Investigation of P-Wave Dispersion in Adult Patients with Beta-Thalassemia Major

Sajad Amirghofran,1 Amir Aslani2, Maryam Zakerinia3

1International branch, Shiraz University of Medical Sciences, Shiraz, IRAN.
2Cardiology Department, Shiraz University of Medical Sciences, Shiraz, IRAN.
3Department of Internal Medicine, Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, IRAN.

ABSTRACT

Background: Paroxysmal atrial tachyarrhythmias, especially atrial fibrillation is a fatal complication that occur more frequently in patients with β-thalassemia major (β-TM) than normal population. This study aimed to compare P-wave dispersion (PWD) in patients with β-thalassemia major with control subjects for the early prediction of arrhythmia risk. Methods: Sixty-six adult patients with β-TM referring to Shahid Motahari hospital of Marvdasht in winter 2015 were compared to 50 non-thalassemic adults. All participants underwent routine 12-leads electrocardiography (ECG) for cardiac evaluation. ECGs were scanned and PWD was calculated as the difference between the maximum and the minimum P-wave duration. Results: Patients with β-TM aged between 18 to 47 years old and were matched by age and gender to the control group. There was a statistically significant difference between the study and control groups in minimum P-wave duration (44.8±9.8 vs 49.1±5.3 ms, p=0.006), maximum P-wave duration (105.3±12.5 vs 97.6±6.4 ms, p<0.001) and PWD (60.5±11.00 vs 48.6±7.8 ms, p<0.001). Conclusion: PWD increased in β-TM patients, thus, these patients should be closely followed up for risk of atrial fibrillation which can be life threatening.

Key words: Electrocardiography, PWD, beta-thalassemia, Atrial Fibrillation, Iron Overload.

INTRODUCTION

β-thalassemia major (β-TM) is an important health problem with a high global incidence.1,2 In Iran, it is considered the most common hereditary disease with estimated 26,000 patients affected and induces a high economic and health burden on the society,3 reduced since 1997 with the implementation of national screening program for thalassemia.4 As β-TM is by nature a fatal hemoglobinopathy, it requires several blood transfusions that causes iron overload in heart, and other organs.5 Although treatment strategies, including iron chelators has improved the prognosis of these patients,6 the longer life expectancy has caused the significance of complications, including cardiac complications, which is considered the first cause of mortality in the affected patients.7 Moreover, different iron chelators have different protective effect on the heart and iron overload in heart also induces cardiomyopathy8. The cardiomyopathy in the patients with β-TM has two phenotypes of dilated and restrictive.9 Various methods have been proposed for diagnosis of heart complications, including monitoring the ejection fraction,10 doppler echocardiography,11 radionuclide angiography and heart rate variability analysis,12 and MRI assessments of heart and liver, identifying the iron overload in tissues.13 As far as heart failure occurs lately in the affected patients, the diagnostic method should be able to detect cardiac pathology in the early stages and should be accurate enough to identify all cardiac complications.14 In addition, paroxysmal atrial tachyarrhythmia, especially atrial fibrillation (AF), is an important cause of death due to cardiac emboli and cerebrovascular accidents in β-TM patients,15 which has been established to cause increasing PWD16 and can be simply determined by P-wave dispersion (PWD) on the electrocardiography (ECG).17 Higher PWD have been associated to higher rates of AF in other diseases, such as essential hypertension,18 severe obesity,19 type 2 diabetes mellitus,20 and metabolic syndrome.21 Also, PWD was reported to be longer in some other cardiac pathologies, like hypertrophic cardiomyopathy,22 acute anterior wall myocardial infarction,23 and secundum atrial septal defect.24 Yet, the PWD in β-TM patients has revealed controversial results in different studies.25 In the present study, we aimed to compare the PWD on the twelve-lead ECG of patients with β-TM with controls, in order to identify whether PWD assessment can be a good predictor of AF in these patients.

MATERIALS AND METHODS

Study design

In this cross-sectional study, all patients with β-TM who referred for blood transfusion to the Shahid Motahari hospital, Marvdasht in winter 2015 were enrolled, who were compared to a control group. Patients and non-thalassemic adults were allocated to case and control groups based on simple randomization method and the sample size was calculated based on previous studies with accuracy (d) of 3.5 and α of 0.05 at 50 in each group. Considering the lost to follow-up, 66 patients with β-TM were selected as the case group who were receiving Deferoxamin therapy as iron chelation. Inclusion criteria for the intervention group consisted of patients with β-TM older than 18 years who had medical document at the hospital and the control group were selected from ENT or general surgery ward who underwent surgical procedure more than 12 hours before and were matched by age and gender with the case group. Exclusion criteria com-
prised of any disease involving main organs, such as heart, lungs, nervous system, liver, and kidneys, any patient with cardiomyopathy, any patient using drugs that affect the P-R interval of the ECG, like calcium channel blockers and beta blockers.

The duration of β-TM and the serum level of ferritin (measured by Vidas IFm method) and serum level of hemoglobin were extracted from medical records in the case group and twelve-lead ECG recorded on a 25 mm/s paper speed at 10 mm/mV amplitude was performed for all participants, in which PWD was compared between the groups.

For calculating P-wave, ECGs were scanned and Adobe Photoshop Software version CC was used to calculate minimum and maximum P-wave duration and PWD, after determining the distance of two minor lines (0.04 seconds or 40 milliseconds) and was analysed by a colleague blind to the groups’ allocation.

**Ethical considerations**

The protocol of the study was approved by Shiraz University of Medical Sciences (SUMS) and Shahid Motahari hospital’s Ethics Committee. The design and objectives of the study were explained to all participants and written informed consent was obtained from those who were willing to participate in the study and they were clarified that they were free to leave the study whenever they wished to.

**Statistical analysis**

Continuous variables are presented as mean ± standard deviation for the normally distributed data, and median and quartiles for skewed data and qualitative variables are reported through frequencies (percentage). Independent-Samples T Test was used to compare two groups and One-Way ANOVA for three groups. Statistical analysis was performed using SPSS software version 22 (IBM SPSS Statistics Inc., Chicago, IL, USA). P-values less than 0.05 were considered statistically significant.

**RESULTS**

A total of 66 β-TM patients were compared to 50 controls. Mean age of participants was 26.56 with no significant difference between the groups (P=0.516). Participants’ age was categorized into three groups including 18-27 years, 28-37 years, and 38-47 years; 64% of participants were in the age group 18-27 years and only 2 participants in the age group 38-47 years with no significant difference in age distribution between the two groups (P=0.984). Regarding gender, 57.58% of the case and 56% of the controls were female (P=0.867). Demographic characteristics of participants are demonstrated in table 1.

Mean duration of blood transfusion was 22.42±6.90 years. Mean serum level of ferritin was 2595.68 ± 2195.36 ng/mL (range: 158-7950). Mean serum level of hemoglobin was 9.667 ± 0.99 g/dL (range: 5.3-12.5). Mean heart beats was statistically not different between group (P=0.268).

Mean of minimum P-wave duration (Pmin) was 44.8 ± 9.8 ms in the cases and 49.1 ± 5.3 ms in the controls (P=0.006). Mean of maximum P-wave duration (Pmax) was 105.3 ± 12.50 ms in the cases and 97.6 ± 6.3 ms in the controls (P<0.001). Median of PWD in the cases was 60.5 ± 11.0 ms and 48.6 ± 7.8 ms in the controls (P=0.006). Also mean PWD was higher in male participants, which was statistically not significant (P=0.189).

Mean of minimum P-wave duration (P min) was 44.8±9.8 ms in the cases and 49.1±5.3 ms in the controls (P=0.006). Mean of maximum P-wave duration (P max) was 105.3±12.5 ms in the cases and 97.6±6.3 ms in the controls (P<0.001). Median of PWD in the cases was 59.6 ms with a range of 29.4-88.9 ms. The highest mean of PWD was in the age group 38-47 years and the least in the age group 28-37 years (P=0.318). Also mean PWD was higher in male participants, which was statistically not significant (P=0.189).

Mean PWD was significantly higher in the case group (60.5±11.0 vs 48.5±7.7, 95%CI: 8.3-15.5) (P=0.0001). Electrocardiographic finding of participants are shown in table 2. Linear Regression showed no association between PWD and the rest of variables (Table 3).

**DISCUSSION**

As the results of the present study indicated, mean PWD and P max was significantly higher, but P min was significantly lower in β-TM patients that

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<th>Table 1: Demographic characteristics of participants</th>
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<td>Age, years</td>
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<td>Sex (F/M)</td>
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<td>Mean duration of blood transfusion, years</td>
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<th>Table 2: Electrocardiographic findings of participants</th>
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<td>Case group (β-TM patients)</td>
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<td>Minimum P-Wave duration, ms</td>
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<th>Table 3: Result of linear regression for the association between PWD and the rest of variables</th>
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identifies the association of P-wave dispersion with AF in β-TM patients that suggests routine ECG assessment for early detection of AF which can be life threatening.

Several studies have focused on the PWD variation in β-TM patients, but have obtained contrary results. An Iranian study by Ghadiri Anari et al have similarly compared 50 β-TM patients with 50 healthy subjects and found significantly higher PWD in β-TM patients. They have also reported higher mean PWD in higher age category (16-31 years), which was also found in the present study, but was the highest in 38-47 years in the present study. But Ghadiri Anari's study has only included patients aged 2-31 years. Nisi and colleagues have compared 81 β-TM children aged 4-20 years with 74 healthy subjects and have reported higher Pmax and PWD in β-TM patients. In their study, Pmax and PWD were respectively 10.14 and 8.22 higher than the control group, which was 7.65 and 11.91, respectively, in the current study. They have justified this difference due to higher sympathetic action, which increase the risk of arrhythmias. Moreover, the wide range of ferritin in the present study, which was also present in Nishi's study, indicates various patient's response to iron chelators that needs to be taken into consideration in management of β-TM patients. Russo and colleagues have also compared 50 β-TM patients with 50 healthy subjects and have concluded strong association between P-wave changes and AF in β-TM patients. They have suggested that the heart structure of β-TM patients may not be normal and AF occurs in the absence of cardiac symptoms; therefore, they have recommended inclusion of ECG in the daily assessment with more focus on P-wave duration and have advised that β-TM patients with abnormal PWD>35.5, and PWave>111 ms are at higher risk of AF and may benefit from ECG holter monitoring. Acar and colleagues have also reported prolonged Pmax and PWD in β-TM patients, but no difference in PWD and have additionally described no relationship between P-wave parameters and T.MRI. Thus, they have concluded no association of P-wave prolongation with iron overload and have suggested assessment of fibrosis in these patients, as it may cause iron overload causing P-wave impairment.

The strengths of the present study included digital assessment of PWD that was suggested as an accurate method in previous studies, in addition to performing the calculations by a colleague who was blind to the groups that reduced the bias. Although similar studies have also chosen 50 participants in each group, a larger sample size may help strengthen the results. As far as few studies addressed this issue, there is a need for a larger study with considering all variables that may affect the results. Although the case and control group in the present study were matched by age and gender, the study results might be limited due to some other confounding factors may affect the results, like systolic and diastolic blood pressure, assessment of iron overload by a more accurate method rather serum levels of ferritin, like T2 MRI, echocardiography, etc. and assessing the presence of AF and cardiomyopathy in patients, and following up patients for future outcomes.

According to limited studies conducted on this issue, it is obvious that P-wave changes in β-TM patients and its association to iron overload need further assessment. As long as previous studies have established PWD a good predictor of AF and AF is an important cause of sudden death, stroke, and embolism in β-TM patients, which usually causes no significant symptoms and regarding the fact that ECG is a simple non-invasive measurement that can be easily performed for patients, the authors of the present study suggest that β-TM patients should be routinely followed up by ECG for any change suggestive of AF, including PWD.

CONCLUSION
In this study, we measured PWD in adult Beta-TM patients. According to the results obtained and processed, PWD was significantly higher in BTM patients; thus, it increased the risk of AF. Our study concludes that these patients should be closely followed up for the risk of AF which can be life-threatening.

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CONFLICT OF INTEREST
The author declare no conflict of interest.

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Amirghofran Sajad et al.: P-wave dispersion in Thalassemia major


