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Correlation between Mean Serum Ferritin Levels and Atrial Electrocardiographic Markers in Beta-Thalassemia Major

Yazdan Ghandi[1]*, Aziz Eghbali[2], Fatemeh Rafiei[3]

[1]Department of Pediatric Cardiology, Amirkabir Hospital, School of Medicine, Arak University of Medical Sciences, Arak, Iran
[2]Department of Pediatric Hematology and Oncologist, Amirkabir Hospital, School of Medicine, Arak University of Medical Sciences, Arak, Iran
[3]Department of Biostatistics, School of Medicine, Arak University of Medical Sciences, Arak, Iran

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**Corresponding author:*
Yazdan Ghandi,
Assistant Professor, Department of Pediatric Cardiology, Faculty of Medicine, Arak University of Medical Sciences, Arak, Iran
Email: Y.ghandi@arakmu.ac.ir
ORCID: 0000-0002-8825-7163

ABSTRACT

Background: Atrial fibrillation (AF) is the most common arrhythmia in patients with β-thalassemia major (β-TM) due to cardiac iron overload. AF may be predicted by changes in P wave parameters. The aim of this study was to evaluate the correlation between P-wave parameters and atrial markers with mean serum ferritin levels measured yearly.
Methods: Fifty patients with β-TM and 50 healthy subjects as control group were enrolled in the study. Both groups underwent electrocardiography (ECG) and echocardiography. P-wave dispersion (PWd), maximum and minimum P-wave duration (P-max and P-min) were measured. Echocardiography was performed by pulse wave Doppler of the lateral mitral valve. Annual mean serum ferritin level was calculated through monthly sampling.
Results: There were 22 men and 28 women with β-TM (mean age: 21.4±8.3 years). Mean serum ferritin levels were 1476.8±919.2 ng/ml. Systolic and diastolic blood pressure were significantly different between thalassemia and control groups (P<0.002 and P<0.004, respectively). There were significant differences between BMI, PWd, P-max and P-min (P<0.0001, respectively). A cut off value of 40 msec for PWd had a sensitivity of 100% and a specificity of 90.7% in identifying mean serum ferritin levels higher than 1078 ng/ml. Mean serum ferritin level of 1024 or more was associated with sensitivity of 100% and specificity of 90.1% for inter-atrial block > 110 msec. There were correlations between mean serum ferritin level and age of the patients along with PWd, P-min and P-max (P<0.0001, respectively).
Conclusion: In β-TM, atrial parameters in ECG were correlated with both mean serum ferritin levels measured yearly and patients' age. We recommend that in patients with thalassemia major with mean serum ferritin levels higher than 1000 ng/ml, P wave parameters should be carefully evaluated and closely followed.

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Introduction

β-TM is the most common hereditary anemia in the world. Chronic transfusion therapy results in iron overload inside the cardiac tissue. The major cause of mortality in β-TM is known to be arrhythmia and cardiac failure.[1]

Atrial fibrillation (AF) frequently occurs in patients with β-TM, specifically in those with dilated cardiomyopathy. In the early years of transfusion, the patients are usually asymptomatic for cardiac complications. Diastolic dysfunction and restrictive cardiomyopathy usually occur in early stages of cardiac iron overload, while atrial fibrillation and flutter occur in the successive years. For early prediction of AF, atrial ECG markers seem to be beneficial. These parameters include P-max, P-min, PWd and inter-atrial block (IAB).[2] PWd is a useful indicator to show continuous propagation and synchronic homogeneous depolarization in right and left atrium. In addition to PWd, prolonged P-wave duration and IAB is correlated with increased risk for AF.[3, 4] Iron toxicity and deposition in the atrial cardiomyocytes also disturb intra-atrial conduction.[5] As a result, designing simple and noninvasive tests to predict AF sounds attractive. The aim of our study was to assess the atrial electrocardiographic parameters in patients with β-TM and their correlation with mean serum ferritin levels measured yearly.

Materials and Methods

This cross-sectional study was performed in pediatric cardiology department of Arak University of Medical Sciences during 2015-2016. The protocol was approved by the local Research Ethics Committee of our center. Fifty patients suffering from β-TM and 50 healthy subjects, matched for age and sex entered into the study. There were 23 women and 27 men (range 5-40 years) with β-TM. All patients with thalassemia were receiving blood transfusion regularly in 3-4 week intervals to have hemoglobin level of 9 g/dl or higher. Iron chelation therapy included deferiprone (DFP), deferrioxamine (DFO) or both according to hematology department guidelines. All subjects were precisely evaluated for any remarkable medical history other than thalassemia, physical examination, annual mean serum ferritin levels, ECG and echocardiographic measurements. Exclusion criteria consisted of presence of cardiac arrhythmia, atrioventricular conduction abnormalities, previous AF episodes, anti-arrhythmic therapy, blood pressure >140/90 mmHg, systolic dysfunction, presence of valvar heart, thyroid, renal and hepatic disease, and diabetes mellitus. Serum ferritin levels were measured monthly for 12 months. Measurement of serum ferritin was performed by sandwich enzyme- linked immunosorbent assay (ELISA).

ECG and echocardiography were performed for both groups. P wave dispersion (PWd) and maximum and minimum P-wave duration (P-max and P-min) were measured. Echocardiography was performed by pulse wave Doppler of the lateral mitral valve.

Electrocardiographic Measurements

Electrocardiogram was recorded on a routine standard 12-lead basis with a standard calibration of 10 mm/mv and also 25 mm/sec paper speed. The ECG was performed before blood transfusion. Measurement of P wave parameters were obtained using calipers and magnifying lens Including five cardiac cycles in eight leads. Measurements were performed manually and by two physicians, who were blinded into the study. P wave duration (maximum and minimum) were measured in a 12 lead ECG. PWd was calculated as the difference between maximum and minimum p wave duration (PWd=P max- P min). IAB was defined as prolonged P wave duration (≥110 msec).

Echocardiographic Measurements

Standard and pulse wave Doppler echocardiography was performed in both groups (VIVD 3, general electric, USA). In patients with β-TM, cardiac evaluation was performed before blood transfusions. Ejection fraction and left ventricular end diastolic diameter (LVEDD) were measured in M-mode according to American society of echocardiography. Diastolic function was evaluated by pulse wave Doppler (PWD) of mitral valve. Peak mitral inflow velocities at early diastole (E), atrial contraction (A), E/A ratio, E wave deceleration time (E-DT) and isovolumetric ventricular time (IVRT) were measured. Diastolic dysfunction was defined as the presence of any abnormality in one of the mentioned parameters. We utilized echocardiography parameters in 3 consecutive cardiac cycles to confirm the analysis.

Statistical Analysis

All variables were expressed as mean±standard deviation. Data analysis was performed using the software version SPSS 20 (SPSS, Inc., Chicago, IL, USA). The statistical Analysis was performed using independent samples Student t-test, Mann-Whitney test and chi-square test. Pearson and Spearman linear correlation coefficient analyses were used to assess the relationship between ECG findings and average annual serum ferritin levels. Roc curve analyzed to determine the best cut-off point for average annual serum ferritin level using MedCalc software. P-value of <0.05 was considered to be statistically significant.

Results

In our study 50 β-TM patients consisting of 22 (41.5%) men and 28 (59.6%) women were compared with 50 healthy subjects. Systolic and diastolic blood pressure were 100.4±12.4 and 65.5±10.3 mmHg, respectively in the case group; while the measurements were 109.8±18.5 and 72.5±13.5, respectively in control group. Mann-Whitney test results showed that systolic and diastolic blood pressure in thalassemia subjects were significantly less than the control group (P<0.05). There was a significant difference in body mass index (BMI) between the two groups (P=0.0001). There was no difference between two groups in terms of heart rate (P=0.9) despite significant differences for P wave parameters such as PWd, P-max and P-min (P<0.0001, respectively). There was not any significant variability using standard echocardiography between two groups; however, we found subclinical left ventricular diastolic dysfunction by using pulse wave Doppler in patients with β-TM. Table 1 summarizes standard echocardiography, PWD echocardiography and electrocardiographic characteristics of the studied populations.

Table 2 summarizes the association between age with ECG parameters and mean serum ferritin levels. The Pearson correlation test demonstrated a statistically significant correlation between PWd, P-min, and P-max with mean serum ferritin levels in the case group. In the control group, there was a weak correlation between mean serum ferritin levels and PWd (Table 2).

Cut-Off Point for Mean Serum Ferritin Levels Based Upon PWd

In our study, 100 subjects were compared for mean serum ferritin levels and PWd in which PWd <40 msec was defined as normal, whereas if PWd was ≥40 msec, it was considered prolonged. There were 75 individuals with PWd less than 40 msec and 25 equal or higher than 40 msec. Roc curve analysis to determine the best cut off for mean serum ferritin levels showed that any person with a mean serum ferritin level higher than 1078 is predictive to have a PWd ≥40 ms with a sensitivity of 100% and specificity of 90.7%. The area under the Roc curve (AUC) was 0.987 (CI=95%, range: 0.940-0.99; P=0.0001) (Figure 1 and Tables 3, 4).

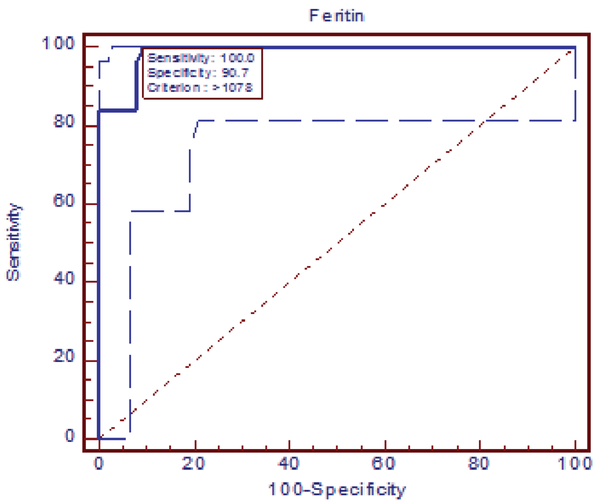

Figure 1: ROC Curve, sensitivity and specificity of ferritin based upon PWd

Cut-Off Point for Mean Serum Ferritin Levels Based Upon IAB

100 subjects were assessed for mean serum ferritin levels and IAB. IAB <110 msec was defined as normal, whereas IAB ≥110 msec was considered abnormally prolonged. There were 71 and 29 individuals with IAB less and higher than 110 ms, respectively. Roc curve analysis to determine the best cutoff for mean serum ferritin level showed that any person with a mean serum ferritin level higher than 1024 ng/ml is predictive to have IAB ≥110 msec with a sensitivity of 100% and specificity of 90.1%. The area under the curve (AUC) was 0.975 (CI=95%, range: 0.921-0.995, P=0.0001) (Figure 2 and Table 5, 6).

Table 1: ECG, standard and PWD echocardiography

	Case	Control	P value*
PWd (ms)	40.5±7.04	24.3±1.90	0.0001
P-MAX (ms)	111.6±12.2	87.6±5.5	0.0001
P-MIN (ms)	65.2±6.5	49.2±4.1	0.000
LVEF (%)	66.4±2.7	65.9±2.5	0.33
LVEDD (mm)	48.5±6.03	47.4±1.4	0.2
Mitral E(m/s)	102.01±8.3	87.2±4.5	0.0001
Mitral A(m/S)	55.5±5.8	53.8±5.9	0.1
Mitral E/A ratio	1.85±0.23	1.6±0.15	0.0001
Mitral E-DT(s)	144.8±9.9	149.7±8.9	0.02

*Mann-Whitney test; PWd: P wave dispersion, P-Max: P maximum, P-Min: P minimum, LVEDD: left ventricular diastolic dysfunction, LVEF: left ventricular ejection fraction, E: velocities at early diastole, A: velocities at atrial contraction, E-DT: early deceleration time of E wave

Table 2: Correlation between PWd, P-min, P-max, Age, MSFL in the patients with β-TM and control

	Case			Control		
Mean serum ferritin levels	PWd	P-Max	P-Min	PWd	P-Max	P-Min
Pearson Correlation	0.88	0.81	0/84	0.297	-0.013	0.23
P value*	0.0001	0.0001	0.0001	0.03	0.9	0.09

*Pearson correlation

Table 3: Cut-off point for mean serum ferritin level based on PWd

Cut off	Sensitivity (%)	CI=95% for sensitivity		Specificity (%)	CI=95% for specificity	
		Lower	Upper		Lower	Upper
1087	100	86.2	100	90.67	81.7	96.1

Table 4: PPV, NPV, PLR, and NLR with 95% confidence interval for the cut off point of mean serum ferritin level according PWD measurements.

Cut-off Point	PLR	CI 95% for PLR		NLR	CI 95% for NLR		PPV (%)	CI 95% for PPV		NPV (%)	CI 95% for NPV	
		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper
1087	10.71	10	11.5	0	-	-	78.1	60	90.7	100	94.7	100

Positive predictive value: PPV, Negative predictive value: NPV, Positive likelihood ratio: PLR, Negative likelihood ratio: NLR

Table 5: Cut-off point for mean serum ferritin level based on IAB

Cut off	Sensitivity (%)	CI=95% for sensitivity		Specificity (%)	CI=95% for specificity	
		Lower	Upper		Lower	Upper
1024	100	87/9	100	90/14	80/7	95/9

Table 6: PPV, NPV, PLR, and NLR with 95% confidence intervals for mean serum ferritin levels cut off based upon IAB

Cut-off point	PLR	CI 95% for PLR		NLR	CI 95% for NLR		PPV (%)	CI 95% for PPV		NPV (%)	CI 95% for NPV	
		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper
1024	10/4	9/4	11	0	-	-	80/6	64	91/8	100	94/3	100

Positive predictive value: PPV, Negative predictive value: NPV, Positive likelihood ratio: PLR, Negative likelihood ratio: NLR

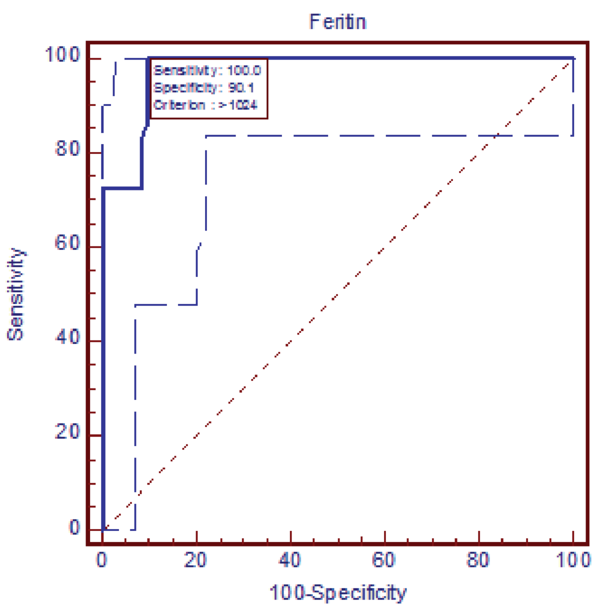

Figure 2: ROC Curve, sensitivity and specificity for IAB based upon serum ferritin levels

Discussion

Obviously, serum ferritin level is not a precise predictor of iron overload in patients with thalassemia major specifically for estimation of cardiac siderosis. Cardiac MRI T2* (CMR) is an excellent examination not available everywhere for assessment of cardiac iron overload. Iron deposition in cardiomyocytes of patients with β-TM can alter electrophysiological processes, and as a result, QTc interval measurements could be affected. QTc dispersion can be used as an early marker for detection of cardiac depolarization mainly in patients with serum ferritin levels higher than 2500 ng/ml.[6] Positive correlations has been shown between age and QTc and QTc dispersion. There is also a negative correlation between annual mean serum ferritin levels and right precordial lead (V5R) readings.[6]

P-wave duration could be altered due to inhomogeneous and prolonged atrial conduction. PWd is a reliable measure for the prediction of paroxysmal AF. PWd >40 msec is a predictor of AF occurrence among patients with β-TM.[7] PWd is considered independent of age and gender. In this study, PWd, P-max and P-min were significantly prolonged in the patients compared to healthy controls. There was a positive correlation between PWd and other atrial ECG parameters with age and mean serum ferritin levels. These findings support the theory that iron overload might be associated with impaired homogeneous atrial propagation and decreased atrial conduction time.

Acar Kadir and colleagues demonstrated that PWd was not different between thalassemia and control group; however, P-max and P-min were significantly different.[3] In another study from Turkey, it was found that PWd and P-max were significantly higher in patients with β-TM (P=0.000).[8] Similar to our study, positive correlation between duration of the disease and P-wave durations has been reported. Russo and co-workers showed PWd and P-max prolongation in patients with β-TM.[9]

Rago and colleagues showed that the PWd were significantly increased in β-TM subjects with normal cardiac function. PWd represents a simple parameter to assess risk of developing AF in patients with β-TM.[10] In fact, PWd detects inhomogeneous depolarization in atrial tissues due to myocardial fibrosis.[11, 12] we found increased PWd, P-max and p-min in β-TM patients with preserved LV function.

Russo and co-workers indicated that P-max and PWd are useful electrocardiographic markers for identifying high risk patients with β-TM for AF, even when the cardiac function is conserved.[13]

Higher end-diastolic volume and stroke volumes were also detected in patients with beta thalassemia intermedia.[14] Amoozgar and colleagues showed that atrial arrhythmias were common in both patients with beta thalassemia intermedia and major.[14] Association between the development of atrial arrhythmias especially supraventricular arrhythmia and increase in left atrial diameter, interventricular septum diameter, and left-ventricle posterior wall diameter in patients with thalassemia major have been reported.[15]

Decreased inter-atrial and intra-atrial conduction due to increased sympathetic tone and atrial dilation has been reported recently.[9] It is indicated that myocardial iron overload has associations with PWd and prolonged P-max and P-min.[9, 16]

In our study, mean age of the patients was 21.4±8.3 years; hence a prolonged p wave could predict a high risk of development of AF in subsequent years in this group of patients. Diastolic dysfunction, myocardial fibrosis, apoptotic pathways and oxidative stress in atrial tissue have been suggested as detrimental factors in AF development.[17]

Non-human models have blamed iron toxicity as the sole responsible mediator for atrial arrhythmia in transfusional iron overload.[11, 18] however, other studies suggested that iron overload is not sufficient per se to raise the possibility of emerging cardiac arrhythmia.

Our study was novel in detection of a cut off point for mean serum ferritin levels which could predict abnormal PWd, P-max, P-min and IABs in patients with β-TM. In other studies, PWd >40 msec is associated with increased risk of AF.[6, 19]

In our study, patients with β-TM were subdivided according to the identified cut-off values. Figure 1 shows Kaplan-Meier curves with log rank tests in these subgroups. Based on the results of our study, PWd would be expected to be higher than 40 msec in patients with serum ferritin levels more than 1078 ng/ml. However, despite these values none of the patients developed AF.

In addition, IAB is a predictor for evolving atrial arrhythmia. Meanwhile, the patients were subdivided accordingly based on detected cut-off value of serum ferritin levels that predispose patients to develope IAB. Mean serum ferritin levels higher than 1024 ng/ml was more likely associated with IAB >110 msec with a sensitivity of 100% and specificity of 90.1% (figure 2).

Conclusion

It seems that in patients with β-TM, ECG atrial parameter alterations are correlated with age and mean serum ferritin levels. These changes are mostly related to toxicity due to iron overload. As it is expected, myocardial impairment occurs more commonly in older patients. Future studies with larger population are necessary to prove more precisely that abnormalities in these measurements may be correlated with risk of development of atrial fibrillation in patients with thalassemia major.

Conflict of Interest: None declared.

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