, and limited use in patients with claustrophobia. The sensitivity and specificity of ECG in assessing abnormal T2*CMR values are 54% and 67%, respectively (1).

The relationship between T2*CMR values and electrocardiographic cardiac depolarization and repolarization parameters remains controversial in different studies (2,3). Tp-e has been evaluated in several clinical conditions, demonstrating its usefulness in predicting malignant arrhythmias and sudden cardiac death, and it has been considered more useful in predicting cardiac arrhythmias in comparison to QTc and its dispersion. So far, however, there has been little published data about it, and it should be studied in further investigations (4,5). The Tp-e/QT ratio, which indicates the indices of transmural dispersion (Tp-e) and spatial dispersion (QT) of ventricular repolarization, is a novel index to predict cardiac arrhythmias (6).

To date, there are far too little studies have investigated the correlation between ECG parameters, including Tp-e,

Tp-e d, Tp-e/QT, JTcd, and cardiac T2*MRI. Only one study conducted by Russo et al (7) showed an increase in the duration of JTcd in patients with thalassemia major; nevertheless, they did not investigate its correlation with T2*CMR. In the study of Kayrak et al (3), the relationship between Tp-e, Tp-e d, Tp-e/QT, and T2*CMR was investigated, and no significant correlation was found. The relationship between Tp-e/JT and Tp-e/JTc ratios with T2*CMR and its measurement in beta-thalassemia patients has been investigated for the first time in our study.

The present study aims to evaluate the relationship between atrial and ventricular depolarization and repolarization ECG parameters and T2*CMR values to use ECG parameters to detect cardiac disease associated with iron overload in the early stages.

Materials and Methods

Study population

This cross-sectional analytical study was conducted in Amirkabir hospital in Arak. The diagnosis of β-TM was made on hemogram, blood smear, hemoglobin electrophoresis, and clinical evaluation. The patients had been regularly transfused (every 3–4 weeks), and everyone had received chronic chelation therapy (deferoxamine or deferasirox). Exclusion criteria were history of diabetes mellitus (hyperglycemia), coronary artery disease, congestive heart failure, congenital or acquired arrhythmia syndromes, and patients under treatment with medications that lengthen the QT interval, current AF, bundle branch block, atrioventricular blocks, and unmeasurable T waves (< 0.15 mV) on surface ECG, electrolyte disturbances, including calcium, magnesium, sodium, potassium, and glucose, which affect the P wave and the corrected QT.

Cardiac magnetic imaging

MRI was performed by Magneto Symphony Graniand 32, 1.5 Tesla (Siemens, Germany, 2003). Each scan lasted about 30 minutes and included the measurement of cardiac T2*. The respiratory triggering technique was carried out for all the patients. A short-axis mid-ventricular slice (10 mm) was acquired at eight echo times. Each image was taken during a 10–15 second breath-hold. T2* > 20 msec indicates no cardiac iron overload, T2* between 10 and 20 msec indicates mild to moderate iron load, and T2* < 10 msec indicates severe iron overload.

ECG recording and analyses

Surface 12-lead standard ECGs were recorded from each patient with a 25 mm/s paper speed at 10 mm/mV amplitude. The timing of electrocardiographic measurements was adjusted to the last blood transfusion, so ECG was performed at least two weeks after blood transfusion. Measurements were performed manually and by two physicians, one of whom was a pediatric cardiologist blind to the study. Three consecutive ECG complexes were analyzed, and averaged measures were given for each lead.

The QT interval was measured from the beginning of the QRS complex to the end of the T wave, where it returns to the T-P baseline. When the U wave was present, the QT interval was measured up to the lowest point of the curve between the T and U waves. If the T wave was flat, the end of the T wave was challenging to detect, or if the T wave amplitude was < 0.15 mv, the lead was excluded from measurement. The corrected QT interval (cQT) was calculated using Bazett's formula (cQT = QT ÷ √R-R). The Tp-Te interval was measured in precordial leads as the interval between the T wave's peak and the T wave's end. Tp-e/QT measured in precordial lead V6 which is the best reflection of the transmural axis of the left ventricle. JTc was calculated using JT/√R-R. Pmax, Pmin, and Pwd were measured as the atrial parameters in all 12 leads of the surface ECG recordings.

Statistical analysis

Statistical analysis was performed using the Stata software (version 11.0). The data were expressed as mean ± standard deviation or median and inter-quartile range according to the distribution properties, and a *P* value below 0.05 was considered statistically significant. A Pearson correlation test was used to assess linear associations. Student t-test and chi-square were applied to determine the difference between the two groups for parametric variables.

Results

Table 1 summarizes the demographic characteristics

Table 1. Demographic and laboratory information in participants according to T2*CMR

Variables	T2*MRI < 20 ms (*n* = 12)	T2*MRI ≥ 20 ms (*n* = 14)	*P* value
Gender (%)			
Female	7 (58.33)	10 (71.43)	0.484
Male	5 (41.67)	4 (28.57)	
Age (y)	27.66 ± 3.42	24.92 ± 8.8	0.161
BMI (kg/m^2)	21.41 ± 3.07	21.63 ± 2.78	0.426
SBP (mm Hg)	105 ± 12.24	103.57 ± 8.41	0.364
DBP (mm Hg)	65.41 ± 5.82	63.92 ± 5.6	0.256
HR (bpm)	83.25 ± 8.2	83.28 ± 15.9	0.497
Ferritin (ng/dL)	2554.33 ± 1490.8	1565.21 ± 1294.9	0.041
RBC (10*6/μL)	3.18 ± 0.44	3.65 ± 0.6	0.033
Hb (g/dL)	8.96 ± 0.5	9.36 ± 1.07	0.237
MCV (fl)	83.42 ± 2.99	81.14 ± 9.84	0.432

Data are expressed as mean ± SD
BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate.

of the study population. Serum ferritin levels were significantly higher in patients with T2*CMR < 20ms than in patients with T2*CMR ≥ 20 ms ($P = 0.041$). The mean age of patients was 26.19, the mean BMI was 21.53, the mean serum ferritin level was 2021.73 ng/ml, and the mean T2*CMR value was 21.53 ms (46.15% < 20 ms, 53.85% ≥ 20 ms). Moreover, 65.38% of patients were female and 34.62% were male.

The twelve-lead surface ECG analysis of atrial and ventricular depolarization and repolarization parameters is presented in Table 2. Based on the results, among the ECG parameters, only QTcd, QTc, and Pwd were statistically prolonged in individuals with T2* < 20 ms compared to individuals with T2 * ≥ 20 ms. Table 3 evaluates the correlation of atrial and ventricular parameters with T2*CMR. An inverse and statistically significant correlation was detected between the T2* values and Pwd ($P = 0.021$) and QTcd ($P = 0.028$).

Discussion

Based on the results of the present study, only the correlation between Pwd and QTcd, which are atrial and ventricular heterogeneity parameters and T2*CMR values, was statistically significant, which represents the effect of cardiac iron overload on altering the heterogeneous distribution of connections between atrial and ventricular myocyte fibers.

Pwd indicates the heterogeneous distribution of connections between myocardial fibers of atrial tissue. The generally accepted cutoff values for the Pwd and Pmax are durations above 40 and 120 ms, respectively (8).

The studies of Russo et al (9) illustrated a correlation between Pwd and myocardial iron overload assessed by T2*CMR in B-TM patients, which is similar to the results of our study. However, in the study of Acar et al (10), no correlation was found between Pwd and T2*CMR. The Pwd values measured in both studies were within the normal range. Therefore, they could not find a relationship between P-wave parameters and the risk of atrial fibrillation. In the present study, the mean Pwd was 53.3 ms (above the standard limit) in patients with T2* less than 20 ms and 40 ms in patients with T2* above 20 ms. However, Pmax values were less than 120 ms in both groups. Therefore, according to the results of our study, iron overload can affect atrial conduction time and Pwd values.

According to the results of the previous studies, abnormal values of repolarization parameters, including prolonged QT, QTc, QTd, and QTcd, are known risk factors for sudden death in patients with heart failure and coronary disease and can be the predictor of cardiac mortality and morbidity (11). The results of the present study confirm the relationship between cardiac iron load and QT parameters.

Abnormal proposed values of QTc for adults are ≥ 450 ms in men and ≥ 460 ms in women (12). QTd represents the heterogeneous state of ventricular repolarization. An increase in ventricular heterogeneity extends the duration of vulnerability in the heart and makes it prone to ventricular arrhythmias (13). It was carried out in

Table 2. Electrocardiographic parameters of B-TM patients according to T2*CMR values

ECG parameters	T2*CMR < 20 ms (n = 12)	T2*CMR ≥ 20 ms (n = 14)	*P* value
P max (ms)	103.23 ± 3.8	95.21 ± 7.0	0.395
P min (ms)	50.13 ± 0.4	55.13 ± 7.9	0.150
Pw d (ms)	53.15 ± 3.5	40.17 ± 0.5	0.026
QT (ms)	364.35 ± 1.0	347.25 ± 1.8	0.167
QTd (ms)	71.49 ± 6.1	51.19 ± 4.9	0.085
QTc (ms)	422.37 ± 5.2	397.28 ± 14.6	0.030
JTc (ms)	327.29 ± 5.2	295.86 ± 7.4	0.118
QTcd (ms)	91.48 ± 6.5	51.26 ± 4.8	0.006
JTcd (ms)	55.26 ± 0.2	63.28 ± 5.7	0.221
Tp-e (ms)	70.26 ± 0.2	64.12 ± 2.2	0.236
Tp-e d (ms)	50.21 ± 0.7	38.18 ± 5.7	0.081
Tp-e/QT	0.18 ± 0.04	0.18 ± 0.001	0.406
Tp-e/QTc	0.15 ± 0.05	0.16 ± 0.02	0.365
Tp-e/JT	0.22 ± 0.03	0.23 ± 0.03	0.393
Tp-e/JTc	0.19 ± 0.08	0.20 ± 0.02	0.300

B-TM: beta-thalassemia major, Pmax: maximum P-wave duration, Pmin: minimum P wave duration, Pwd: P wave dispersion, QTd: QT dispersion, QTc: QT corrected, QTcd: QT corrected dispersion, JTc: JT corrected, JTcd: JT corrected dispersion, Tp-e: difference between T-peak and T-end, Tp-e d: Tp-e dispersion.

Table 3. Correlation of Atrial and Ventricular parameters with T2*CMR values

ECG parameters	r	*P* value
P max (ms)	-0.309	0.124
P min (ms)	0.080	0.699
Pw d (ms)	-0.451	0.021
QT (ms)	-0.186	0.363
QT d (ms)	-0.214	0.294
QTc (ms)	-0.377	0.058
JTc (ms)	-0.277	0.171
QTc d (ms)	-0.431	0.028
JTc d(ms)	0.312	0.120
Tp-e(ms)	-0.068	0.743
Tp-e d (ms)	-0.307	0.127
Tp-e/QT	-0.062	0.767
Tp-e/QTc	0.097	0.637
Tp-e/JT	0.044	0.832
Tp-e/JTc	0.141	0.492

B-TM: beta-thalassemia major, Pmax: maximum P-wave duration, Pmin: minimum P wave duration, Pwd: P wave dispersion, QTd: QT dispersion, QTc: QT corrected, QTcd: QT corrected dispersion, JTc: JT corrected, JTcd: JT corrected dispersion, Tp-e: difference between T-peak and T-end, Tp-e d: Tp-e dispersion.

clinical practice by Day et al (14) and has been suitably evaluated as a marker to predict malignant ventricular arrhythmias. The values of QTd in normal subjects and the general population are controversial. Reports from several studies reveal values of 33.4 ± 20.0 ms, with a range from 10.5 ± 10.0 ms to 71 ± 7.0 ms and a median of 37 ms. Recently published data have shown that in healthy individuals, a QTd > 58 ms increases the risk of cardiovascular mortality 3.2-fold (15, 16). In our study, the mean QTd was 71.49 ± 6.1 in patients with T2*MRI < 20 ms, which is within cardiac mortality risk. The relationship between T2* values and electrocardiographic ventricular depolarization parameters was controversial in different studies.

In the study conducted by Kayrak et al (3), no correlation was found between QT parameters and T2*CMR. Magrì et al (17) found no correlation between QTc and T2* values, which is in contrast with the results of the present study. The study of Magrì et al demonstrated that T2*CMR was significantly correlated with the QT variability index. We hypothesized that the QT variability index might be more reliable for predicting iron overload-related arrhythmias than conventional QT parameters. However, the QT variability index measurement has some limitations, including the need for more time records, additional software programs, and complex formulas. Therefore, clinical use of QT variability parameters is limited, and it is not assessed in our study.

In a study performed by Oztarhan et al (18), QTcd was significantly higher in patients with T2* 0–10 ms, which is similar to the results of our study.

In the study conducted by Detterich et al (19), QT and QTc were significantly prolonged in beta-thalassemia patients with T2* < 20 ms. Moreover, in the study of Advani et al (2), there was a statistically significant correlation between QTc and T2*CMR values, similar to the current study's results.

JTcd is another parameter for evaluating regional differences in cellular action potential duration and ventricular rest time. Due to the lower dependence of this parameter on ventricular depolarization, it shows ventricular repolarization heterogeneity better than QTcd. To date, few studies have investigated this parameter; only one study conducted by Russo et al showed an increase in the duration of JTcd in patients with thalassemia major. Nevertheless, they did not investigate its correlation with T2*CMR. According to the results of their study, a cutoff value of 70 ms for QTcd had a sensitivity and specificity of 77% in identifying patients at risk for sudden cardiac death. A cutoff value of 100 ms for JTcd had a sensitivity of 65% and specificity of 94% in identifying this category of patients (7). In the present study, the mean QTcd was 91.48 ms in patients with T2* < 20 ms and 51.26 ms in patients with T2* ≥ 20 ms, and the mean JTcd was 63.28 ms and 55.26 ms in patients with cardiac T2* < 20 ms and ≥ 20 ms, respectively.

For the first time, we investigated the correlation of JTc and JTcd with cardiac T2* values. Our study found no statistically significant correlation between JTc and JTcd and cardiac T2* values.

The myocardial layers are at different repolarization phases, making transmyocardial heterogeneities, which become underlies for reentry, causing malignant arrhythmias. These trans-myocardial non-homogeneities are determined by the ECG parameters *Tp -Te*, (*Tp - Te*) d, and (*Tp - Te*)/QT ratio (20).

In V5 lead of healthy subjects, Tp-e has a mean value of 94 ± 10 ms in men and 92 ± 11 ms in women. However, there is no consensus about the normal values of Tp-e. Therefore, further investigations are needed to define them.

The tp-e/QT ratio has almost no variations between 60-100 beats/min and does not need to be corrected by heart rate. As a result, it has a substantial advantage over the other markers. It has a mean value of 0.21 ± 0.03 and a range from 0.15 to 0.25 (21,22).

There is little published data on these parameters in beta-thalassemia patients. In a study conducted by Kocharian et al, Tp-e and Tp-e d were more prolonged in beta-thalassemia major patients than in healthy controls. However, this difference was not statistically significant compared to QT and QTc (23). In the study of Kayrak et al (3), the relationship between these three parameters and T2*CMR was investigated, and no significant relationship was found, which is consistent with the results of our study.

The relationship between Tp-e/JT and Tp-e/JTc ratios with T2*CMR, as well as its measurement in beta-thalassemia patients, has been investigated for the first time in the present study, and no statistically significant correlation was found between these two parameters and T2*CMR.

Our study had some limitations. First, this is a cross-sectional study with small sample size, and extensive randomized studies are needed to determine the correlation between ECG depolarization and repolarization parameters and subsequent cardiac iron overload measured by T2*CMR. Secondly, ECG analyses were performed manually. Further studies need to be carried out emphasizing JT and Tp-e parameters, which have been investigated inadequately.

Conclusion

T2*CMR is the gold standard technique for evaluating myocardial iron levels. It is done annually for thalassemia patients due to its complication-free nature. According to the results of the present study, Pwd and QTcd, which are atrial and ventricular heterogeneity parameters, can be used as alternatives to T2*CMR to predict cardiac iron load levels in situations where accessibility to the medical centers

equipped with T2*CMR is low due to economic limitations.

Authors' Contribution
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Writing–review & editing: Bita Ghahremani.

Competing Interests
All authors declare no conflicts of interest that might be relevant to the contents of this manuscript.

Ethical Approval
This study was approved by the Ethics Committee of the Faculty of Veterinary Medicine of Arak Medical University, Iran (license number: IR.ARAKMU.REC.1397.289).

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