

## Effect of Average Annual Mean Serum Ferritin Levels on QTc Interval and QTc Dispersion in Beta-Thalassemia Major

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### Abstract

#### Background

There is evidence indicating impaired cardiomyocytic contractility, delayed electrical conduction and increased electrophysiological heterogeneities due to iron toxicity in beta-thalassemia major patients. In the present study, we compared the electrocardiographic and echocardiographic features of beta-thalassemia major patients with a healthy control group.

#### Materials and Methods

The average annual serum ferritin levels of fifty beta-thalassemia major patients were assessed. For each patient, corrected QT (QTc) intervals and QTc dispersions (QTcd) were calculated and  $V_{1S}$  and  $V_{5R}$  were measured. All subjects underwent two-dimensional M-mode echocardiography and Doppler study and were compared with 50 healthy subjects as a control group.

#### Results

QTc interval and dispersion were significantly higher in beta-thalassemia major patients ( $P=0.001$ ). The mean  $V_{5R}$  ( $20.04 \pm 4.34$  vs.  $17.14 \pm 2.55$  mm) and  $V_{1S}$  ( $10.24 \pm 2.62$  vs.  $7.83 \pm 0.38$  mm) showed considerably higher mean values in patients in comparison with control group. Peak mitral inflow velocity at early diastole and early to late ratio in the case- group was markedly higher ( $P<0.001$ ), whereas, early deceleration time ( $P=0.01$ ) and Isovolumic relaxation time (IVRT) ( $P=0.001$ ), were meaningfully lower than the control group. There was positive correlation between age and QTc ( $r=0.831$ ,  $P=0.001$ ) and QTc dispersion ( $r=0.710$ ,  $P=0.001$ ) and negative correlation between serum level of ferritin and  $V_{5R}$  ( $r=-0.271$ ,  $P=0.05$ ).

#### Conclusion

Measurement of the QTc interval and dispersion can be used for early detection of cardiac involvement, especially in asymptomatic beta-thalassemia patients with ferritin levels higher than 2,500 ng/dl.

**Key Words:** Arrhythmia, Beta-thalassemia major, Ferritin.

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## 1- INTRODUCTION

Beta-thalassemia major (B-TM) is a relatively common and potentially fatal genetic disease especially in developing countries, affecting 60,000 neonates annually. It results in extreme anemia early in childhood (1). Regular blood transfusions and systemic iron chelation therapy is a common practical treatment strategy which has led to significant improvement in the quality of life and life expectancy of these patients (2). Despite iron chelation therapy in the treatment of  $\beta$ -thalassemia major patients, iron overload and its ensuing cardiovascular complications such as heart failure and arrhythmia remain the major cause of death (3, 4). There is evidence indicating impaired cardiomyocyte contractility, delayed electrical conduction and increased electrophysiological heterogeneities due to iron toxicity (5, 6).

In addition, chronic anemia may lead to myocardial fibrosis, structural changes, and ventricular hypertrophy in these patients (7). Electrocardiography (ECG) and echocardiography are useful and noninvasive diagnostic tools for early detection of heart disorders even in asymptomatic patients (8, 9). In the present study, we compared the echocardiographic and such electrocardiogram variables as QT interval and dispersion of  $\beta$ -thalassemia major patients with a healthy control group.

## 2- MATERIALS AND METHODS

In this cross-sectional study, all  $\beta$ -thalassemia major patients of our referral hematology center, Amir Kabir hospital in Arak- Iran, from July 2014 to July 2015, were considered eligible for the investigation. We evaluated fifty  $\beta$ -thalassemia major patients (case group) and 50 healthy subjects (control group) chosen from family members of B-TM patients, that were matched for age and gender. There were 28 females and 22

males with the range of 5-40 years in B-TM group. All patients were managed by a regular blood transfusion at 3-4 weekly intervals manner and iron chelation therapy by subcutaneous desferrioxamine (DFO) 40-50 mg/kg, 5 days a week or a daily dose of deferiprone (DFP) 75 mg/kg, either single or in a combination regimen. The ferritin level more than 2500  $\mu$ g/L was considered a risk factor for cardiac complications (10).

The investigation was approved by our Institutional Review Board (Arak University of Medical Sciences Ethics Committee) (ID number: 93-174-9). Informed written consent was taken from all individuals or their guardians involved in our study. Body weight and height of each patient were measured with Body Scale BS703, Seca, (made in Germany), by a pediatric cardiologist, in standing position, 2 hours after eating and blood transfusion. Body mass index (BMI) was calculated by the formula;  $BMI = \text{weight (kg)} / \text{height (m}^2\text{)}$ . The cardiovascular evaluation was set to blood transfusion interval and was performed at a median of 5 days following transfusion (ranging from 1-8 days). The average of two measurements of blood pressure (BP) from right hand with appropriate cuff was recorded after at least 15 minutes of rest.

### 2-1. Laboratory tests

Laboratory tests (hemoglobin, serum ferritin) were obtained before blood transfusion. Ferritin measurement was achieved only in the case group. The severity of iron overload was defined by average annual serum ferritin levels. The average of serum level of ferritin was recorded at the 1-month intervals for 12 months (12 measurements for each subject). Serum ferritin levels were measured by sandwich enzyme-linked immunosorbent assay (ELISA).

### 2-2. Electrocardiography variables

Standard 12-lead electrocardiography (ECG), were recorded at a paper speed of 25 mm/sec. To increase the accuracy of interpretation of the ECGs, studied variables were measured and calculated as following formulas in a blinded fashion by two pediatric cardiologists: heart rate= average RR interval of tracing; QT interval: the average of three consecutive cycles from the onset of QRS complex to the end of the T wave on the isoelectric line or nadir between the T and U waves; QT dispersion (QTd): the difference between longest and shortest QT interval in one ECG record. QT intervals were corrected for heart rate based on Bazett's formula ( $QTc = QT/\sqrt{RR}$ ) (11), and the QT dispersion was calculated. As an indicator of left ventricular forces, S wave in V1 and R wave in V5 were measured (8).

QT dispersion (QTd) is defined and calculated as maximum QT interval minus minimum QT interval in one ECG. QTd has been shown to increase in inhomogenous depolarization and repolarization in the setting of ventricular dysfunction. The normal range of QTd value is 10–70 ms with mean  $29 \pm 26$  ms in the young age (12). Again JTc is defined as the interval between the J (junction) points to the end of T wave, corrected by heart rate. JTc dispersion (JTcd) is the difference between the maximum and minimum JTc intervals.

### 2-3. Echocardiography parameters

Standard echocardiography was perfected for every child, and then Pulsed-wave Doppler (PWD) was accomplished. All calculations in Standard echocardiography and PWD were obtained from the average of three cycles. In children, echocardiography was performed by a pediatric cardiologist and in adults, was conducted by an adult cardiologist. Two-dimensional M-mode echocardiogram and Doppler study were performed by Vivid 3 (GE Vingmed Ultrasound) with 8 and 5

MHZ probes for all subjects, who were at rest and lying in the left decubitus position during the examination. Measurements of left ventricular end diastolic diameter (LVEDD), interventricular septum thickness (IVSTd) and the left ventricular posterior wall thickness at the end of diastole (LVPWTd), and the ejection fraction (EF) were obtained from M-mode echocardiographic tracings with 2D imaging. Measurements were determined with standard techniques in accordance with the recommendations of the American Society of Echocardiography (13). Left ventricular mass (LVM) and left ventricular mass index (LVMI) were calculated with standard formulas (7, 8):  $LVM = (0.8 \times (1.04 [(LVEDD + IVSTd + LVPWTd)^3 - (LVEDD)^3]) + 0.6$  and  $LVMI = LVM$  divided by height to the 2.7 power.

### 2-4. PWD echocardiography

Pulsed-wave Doppler examination was performed to attain the following indices of LV diastolic function: peak mitral inflow velocities at early (E) and late (A) diastole, E/A ratio, early deceleration time (E-DT), and isovolumic relaxation time (IVRT). Average values of these indices obtained from 3 consecutive cardiac cycles were used for analysis. The measurement was performed in the 4-chamber view on lateral decubitus. Sample value was placed 1-3 mm at the tip of the mitral valve, for increasing the accuracy of calculations and obtaining better quality.

### 2-5. Exclusion criteria

Patients with a history of arrhythmia or atrioventricular conduction abnormalities, previous atrial fibrillation (AF) episodes, antiarrhythmic agent therapy, blood pressure >140/90, valvular heart disease, thyroid, renal and hepatic disease, systolic dysfunction and diabetes mellitus were excluded.

In summary, the following essays were conducted for all subjects in either group (Case and Control group):

- Body weight and height (BMI),
- Blood pressure from right hand,
- The hemoglobin and serum ferritin (average annual mean serum ferritin in the study group),
- The Standard 12-lead electrocardiography (ECG),
- Standard and PWD echocardiography.

### 2-6. Statistical analysis

Statistical analysis was fulfilled using the SPSS version 24.0 software version (SPSS, Inc., Chicago, IL, USA). Descriptive statistics are presented as mean  $\pm$  standard deviation (SD). The statistical inquiries were performed using Independent Samples Student t test, and Chi-square test. Chi-square test was utilized to compare sex distribution. Pearson's linear correlation coefficient analyses were used to assess the relationship between echocardiography and other electrographic parameters. Statistical significance was taken at P values less than 0.05.

### 2-7. Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Also, informed consent was obtained from all individual participants or their parents included in the study. As mentioned earlier, the study was ratified by our institutional ethics committee. (ID number: 93-174-9).

## 3- RESULTS

Fifty patients with  $\beta$ -thalassemia major (22 males and 28 females) aged 5–40 years ( $21.6 \pm 8.55$ ), met the study criteria and were compared with 50 healthy subjects (23 males and 27 females) with a mean age of  $19.64 \pm 1.6$  years matched for age and gender as a control group. BMI values in patients were significantly lower than the control group ( $19.73 \pm 3.98$  vs.  $20.99 \pm 1.95$  respectively;  $P= 0.048$ ). The mean value of serum ferritin in the patient's group were  $1389.9 \pm 1318.7$  ng/dl that showed a wide standard deviation in spite of sufficient chelation therapy. All patients were hemodynamically stable without overt signs of cardiovascular disease. All ECGs showed sinus rhythm without any evidence of cardiac failure.

Clinical characteristics and echocardiographic findings of  $\beta$ -thalassemia major patients and control group were summarized in **Table.1**. The heart rate of the study group was significantly higher and systolic and diastolic blood pressure was remarkably lower than the control group (**Table.1**).

There was no statistically significant difference between study and control groups in terms of left ventricular end diastolic diameter and interventricular septum thickness ( $P>0.05$ ). LVPWTd and left ventricular ejection fraction in the case group were significantly higher than the control group. There was no statistically significant difference between the study and control groups with respect to LVM. However, LVMI in  $\beta$  thalassemia major patients was notably lower than the control group (**Table.1**).

Peak mitral inflow velocity at early diastole and early to the late ratio (E/A) in the case group was significantly higher than the control group, but there was no significant difference in regards peak mitral inflow velocity at late diastole among groups (**Table.1**). Early

deceleration time (E-DT) and isovolumic relaxation time (IVRT) in  $\beta$ -thalassemia major patients were enormously lower than the control group. All of these findings indicate a restrictive pattern of diastolic dysfunction in patients group.

Corrected QT interval as an index of ventricular depolarization and repolarization was significantly higher in  $\beta$ -thalassemia major patients in comparison with control group ( $388.22 \pm 29.04$  vs.  $360.70 \pm 8.04$  milliseconds, [ms]).

QTc dispersion was calculated and showed significantly higher mean values in patient's category in comparison with control group. The mean height of R wave

in V5 [V5R] ( $20.04 \pm 4.34$  vs.  $17.14 \pm 2.55$  mm) and mean depth of S wave in V1 [V1S] ( $10.24 \pm 2.62$  vs.  $7.83 \pm 0.38$  mm) revealed immensely higher mean values in the case group in comparison with control group which is an index of more left ventricular contractility in  $\beta$ -thalassemia major patients (**Table.2**).

There was positive correlation between age and corrected QT ( $r= 0.831$ ,  $P=0.001$ ) and corrected QT dispersion ( $r= 0.710$ ,  $P=0.001$ ); in contrast, there was a negative connection between serum level of ferritin and V5R ( $r= -0.271$ ,  $P= 0.05$ ). There was no significant correlation between serum levels of ferritin and other ECG and echocardiographic variables (**Tables 3, 4**).

**Table-1:** Clinical and echocardiographic characteristics of  $\beta$ -thalassemia major patients and control group (mean  $\pm$  SD)

Variables	$\beta$ Thalassemia major group (n=50)	Control group (n=50)	P- value
Gender (M/F)	22/28	23/27	0.109
Mean age (years)	$21.60 \pm 8.55$	$19.64 \pm 1.60$	0.114
BMI (kg/m <sup>2</sup> )	$19.73 \pm 3.98$	$20.99 \pm 1.95$	0.048*
Heart rate (bpm)	$81.86 \pm 8.84$	$73.30 \pm 5.23$	0.001*
Systolic BP (mmHg)	$102.90 \pm 9.85$	$118.20 \pm 3.88$	0.001*
Diastolic BP (mmHg)	$64.40 \pm 8.95$	$78.20 \pm 3.15$	0.001*
LVEDD (cm)	$5.57 \pm 0.90$	$5.47 \pm 0.22$	0.472
IVSTd (cm)	$1.08 \pm 0.12$	$1.12 \pm 0.9$	0.121
LVPWTd(cm)	$1.07 \pm 0.13$	$1.00 \pm 0.16$	0.039*
EF (%)	$66.45 \pm 2.78$	$64.97 \pm 2.55$	0.007*
LVM (g)	$114.66 \pm 30.13$	$116.06 \pm 8.03$	0.752
LVMi (g/m <sup>2.7</sup> )	$54.13 \pm 17.31$	$66.10 \pm 3.44$	0.001*
Mitral E (cm/sec)	$102.01 \pm 8.38$	$87.22 \pm 4.53$	0.001*
Mitral A (cm/sec)	$55.56 \pm 5.89$	$53.88 \pm 5.92$	0.157
Mitral E/A ratio	$1.85 \pm 0.23$	$1.63 \pm 0.15$	0.001*
E -DT (ms)	$144.82 \pm 9.93$	$149.76 \pm 8.95$	0.01*
IVRT (ms)	$67.00 \pm 5.38$	$75.04 \pm 2.53$	0.001*

\*statistically significant.

BMI: Body mass index; HR: heart rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; LVEDD: left ventricular end-diastolic diameter; IVSTd: interventricular septum thickness at the end of diastole; LVPWTd: left ventricular posterior wall thickness at the end of diastole; EF: Ejection fraction; LVM: left ventricular mass; LVMi: LVM index; E: early diastole mitral flow; A: late diastole mitral flow; E/A ratio: early mitral to late mitral flow; E-DT: early deceleration time, IVRT: Isovolumic relaxation time, SD: Standard deviation.

**Table-2:** The electrocardiographic findings of  $\beta$  thalassemia major patients and control group (mean  $\pm$  SD)

Parameters	$\beta$ Thalassemia major group (n=50)	Control group (n=50)	P-value
JTc (ms)	353.24 $\pm$ 36.05	340.64 $\pm$ 7.78	0.018*
QTc (ms)	388.22 $\pm$ 29.04	360.70 $\pm$ 8.04	0.001*
JTc dispersion (ms)	72.08 $\pm$ 13.81	39.07 $\pm$ 6.24	0.001*
QTc dispersion (ms)	79.72 $\pm$ 12.45	54.74 $\pm$ 4.20	0.001*
V5R (mm)	20.04 $\pm$ 4.34	17.14 $\pm$ 2.55	0.001*
V1S (mm)	10.24 $\pm$ 2.62	7.83 $\pm$ 0.38	0.001*

SD: Standard deviation; \*statistically significant; JTc: JT corrected, QTc: QT corrected.

**Table-3:** Correlation between QTc, QTcd, JTc, JTcd, age and serum ferritin level in the beta-thalassemia major patients

Variables	Ferritin	QTc	QTcd	JTc	JTcd
Pearson correlation	0.067	0.831	0.710	0.921	0.577
Age P- value	0.644	0.001	0.001	0.001	0.001
Number	50	100	100	100	100

QTc: Corrected QT interval; QTcd: QTc dispersion; JTc: Corrected J Point-T interval; JTcd: JTc dispersion.

**Table-4:** Correlation between serum ferritin level and QTc, QTcd, JTc, JTcd in the beta-thalassemia major patients

Variables	QTc	QTcd	JTc	JTcd	S inV1	R inV5
Pearson correlation	0.047	0.066	0.054	0.060	0.023	-0.271
Ferritin P- value	0.746	0.647	0.710	0.677	0.873	0.050
Number	50	50	50	50	50	50

QTc: Corrected QT interval; QTcd: QTc dispersion; JTc: Corrected J Point-T interval; JTcd: JTc dispersion.

#### 4- DISCUSSION

Beta-thalassemia major B-TM patients require repeated transfusion of the packed cell (PC). Iron deposits in the body organs especially in the heart. The QTc interval shows the duration between the beginning of ventricular depolarization and the end of ventricular repolarization. There is some evidence of higher QTcd in patients with  $\beta$ -thalassemia major (1, 8). QT dispersion is a variable for evaluating ventricular repolarization and depolarization. Impaired

ventricular recovery times and inhomogeneity in the repolarization has been shown with altered QT interval and QTd. Increased QT dispersion is a predictor of sudden death and ventricular arrhythmias (8). Likewise, QTd might be elevated in various high-risk groups such as essential hypertension, patients with cardiac failure, iron overload in cardiac tissue, acute myocardial infarction (AMI), left ventricle hypertrophy (HCM), heart failure(HF), dilated cardiomyopathy

(DCMP), and also in patients with end-stage renal disease requiring hemodialysis (8). To date, many investigations have been carried out in B-TM patients, focusing on QTc dispersion as a predictor of cardiac dysfunction (1, 8, 12, 14). Increased QTc dispersion has been shown to cause differences in myocardial recovery times (14). We documented that QTc interval and QTc dispersion were greater in B-TM patients compared to the control group; though, there were no any clinical or echocardiographic signs of serious cardiac disease. Increased QTc dispersion in B-TM patients may be an index of higher risk for sudden death and ventricular arrhythmia.

In the present study, a wide series of  $\beta$ -thalassemia major patients as regards age category were evaluated with 12-lead electrocardiogram and echocardiography. Our study showed QTc interval and dispersion values increased in  $\beta$ -thalassemia major patients which have a positive correlation with age. It suggests that duration of exposure to blood transfusion and iron overload despite precise iron chelation therapy may affect myocardial repolarization. Similar to our findings, Ulger et al. showed QTc interval values in  $\beta$ -thalassemia major patients are significantly higher than control group even in asymptomatic patients (8).

The result of a study by Farahani et al. showed an insignificant increase in QTc intervals in these patients at rest and a significant increase in Bruce exercise tolerance- test (14). The prolongation of QT interval, as an index of ventricular depolarization and repolarization, is a risk factor for life-threatening ventricular arrhythmias and sudden death (15). The studies have revealed that myocardial iron overload changes electrical conduction of the myocardial tissue and can lead to ventricular arrhythmia in the B-TM patients. In this survey, we did not establish a correlation between QT

dispersion and annual average serum ferritin levels of the patients. It could be suggested that serum ferritin may not reflect ventricular arrhythmia and sudden death due to cardiac iron overload. Of course, QT dispersion is a noninvasive method that can be used for cardiac evaluation in B-TM patients. Ulger in his study revealed higher left ventricular mass index in patients in comparison to control group (8), but our results showed the opposite findings. It may be due to the wide range of age in our patients; we studied patients with age of 5-40 years old. Noori et al. tried to define a cut-off point for LVMI in  $\beta$ -thalassemia patients to detect probable and asymptomatic heart failure but finally, they concluded that LVMI cannot definitely portend the presence of cardiac dysfunction in asymptomatic patients with thalassemia and patients with normal LVMI might have some degrees of heart failure (16).

Similar to previous findings, our results showed higher early diastolic filling of the left ventricle and high E/A ratio, shorter deceleration time of E wave and shorter isovolumic relaxation time (IVRT), suggesting a restrictive diastolic pattern and stiff LV wall (12, 17). Increased E/A ratio are the most common finding in  $\beta$ -thalassemia patients (18). According to our results, systolic and diastolic blood pressure of patients was remarkably lower and heart rate was significantly higher than the control group.

It could be due to reduced vascular resistance following cardiac high output state, as our results confirmed increased ejection fraction in patients group, similar to previous findings (14). In contrast, there is some evidence of normal myocardial systolic function and ejection fraction in asymptomatic  $\beta$ -thalassemia major patients (12). There are suggestions of increased dimension of LV cavity and volume in systolic and diastolic state and wall thickness (12), but in the present

study, we did not find any significant difference of LVEDD between the patients and control group. However, LVPWtd in patients was significantly higher than the control group. We did not find a correlation between serum levels of ferritin with ECG variables except for negative correlation with V5R, as an index of left ventricular contractility. Previous studies have mentioned that increasing serum level of ferritin especially more than 2500 ng/dl is associated with poor cardiovascular outcomes (14).

More recent papers further emphasize the relation between iron overload and cardiac disturbances in B-TM patients. In a study by Faruqi et al. (19), increased QTc and QTc dispersion (QTcd) was noted in B-TM patients with serum ferritin levels more than 2,500 ng/dl. The QTc and QTcd had a positive linear correlation with serum ferritin levels. They suggested that ECG variables could help in the preclinical diagnosis of cardiac disorders owing to iron overload in B-TM cases. Henriksen et al. (20), showed that increased iron stores could result in prolongation of the QTc interval in men. Additionally, their meta-analysis revealed prolonged QT interval in B-TM patients compared to healthy controls. Hamed et al. (21) hypothesized that in patients with thalassemia, the increase in left atrial, interventricular septum, and left ventricular posterior wall diameters may be related to the occurrence of arrhythmia, especially supraventricular arrhythmias. They utilized modalities such as 24 hours Holter recording, Stress electrocardiogram, and M-mode echocardiography.

Serum ferritin and cardiac MRI were used to assess the rate of iron accumulation. Refaat et al. (22), reported a unique case of Torsades de Pointes in a  $\beta$ -thalassemia major patient with early signs of iron overload in the absence of any structural abnormalities as seen in hemochromatosis. They discovered a novel KCNQ1 gene

mutation. The authors conclude that iron overload combined with the KCNQ1 gene mutation induce increased QTc interval and Torsades de Pointes. Finally, it seems that cardiovascular complications in  $\beta$ -thalassemia patients depend on several factors such as patient's age and the duration of exposure to blood transfusion and the strategy of chelation therapy. Iron deposition in myocytes can alter electrophysiological actions, QTc interval and QTc dispersion without clinical features and significant findings in clinical modalities such as echocardiography. The restrictive pattern of diastolic LV dysfunction may be found in echocardiography which is helpful for early diagnosis as well.

#### 4-1. Study limitations

Given the ethical issues, ferritin was not measured in the control group. Moreover, due to cost-related problems, patients did not undergo T2 weighted cardiovascular magnetic resonance imaging (T2 CMR) to further assess iron deposition in the heart muscle as well as the cardiac contractility. Undoubtedly more research with greater samples is warranted to precisely ascertain whether there is a link between ECG findings and the occurrence of cardiac disturbances in these high-risk groups of patients.

#### 5- CONCLUSION

Iron deposition in myocytes of B-TM cases can alter electrophysiological processes, and as a result, prolong QTc interval and QTc dispersion in ECG without any significant clinical and echocardiographic findings. Thus, the measurement of the QTc interval and QTc dispersion can be used for early detection of cardiac depolarization involvement in asymptomatic  $\beta$ -thalassemia major patients especially in patients with ferritin higher than 2,500 ng/dl.



## 6- CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

## 7- ACKNOWLEDGEMENTS

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