Original Article

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Evaluation of the Correlation Between Electrocardiographic Abnormalities, Cardiac Iron Overload, and Magnetic Resonance T2* Values in Patients with Beta Thalassemia Major

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Abstract

Background: Beta thalassemia major (β-TM) is an inherited blood disorder. Affected patients require frequent blood transfusions, leading to iron deposition and end organ damage, particularly myocardial dysfunction. A 12-lead ECG is a readily available tool that could be used to screen for conduction abnormalities and arrhythmias as a marker of worsening myocardial function.

Methods: A total of 108 β-TM patients were evaluated for correlation between abnormal findings on the surface ECG and severity of myocardial iron deposition in magnetic resonance imaging as measured by T2* levels.

Results: Patients with T2* below 20 *msec* had significantly longer PR intervals, P wave durations, and QTc intervals. Patients with T2* below 10 *msec* had the longest QRS duration and QRS activation times. Atrial fibrillation was more prevalent in patients with lower T2* levels. With a decrease in T2*, the probability of notching of QRS in the limb and precordial leads increased.

Conclusion: Abnormal ECG is prevalent in β-TM patients, and the frequency of changes increases with the severity of iron overload. A 12-lead ECG is a valuable and readily available tool for the early assessment of myocardial damage and the implementation of a timely and appropriate management strategy.

Keywords: Beta thalassemia major, Electrocardiography, Iron overload, Magnetic resonance imaging

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Introduction

Thalassemia is an inherited disease that results in the production of damaged hemoglobin chains. In Beta thalassemia, production of the beta-globin chain of hemoglobin is deficient. Patients with Beta thalassemia major (β-TM) require frequent blood transfusions to compensate for the severe anemia caused by ineffective erythropoiesis. The resultant iron overload and organ deposition lead to multi-organ damage, including cardiomyopathy and advanced heart failure. These patients are also at risk of serious cardiac arrhythmias. Regular measurement of cardiac iron load by Cardiac Magnetic Resonance (CMR) and T2* value is now the standard of care. However, considering the costly nature and limited access to CMR for many patients, validating simple clinical tools, including twelve lead ECG to predict forthcoming organ damage is important in follow-up and treatment. Changes in the surface ECG, such as fragmentation of the QRS, are believed to be reliable markers of myocardial scarring and fibrosis (1-4).

In the current study, we sought to evaluate the relation between myocardial iron load as measured by CMR T2* value and related changes in the surface ECG and the reliability of the twelve-lead ECG to predict worsening myocardial function as a readily accessible clinical tool.

Materials and Methods

In a prospective study, 108 consecutive adult β-TM patients who are under cardiology care in our center and had reliable clinical and para-clinical data, including ECG, echocardiography, and CMR, were included. Data regarding age, sex, and hemoglobin concentrations were collected. CMR data and T2* levels were also evaluated. Twelve-lead ECG of patients were assessed by an electrophysiologist, and data regarding rate, rhythm, axis, QRS width, QRS fragmentation, PR and QT intervals, conduction blocks, evidence of chamber enlargement and hypertrophy, and ST-T changes in limb and precordial leads were obtained and recorded. The severity of iron deposition was defined based on T2*. A T2* level below 20 was considered an indicator of myocardial iron overload. Patients with T2* levels below 10 were classified as having severe myocardial iron deposition.

Statistical analysis

Categorical variables were described as frequencies (percentages) and compared between groups by Pearson's chi-square or Fisher's exact test for nominal variables and the chi-square or trend test for ordinal variables. Numerical variables were assessed for normal distribution via one sample Kolmogorov-Smirnov test. They were described by median (interquartile range, Q1–Q3) and compared between groups using the Mann-Whitney U or Kruskal-Wallis test. p-values< 0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics 24 for Windows (IBM Inc., Armonk, NY, USA).

Results

A total of 108 patients were evaluated in this study. Fifty-seven patients (52%) were female. The mean age of the participants was 33 years (SD = 10.8). Mean hemoglobin levels were 9 *g/dl* (SD = 1). Mean ferritin levels were 2164 *g/dL* (SD = 2815). Fifty-six (52%) of the patients had CMR T2* values > 20 *msec*, fifteen had values > 10 *msec* and 20 *msec*, and in thirty-seven (3%) patients, the T2* level was reported below 10 *msec*. Eighty-eight percent of the patients had normal sinus rhythm, 6.5% atrial fibrillation, 4.6% atrial flutter, and 0.9% atrial tachycardia. (Table 1).

β-TM patients with T2* below 20 *msec* demonstrated a significantly longer P wave duration, PR interval, maximum ventricular activation time (in both limb and precordial leads), maximum QRS duration (in both limb and precordial leads), and QTc interval compared to those with T2* equal to or over 20 *msec* (p-values=0.021, 0.020, 0.000, 0.000, and 0.001, respectively). Poor R wave progression, QRS notching in limb leads, QRS notching in precordial leads, T wave inversion in limb leads, and T wave inversion in precordial leads were significantly more prevalent in β-TM patients with T2* below 20 *msec*, compared to those with T2* equal to or over 20 *msec* (p-values=0.001, 0.003, 0.017, 0.007, and 0.008, respectively). β-TM patients with T2* below 20 *msec* demonstrated a significantly higher ferritin level and were younger compared to those with T2* equal to or over 20 *msec* (p-values = 0.000 and 0.023, respectively) (Table 2).

β-TM patients with severe iron overload (T2* less

Table 1. Baseline characteristics of the study population

Age (mean-years) (SD)	33 (10.8)
Male/Female (n)	51/57
Sinus rhythm/AF/AFL/AT (n,%)	95(88%)/7(6.5%)/5(4.6%)/1(0.9%)
Normal Axis/Left axis deviation/Right axis deviation (n,%)	93(86%)/2(1.9%)/13(12%)
QRS notching-limb leads (n,%)	33 (30%)
QRS notching-precordial leads (n,%)	30 (28%)
T wave inversion-limb (n,%)	36 (33.3%)
T wave inversion-precordial leads (n,%)	46 (42.6%)
ST depression-limb leads (n,%)	15 (13.9%)
ST depression-precordial leads (n,%)	15 (13.9%)
Poor R wave progression (n,%)	23 (21.3%)
LVH (n,%)	2 (1.9%)
RVH (n,%)	0

AF: Atrial Fibrillation; AFL: Atrial Flutter; AT: Atrial Tachycardia; LVH: Left Ventricular Hypertrophy; RVH: Right Ventricular Hypertrophy.

Table 2. Prevalence of ECG abnormalities in patients with T*2 below and above 20 *msec*

Iron deposition in the heart (T2*)	T2*=or >20 n=56	T2* < 20 n=52	Total n=108	p-value
QRS notching in limb leads	10 (9.2%)	23 (21.2%)	33 (30.5%)	0.003
QRS notching in precordial leads	10 (9.2%)	20 (18.5%)	30 (27.7%)	0.017
T-wave inversion in limb leads	12 (11.1%)	24 (22.2%)	36 (33.3%)	0.007
T-wave inversion in precordial leads	17 (15.7%)	29 (26.8%)	46 (42.6%)	0.008
ST-depression in limb leads	10 (9.2%)	5 (4.6%)	15 (13.8%)	0.21
ST-depression in precordial leads	10 (9.2%)	5 (4.6%)	15 (13.8%)	0.21
Poor R-wave progression	5 (4.6%)	18 (16.6%)	23 (21.3%)	0.001
First degree AV block	1 (0.9%)	3 (2.7%)	4 (3.7%)	0.28
AV blocks other than first degree AV block	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
LVH	1 (0.9%)	1 (0.9%)	2 (1.8%)	0.95
RVH	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Atrial flutter	3 (2.7%)	2 (1.8%)	5 (4.6%)	0.15
Atrial fibrillation	2 (1.8%)	5 (4.6%)	7 (6.4%)	0.15
Atrial tachycardia	0 (0.0%)	1 (0.9%)	1 (0.9%)	0.15
Left axis deviation	1 (0.9%)	1 (0.9%)	2 (1.8%)	0.47
Right axis deviation	8 (7.4%)	5 (4.6%)	13 (12.0%)	0.47
Extreme right axis deviation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.47

AV: Atrio-Ventricular ;LVH: Left Ventricular Hypertrophy; RVH: Right Ventricular Hypertrophy.

Table 3. Prevalence of ECG abnormalities in patients with severe (T2*<10 *msec*) and non-severe iron overload

Severity of iron deposition in the heart (T2*)	T2*=or >20	> or=10 - <20	<10	Total	p-value
QRS notching in limb leads	10 (9.2%)	9 (8.3%)	14 (12.9%)	33 (30.5%)	0.025
QRS notching in precordial leads	10 (9.2%)	8 (7.4%)	12 (11.1%)	30 (27.7%)	0.048
T-wave inversion in limb leads	12 (11.1%)	4 (3.7%)	20 (18.5%)	36 (33.3%)	0.001
T-wave inversion in precordial leads	17 (15.7%)	4 (3.7%)	25 (23.1%)	46 (42.6%)	0.001
ST-depression in limb leads	10 (9.2%)	0 (0.0%)	5 (4.6%)	15 (13.8%)	0.47
ST-depression in precordial leads	10 (9.2%)	0 (0.0%)	5 (4.6%)	15 (13.8%)	0.47
Poor R-wave progression	5 (4.6%)	3 (2.7%)	15 (13.8%)	23 (21.3%)	0.000
First degree AV block	1 (0.9%)	0 (0.0%)	3 (2.7%)	4 (3.7%)	0.13
AV blocks other than first degree AV block	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
LVH	1 (0.9%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	0.61
RVH	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Atrial flutter	3 (2.7%)	0 (0.0%)	2 (1.8%)	5 (4.6%)	-
Atrial fibrillation	2 (1.8%)	0 (0.0%)	5 (4.6%)	7 (6.4%)	0.03
Atrial tachycardia	0 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.9%)	-
Left axis deviation	1 (0.9%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	0.74
Right axis deviation	8 (7.4%)	0 (0.0%)	5 (4.6%)	13 (12.0%)	0.74
Extreme right axis deviation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.74

AV: Atrio-Ventricular; LVH: Left Ventricular Hypertrophy; RVH: Right Ventricular Hypertrophy.

than 10 *msec*) demonstrated a significantly longer P wave duration, PR interval, maximum ventricular activation time (in both limb and precordial leads), maximum QRS duration (in both limb and precordial leads), and QTc interval compared to those with non-severe iron overload (T2* equal to or more than 10 *msec* but less than 20 *msec*) and also to those with T2* equal to or more than 20 *msec* (p-values = 0.048, 0.001, 0.000, 0.000 and 0.003 respectively). Poor R wave progression, QRS notching in limb leads, QRS notching in precordial leads, T wave inversion in limb leads, and T wave inversion in precordial leads were significantly more prevalent in β-TM patients with severe iron overload (T2* less than 10 *msec*), compared to those with non-severe iron overload (T2* equal or more than 10 *msec* but less than 20 *msec*) and also to those with T2* equal or more than 20 *msec* (p-values = 0.000, 0.025, 0.048, 0.001 and 0.001 respectively). β-TM patients with severe iron overload (T2* less than 10 *msec*) demonstrated a significantly higher ferritin level compared to those with non-severe iron overload (T2* equal or more than 10 *msec* but less than 20 *msec*) and also to those with T2* equal or more than 20 *msec* (p-value = 0.001). The prevalence of atrial fibrillation among β -TM patients was estimated at 6.5% and was significantly more prevalent in β-TM patients with severe iron overload (T2* less than 10 *msec*), compared to those with non-severe iron overload (T2* equal or more than 10 *msec* but less than 20 *msec*) and also to those with T2* equal or more than 20 *msec* (p-values = 0.034) (Table 3).

Discussion

Adult patients with β-TM are generally struggling with sequelae of extensive iron disposition in vital organs that are poorly controlled by chelation. Iron deposition in the heart with resultant heart failure and cardiac arrhythmias leads to significant morbidity and mortality in transfusion-dependent β-TM patients.

Patients with cardiomyopathy generally have a poor prognosis despite receiving guideline-directed medical therapy. A heart transplant is not usually an option (3,5-7).

CMR is a valuable modality for assessing cardiac function. T2* is a magnetic indicator of tissue relaxation, and higher CMR myocardial T2* values are related to better cardiac function. Management and monitoring of response to treatment of iron overload in β-TM patients have greatly improved since the introduction of T2*. In fact, there is an inverse relation between myocardial intracellular iron deposition and CMR T2* values, with 20 *msec* considered the cut-off point for normal. In a large prospective study, almost all β-TM patients with heart failure had a T2*<10 *msec* and the majority of patients who suffered from cardiac arrhythmias had a T2* of less than 20 *msec* (3,8-12). Although CMR is a reliable method of measuring iron levels and helps in the early detection of myocardial iron overload before the initiation of cardiomyopathy, it is an expensive modality, not readily accessible in many centers, and requires meticulous interpretation by skilled professionals. Many patients who live in underserved areas may not have regular and routine access to CMR. Finding simple clinical tools to help physicians predict worsening cardiac failure and the risk of arrhythmic death could improve patient care. A 12-lead ECG is one such tool that is inexpensive and widely available. Abnormalities in depolarization and repolarization are substrates for reentry and malignant ventricular arrhythmias. Prolonged QTc intervals could lead to arrhythmias and sudden cardiac death. Increased cardiac iron deposition is reported to be related to abnormal heart rate recovery in exercise stress testing, and fragmentation of the QRS on the surface ECG could predict cardiac iron overload. Cardiac autonomic abnormalities and impaired heart rate recovery are also observed in this patient population (5,13-16).

There are conflicting results in previous studies regarding abnormal ECG parameters in β-TM patients who had T2* CMR values below or above 20 *msec*. Tulay Demircan *et al* found that P wave, QT and QTc dispersion, and QTc interval were prolonged in β-TM patients; however, no significant association was found between electrocardiographic parameters and cardiac T2* values (3). Advani *et al* reported cardiac iron overload with CMR T2* less than 20 *msec* to be correlated with prolonged QTc in 50 adolescents with β-TM (17). These findings were in accordance with our study; however, we also observed that QTc interval was significantly more prolonged in severe iron deposition as measured by CMR T2* less than 10 *msec* compared to those with T2*< 20 *msec*. Patsourakos *et al* observed a higher prevalence of a prolonged PR interval, atrial fibrillation, and late potentials in β-TM patients and recommended twelve-lead and signal-averaged ECG as a readily available tool for evaluation of electrophysiological abnormalities in this patient group (1). Rago *et al* reported P-wave dispersion and atrial electromechanical delay to be significantly increased in β-TM patients and are simple parameters to predict the occurrence of atrial fibrillation. Myocyte iron overload and the resultant generation of reactive oxygen species and increased oxidative stress could contribute to the development of atrial fibrillation (18-20).

In our study, we observed that patients with myocardial iron deposition as expressed by CMR T2* values have a higher prevalence of electrocardiographic abnormalities, including prolonged PR and QTc intervals, QRS notching, T-wave inversions, and ST-depression in the limb and precordial leads. As the iron deposition progresses, the more evident and prevalent the ECG changes become. We included and evaluated the subgroup of patients with T2* CMR values less than 10 *msec*. Abnormal depolarization and repolarization, as evidenced by QRS notching, QT interval, ST-T, and T-wave changes, were more prevalent in the surface ECG of those with T2* CMR values less than 10 *msec*, which could be clinically relevant.

The risk assessment for malignant arrhythmias in β-TM patients without overt evidence of cardiomyopathy is clinically challenging. The twelve-lead ECG could frequently be used to examine these patients. As the ECG is noninvasive and low cost, it is reasonably one of the best screening methods, and a thorough ECG analysis might have remarkable value in the management of these patients (1,21).

Therefore, we recommend all β-TM patients be periodically evaluated by twelve lead ECG and monitored for new changes and risk markers of malignant cardiac arrhythmias.

Conclusion

In the current study, we evaluated the prevalence of cardiac conduction abnormalities among β-TM patients with varying degrees of myocardial iron deposition. Patients with a more severe cardiac iron load have a higher prevalence of ECG repolarization and depolarization abnormalities. We recommend frequent ECG monitoring in β-TM patients for screening and prompt initiation of suitable treatment to improve patient quality of life and survival.

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Ethics committee of Rajaei Cardiovascular Medical Research Center (Tehran, Iran) approved the study protocol (committee's reference number: 008754).

Conflict of Interest

The authors have no conflicts of interest to declare.

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