Cardiac Iron Load and Novel P-Wave Measurements in Patients with Thalassemia Major

The role of P index and Interatrial Block

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ABSTRACT

The deleterious effects of cardiac iron load on the ventricular repolarization were demonstrated in beta-thalassemia major (β-TM), but little is known about the P wave measurements, an independent risk factor for development of atrial fibrillation (AF). We aimed to examine relationship between P-wave parameters and iron loading using cardiac T2 Magnetic Resonance Imaging (MRI) in asymptomatic β-TM patients. The study involved 22 β-TM patients and 22 age- and gender-matched healthy controls. Although P-wave parameters were within normal limits, P max, P min, and Pi were significantly prolonged in the β-TM group compared to the healthy controls (p=0.005, p=0.01, and p=0.03, respectively). Pd was found similar between groups (p=0.46). The prevalence of partial IAB was increased in patients with β-TM (p=0.001) and complete IAB was detected only in one patient. P-wave parameters of patients with cardiac T2*<20 msec and T2*>=20 msec were comparable in patients with β-TM. There was no correlation between P-wave parameters and cardiac T2*MRI values. The present study demonstrated that P-wave measurements were slightly affected in β-TM patients with preserved LV functions and this influence was not related with cardiac T2*MRI values. We concluded that the effect of β-TM on the AF development is still controversial.*

Key words: *Thalassemia major, atrial fibrillation, electrocardiography, cardiac iron load, P-wave parameters*

Kalpteki Demir Yükü ve Talesemi Majör Hastalarında Yeni P-Dalga Ölçümleri

ÖZET

Kalpteki demir yükünün ventriküler repolarizasyon üzerindeki olumsuz etkileri beta-talasemi hastalarında gösterilmiştir. Fakat atriyal fibrilasyon (AF) gelişiminin bağımsız risk faktörleri olan P-dalga parametreleri ile ilgili beta talasemili hastalarda kısıtlı bilgi vardır. Bu nedenle biz asemptomatik beta talasemili hastalarda P-dalga parametreleri ile magnetic rezonans görüntülemede (MRG) elde edilen demir yükü arasındaki ilişkiyi araştırmayı amaçladık.Çalışmaya 22 β-TM hastaları ve yaş ve cinsiyetle uyumlu olan 22 sağlıklı kontrol dahil edildi. P max, P min, and Pi β-TM grupta sağlıklı kontrole gore anlamlı derecede yüksek tespit edildi (p=0.005, p=0.01, and p=0.03, sırasıyla). Pd gruplar arasında benzer bulundu (p=0.46). Kısmı IAB prevalansı β-TM hastalarında artmış bulundu ve komplet IAB sadece bir hastada görüldü P-dalga parametreleri kardiyak T2<20 msan and T2*>=20 msan olan hastalarda benzer bulundu. P-dalga parametreleri ile kardiyak T2* MRG değerleri arasında anlamlı korelasyon izlenmedi. Bu çalışma gösterdi ki, P-dalga parametreleri sol ventrikül fonksiyonları korunmuş olan β-TM hastalarında kısmen etkilenmiştir ve bu bozulma kardiyak demir yükü ile ilişkili değildir. Sonuç olarak, β-TM'nin AF gelişmesindeki rolü halen tartışmalıdır.*

Anahtar kelimeler: *Talesemi majör, atriyal fibrilasyon, elektrografi, kardiyak demir yükü, P-dalga ölçümleri*

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INTRODUCTION

Beta-thalassemia major (ß-TM) is a hereditary hemoglinopathy caused by reduced synthesis of ß-globin chain and requires frequent blood transfusions (1). In a consequence of blood transfusions, iron accumulates in the heart and may cause heart failure and arrhythmias. The incidence of iron-overload cardiomyopathy ranges between 11.4 and 15.1% in ß-TM patients (2-3). Cardiac complications including heart failure and arrhythmias may occur in the early stage of disease. In the late stage, especially atrial arrhythmias including atrial premature beats, atrial flutter and fibrillation have been demonstrated (4).

It was reported that iron-overload cardiomyopathy is associated with a four- to six-fold increase in the risk of developing atrial fibrillation (AF) (5). Several noninvasive electrocardiographic (ECG) parameters have been suggested to predict AF. P-wave parameters including maximal P-wave duration (P max) and P-wave dispersion (Pd) on 12-lead ECG were considered as noninvasive predictors of AF (6-7). A novel parameter, P index (Pi) may independently predict future development of AF in general population. In addition, another novel parameter, interatrial block (IAB) is defined as delayed conduction between the right and left atrium, which results in prolonged P-wave duration (≥110 msec).

Prevalence of IAB was reported as 32.8% among patients in a general hospital population (8). IAB is divided into partial and advanced forms, depending on the severity of conduction delay (9). Advanced form of IAB has strong associations with multiple medical conditions including atrial fibrillation, myocardial ischemia, left atrial enlargement, and systemic emboli (10-11). Neither Pi nor IAB, reliable and novel markers of P wave abnormality, were examined in patients with ß-TM. On the other hand, only two small studies have found increased Pd in patients with ß-TM where Russo et al. (12) have assessed the relationship between Pd and myocardial iron deposit as assessed by cardiac T2* magnetic resonance imaging (MRI) (12-13).

Hence, the purpose of this study was to evaluate P-wave measurements (especially Pi and IAB) in patients with ß-TM and examine the relation of these ECG parameters with cardiac T2* MRI value.

MATERIALS AND METHODS

Study population

This is a cross-sectional case-control study which was conducted at the Hematology Department, Selcuk University, in Konya, Turkey. Twenty-two (13 men, mean age 25±8 years) patients with diagnosis of ß-TM and 22 age- and gender-matched healthy subjects were recruited. Included patients gave their verbal and written consent for participation in the study. The study was approved by the local ethical committee. The diagnosis of ß-TM was made on hemogram, blood smear, hemoglobin electrophoresis, and clinical evaluation. The patients had been regularly transfused (every 3-4 weeks), and everyone received chronic chelation therapy (desferoxamine or deferiprone). Patients with a history of diabetes mellitus, coronary artery disease, congestive heart failure, congenital or acquired arrhythmia syndromes were excluded from the study. In addition, patients under treatment of medications that lengthen the QT interval, with current AF, bundle branch block, atrioventricular blocks, and unmeasurable T waves (<0.15 mV) on surface ECG were not included to the study.

ECG recording and analyses

Surface 12-lead standard ECGs were recorded from each patient with a 50 mm/s paper speed at 10 mm/mV amplitude. Timing of electrocardiographic measurements was adjusted to the last blood transfusion, so ECG was performed at least two weeks later after blood transfusion. The ECGs were scanned at a 600 dpi resolution and measurements made by electronic cursor from the screen by two experts who were blinded to the clinical status of the study population. Three consecutive ECG complexes were analyzed and given averaged measures for each lead.

P-wave parameters (P max, P min, and Pd) were measured in all 12-leads of the surface ECG recordings. The onset of the P wave was determined as the point of the first visible upward of the trace from the bottom of the baseline for the positive waves and as the point of first downward departure from the top of the baseline for negative waves. The return to baseline was considered to be the end of the P wave. The P max was defined as the longest atrial conduction time measured from the 12 leads and P min, as the shortest atrial conduction time. The difference between P max and P min was calculated and defined as Pd (Pd=P max-Pmin) (Figure

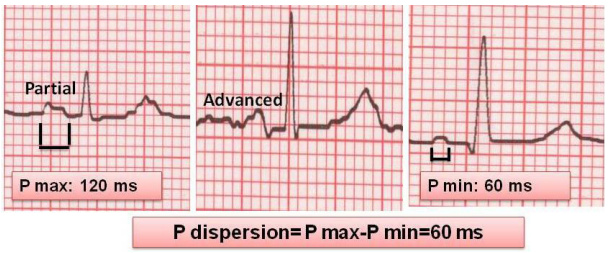

***Figure 1**. Measurement of P-wave parameters. Partial and advanced interatrial block (IAB) definition. With partial IAB, the impulse still crosses through via Bachman bundle (interatrial conduction), but is delayed (P wave ≥ 110 msec and bifid P waves). With advanced IAB, the impulse is completely blocked (P wave ≥ 110 msec and biphasic P waves).*

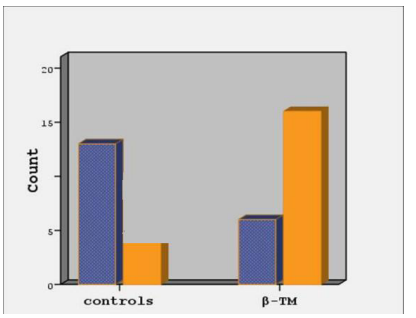

***Figure 2**. The prevalence of interatrial block in patients with β-TM and healthy controls.*

1). Pi was calculated digitally as the standart deviation (SD) of the P-wave duration across the 12 ECG leads. Prolonged P-wave duration (≥110 msec) in all 12-leads of the surface ECG was defined as IAB. Partial IAB was defined as prolonged, bifid P-waves in all 12-leads. Advanced IAB was defined as prolonged, biphasic (+,-) P-waves in all 12-leads (Figure 1). The intra-observer and inter-observer variabilities were calculated for the P-d as 7.5% and 4.8%, respectively.

Echocardiography

Echocardiographic examinations were performed with a Philips EnVisor C HD ultrasound machine (Royal Philips Electronics, Bothell, WA, USA) with a 2.5 MHz transducer. Ejection fraction was measured using modified Simpson method from the apical 4-chamber view. LV diastolic filling patterns were determined by mitral inflow pulsed wave (PW) Doppler examination. In the apical four-chamber view, the Doppler sample was placed in the middle of the LV inflow tract 1 cm below the plane of the mitral annulus between the mitral leaflet tips, where maximal flow velocity in early diastole was recorded (14). Peak E-wave and late A-wave; transmitral filling velocities, the E/A ratio, and deceleration time (DT) were assessed by PW Doppler echocardiography.

Cardiac Magnetic Imaging

Iron loading in the heart was evaluated with MRI T2*. MR images were acquired for all patients with a single imager equipped with a 1.5T magnet (Siemens Symphony Erlangen, Germany). Body phased array coil to image a single 10mm mid-ventricular short axis slice at eight echoes times (ranging from 3 ms to 21 ms, increment 2.6 ms) with ECG gating, and breath hold were also utilized. A gradient- echo sequence was used (flip angle 35, matrix 128x256).Double inversion recovery pulses were applied to suppress the blood signal and data was acquired every other cardiac cycle. The monoexponential decay model and the nonlinear curve fitting algorithm were used to fit the curve to obtain T2 measurement. We used CMR Tools software (http://www.cmrtools.com) for quantification.

Statistical analysis

The statistical analysis was performed with the Statistical Package for Social Sciences (SPSS for Windows) software (version 15.0) (SPSS Inc., Chicago, IL). The relation between the categorical variables was determined by the chi-square test. The distribution of the variables was analyzed with the Kolmogorov–Smirnow test. Student-t test was applied to determine difference of two groups for the parametric variable. The Mann-Whitney U test was used for non-parametric comparison of two groups. A Spearman correlation test was used to assess a linear association. The data were expressed as mean ± standard deviation or median and inter quartile range according to the distribution properties, and p-value under 0.05 was considered statistically significant.

***Table 1**. Clinical, demographic and laboratory characteristics of the study population*

	Control (n:22)	ß-TM (n:22)	p-Value
Age (years)	27±9	25±8	0.47
Gender			
Female / Male (n)	15/7	13/9	0.33
BMI (kg/m2)	23±1.6	22±2.0	0.44
SBP (mmHg)	122±16	120±15	0.36
DBP (mmHg)	77±7	83±6	0.42
Hemoglobin (g/dL)	13.3±1.2	10.4±1.3	0.001
Hematocrit (%)	44.2±2.6	34.3±6.6	0.001
Cardiac T2*MRI (ms)	-	23.7±11.2	-
Chelation therapy (%)	-	100	-
Ejection fraction (%)	58±11	56±10	0.68

ß-TM, ß-thalassemia major; BMI, body-mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MRI, magnetic resonance imaging.

***Table 2**. Electrocardiographic parameters of the ß-TM group and controls.*

	Control (n:22)	ß-TM (n:22)	p-Value
P max (msec)	104±11	118±17	0.005
P min (msec)	74±9.0	85±18	0.01
P disp (msec)	31±9.0	33±12	0.46
P index	9.2±2.9	11.2±2.9	0.03
Partial IAB, n(%)	4(18)	17(77)	0.001
Complete IAB, n	0	1	NA
QRS (msec)	101±19	99±15	0.86
HR (bpm)	79±7	84±8	0.005

P max, maximum P wave duration; P min, minimum P wave duration, P disp, P wave dispersion; IAB, interatrial block; HR, heart rate; bpm, beat per minute. NA: not assessed

RESULTS

The baseline clinical and laboratory characteristics of the groups are depicted in Table 1. ß-TM patients were not different from the control group in age, gender, body-mass index, or blood pressure levels. The mean cardiac T2* value of patients with ß-TM was 23.7±11.2 ms. Hemoglobin and hematocrit levels were significantly lower in ß-TM group than in the control group (Table 1). Heart rate was significantly higher in ß-TM patients than healthy subjects (p=0.005) (Table 2). Twelve-lead surface ECG analysis of P wave parameters is listed in Table-2. Pi was significantly increased in ß-TM patients compared to controls (11.2 ± 2.9 vs. 9.2 ± 2.9, p=0.03; respectively). Total prevalence of IAB was 81 % in ß-TM group and 18% in control group (Table-2 and Figure 2). As a result of IAB sub-analysis, partial IAB was found in 77 % of ß-TM patients. P max and Pmin were significantly prolonged in ß-TM patients compared to healthy controls (P max, p=0.005 and P min, p=0.01, respectively). Interestingly, Pd was found similar in both groups (p=0.46) (Table 2). ECG findings were similar in patients with cardiac T2*<20 msec and those with cardiac T2*≥20 msec (Table 3). Both traditional and novel P-wave parameters did not show significant correlation with cardiac T2* MRI value (Table 4). From the clinical findings, only EF was weakly correlated with cardiac T2* MR value (r: 0.34, p=0.03). P-wave parameters did not show any significant correlation with clinical findings.

DISCUSSION

In this study, we found that Pi, P max, and P min were significantly prolonged in the ß-TM group compared to the controls, but the prolongation did not exceed the normal limits. In addition, the prevalence of a partial IAB was significantly higher in ß-TM patients compared to healthy subjects. Pd was comparable in both groups. P wave measurements were not correlated with iron load using the cardiac T2*MRI. To our knowledge, this was the first analysis of Pi and IAB in patients with ß-TM. We discovered that the risk of AF development was not increased in asymptomatic ß-TM patients with preserved LV function.

For the first time, we attempted to investigate a novel parameter, Pi, in patients with ß-TM. Pi accounts for the differences in atrial conduction across different vectors that may more accurately predict AF and was firstly introduced by Perez et al. (5). They retrospectively investigated 41.701 ECGs of the normal population with a sinus rhythm who were followed for the development of AF indicated by several ECG characteristics and found that Pi > 35 was one of the strongest predictors of AF. In our study, although Pi was significantly increased in ß-TM patients compared to the controls, Pi values in our study population were lower than the cut-off value used in the previous study. Therefore, we found no evidence that an increased AF risk in ß-TM patients can be ascertained using the Pi evaluation.

***Table 3**. Electrocardiographic findings of patients with ß-TM according to cardiac T2* scores*

	*T2*MRI≥20 n:10*	*T2*MRI<20 n:12*	*p-Value*
P max (msec)	*120±18*	*117±18*	*0.67*
P min (msec)	*85±20*	*84±14*	*0.87*
P disp (msec)	*34±15*	*32±11*	*0.71*
P index	*10.7±2.5*	*11.8±3.3*	*0.39*
IAB, (%)	*80*	*≥75*	*0.84*

P max, maximum P wave duration; P min, minimum P wave duration, P disp, P wave dispersion; IAB, interatrial block; HR, heart rate; bpm, beat per minute.

***Table 4**. Correlation of P-wave parameters with cardiac T2*MRI values.*

	r	*p*
P max	*0.07*	*0.74*
P min	*0.08*	*0.72*
P dispersion	*0.12*	*0.95*
P index	*0.08*	*0.71*

A novel finding of our study was an increased prevalence of interatrial block (IAB) in patients with ß-TM compared to healthy subjects. IAB is defined as a delayed conduction between the right and left atrium, which results in a prolonged P-wave duration (≥110 milliseconds) (15). IAB consistently shows intercellular fibrotic changes and intracellular metabolic inclusions (10). Depending on the severity of the conduction delay between the atria, IAB can be classified as a partial or advanced block (9). In particular, advanced IAB was associated with new onset AF in the current literature (12). Although, in the present study, the prevalence of IAB was significantly higher in ß-TM group (81%), advanced IAB was seen in only one ß-TM patient. ß-TM patients usually have partial rather than advanced IAB (95% vs. 5%). Hence, it seems that ß-TM causes mild atrial fibrosis, but the level of fibrosis may not produce a tendency for AF development in asymptomatic ß-TM patients. Despite its predictive value and the ease of its calculation, IAB has not generated the interest it deserves. IAB may be a useful tool to determine whether patients have an increased risk of developing AF in the future.

P-wave measurements, especially Pd, is a recent contribution to the field of noninvasive ECGs to predict AF (16). Pd represents an inhomogeneous and anisotropic distribution of connections between myocardial fibers in atrial tissues (17). Prolonged inhomogeneity (reflected as increased Pd) is considered to be an independent predictor of paroxysmal AF (18). The generally accepted cut-off value for the Pd is above 40 ms, and for the P max it is above 120 ms of duration, and these values may predict AF development (16, 19). Previously, prolongation of Pd in ß-TM patients was described by Nisli et al. (13), where an increased Pd was related to the depression of intra-atrial conduction due to atrial dilatation and increased sympathetic tone. However, their study did not evaluate diastolic functions and iron deposits using the cardiac T2*MRI, which may contribute to prolonged Pd. These limitations were resolved recently by Russo and colleagues (12). They demonstrated a correlation of Pd with myocardial iron overload assessed by cardiac T2*MRI in ß-TM patients with preserved EF. However, we did not confirm the results of Russo et al. (14) in the present study. Both P max and P min durations were prolonged in ß-TM patients, but the Pd was similar in both groups. In our study, mean age of the patients was approximately twelve years younger than the patients in the study of Russo et al. (12). Thus, a prolonged duration of the disease may affect P-wave measurements and risk of AF development. On the other hand, Pd values of ß-TM patients were within normal limits (Pd<40 ms) in the studies of Nishli et al. (13), Russo et al. (14), and in our study (41 ms, 35 ms and 33 ms, respectively). Similarly, the P max was below 120 ms in all of the abovementioned studies. Therefore, it is difficult to claim, based on P-wave parameters, that ß-TM patients have an increased risk of AF development. The prevalence of AF in ß-TM patients remains unclear, and the role of ß-TM in the development of AF is questionable. We think that the risk of AF development should not be based on the P-wave measurements in patients with ß-TM.

Interestingly, we did not find an association between P-wave parameters and cardiac T2*MRI. These findings did not support the hypothesis that iron overload toxicity per se influences atrial conduction time; i.e., P-wave parameters. Nevertheless, we found no differences in P-wave parameters in patients with T2*<20 msec and those with T2*≥20 msec. Iron overload may lead to myocardial fibrosis (20) and theory that fibrosis as a cause

of iron overload may be more deleterious than iron itself supports the results of our study. In a consequence of iron overload, diastolic functions may impair as a cause of apoptosis, fibrosis, and oxidative stress in the myocardial tissues (20). The theory that iron overload alone is not sufficient to cause arrhythmia was observed in non-human models (21,22). In addition, cardiac arrhythmias were not solely related to iron overload in patients with hemochromatosis (23). Taken together, these data suggest that iron alone may be necessary but insufficient to cause cardiac arrhythmia in iron-overload conditions. Although, chelation therapy may reduce iron overload, there is no evidence about the reverse of fibrosis in these patients. The reversibility of iron-overload fibrosis is still unknown. Therefore, even in asymptomatic ß-TM patients (T2*≥20 ms), diastolic functions may impair as a cause of iron overload and may lead to impaired P-wave parameters. Impairment of P wave parameters in diastolic dysfunction has been demonstrated before (24).

Our study had some limitations. First, this is a cross-sectional study with a small sample size, and large randomized studies are needed to determine the role of individual P-wave parameters in predicting AF development. Secondly, cardiac T2*MRI was not performed in the control group because of the higher cost. Thirdly, chelation therapy may affect P-wave parameters, so our results may not be applicable to patients not undergoing this type of therapy. In addition, transfusion requirements which are potential factors that may lead to impaired P-wave parameters were not assessed in this study. Fourth, because there is speculation that fibrosis may cause an iron overload that may impair P-wave parameters, we think that an investigation of noninvasive markers of fibrosis (metalloproteinase, procollagen type I, procollagen type III, etc.) needs to be undertaken in the future. Lastly, P-wave measurements of ß-TM patients with sinus rhythm were performed using the 12-lead ECG; however, rhythm Holter monitoring and/or an event recorder were not performed in study participants to eliminate paroxysmal AF.

In conclusion, although Pi, P max, and partial IAB were increased in the ß-TM patients independent of myocardial iron deposition, the duration of P max, Pd, and Pi did not exceed normal limits, and none of them was associated with the cardiac iron load. Based on the study results, ß-TM patients with preserved LV function did not demonstrate an increased risk of AF development. We speculate that impairment in P-wave parameters may be mostly related to diastolic dysfunction in ß-TM patients as a cause of iron-overload fibrosis. Future studies with a large sample size are needed to determine whether an abnormality in these measurements may predict development of AF in patients with ß-TM.

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