J Cardiovasc Disease Res., 2016; 7(3): 116-119
A Multifaceted Peer Reviewed Journal in the field of Cardiology
www.jcdronline.org | www.journalonweb.com/jcdr

Original Article

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

Sajad Amirghofran[1], Amir Aslani[2], Maryam Zakerinia[3]

[1]*International branch, Shiraz University of Medical Sciences, Shiraz, IRAN.*
[2]*Cardiology Department, Shiraz University of Medical Sciences, Shiraz, IRAN.*
[3]*Department 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.

Abbreviations
PWD: P-Wave Dispersion; Pmax: P-wave maximum; Pmin: P-wave minimum; β-TM: Beta-Thalassemia Major; ECG: Electrocardiogram; EF: Ejection Fraction; RBC: Red Blood Cell; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hb; MCHC: Mean Corpuscular Hb Concentration; RDW: RBC Distribution Width; HbA2: Hemoglobin A2.

Correspondence
Sajad Amirghofran,
Noavaran st, Chamran blvd
Shiraz, IRAN.
Phone no: +98 917 3012208
Email:
amgs619@gmail.com

Submission Date: 04-03-2016;
Revision Date: 28-03-2016;
Accepted Date: 02-05-2016.
DOI : 10.5530/jcdr.2016.3.4

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 cardiomyopathy [8].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 PWD[16] 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-

Table 1: Demographic characteristics of participants

	Case group (β-TM patients)	Control group (healthy subjects)
Age, years	25.92 ± 5.489	26.56 ± 4.21
Sex (F/M)	38/28	22/28
Mean duration of blood transfusion, years	22.42 ± 6.90	-
Mean heart beats /minute	86.5 ± 12.8	83.2 ±19.3
Hb, gr/dl	9.65 ± 1.01	13.83 ± 2.12
Ferritin, ng/ml	2595.68 ± 2195.36	47.36 ± 36.78

Table 2: Electrocardiographic findings of participants

	Case group (β-TM patients)	Control group (healthy subjects)
Minimum P-Wave duration, ms	44.8 ± 9.8	49.1 ± 5.3
Maximum P-Wave duration, ms	105.3 ± 12.50	97.6 ± 6.3
PWD, ms	60.5 ± 11.0	48.6 ± 7.8

Table 3: Result of linear regression for the association between PWD and the rest of variables

Variables	Correlation (r)	P-value
Sex	-0.373	0.783
Age	0.121	0.312
BloodTransfusionDuration	0.000	0.637
Ferritin (IFmet) Vidas	0.982	0.622
Hb	-0.373	0.498

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 (range: 1-37.5) 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 (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

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.[26] 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. Nisli and colleagues have compared 81 β-TM children aged 4-20 years with 74 healthy subjects and have reported higher P_{max} and PWD in β-TM patients.[25] In their study, P_{max} 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 sympathic action, which increase the risk of arrhythmias. Moreover, the wide range of ferritin in the present study, which was also present in Nisli'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.[27] 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 P_{max}>111 ms are at higher risk of AF and may benefit from ECG holter monitoring. Acar and colleagues have also reported prolonged P_{max}, and P_{min}, in β-TM patients, but no difference in PWD and have additionally described no relationship between P-wave parameters and T_2MRI.[28] 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 T_2MRI, 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[16,17,29] and AF is an important cause of sudden death, stroke, and embolism in β-TM patients,which usually causes no significant symptoms[15,17,30] 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.

ACKNOWLEDGEMENT

The present article was extracted from the thesis written by Sajad Amirghofran and was financially supported by Shiraz University of Medical Sciences (grants number: 86.1014).

CONFLICT OF INTEREST

The author declare no conflict of interest.

REFERENCES

1. Weather all D, Clegg J. Inherited haemoglobin disorders: an increasing global health problem. Bulletin of the World Health Organization. 2001;79(8):704-12. PMid:11545326 PMCid:PMC2566499.
2. Vichinsky EP. Changing patterns of thalassemia world wide. Annals of the New York Academy of Sciences. 2005;1054(1):18-24. http://dx.doi.org/10.1196/annals.1345.003; PMid:16339647.
3. Ghotbi N, Tsukatani T. Evaluation of the national health policy of thalassaemia screening in the Islamic Republic of Iran. 2005.
4. Samavat A, Modell B. Iranian national thalassaemia screening programme. Bmj. 2004;329(7475):1134-7. http://dx.doi.org/10.1136/bmj.329.7475.1134; PMid:15539666 PMCid:PMC527686.
5. Peters M, Heijboer H, Smiers F, Giordano P. Diagnosis and management of thalassaemia. BMJ. 2012;344:e228. http://dx.doi.org/10.1136/bmj.e228.
6. Borgna PC, Rugolotto S, De Stefano P, Zhao H, Cappellini MD, Del Vecchio GC, *et al*. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. haematologica. 2004;89(10):1187-93.
7. Borgna-Pignatti C, Cappellini M, Stefano P, Vecchio G, Forni G, Gamberini M, *et al*. Survival and complications in thalassemia. Annals of the New York Academy of Sciences. 2005;1054(1):40-7. http://dx.doi.org/10.1196/annals.1345.006. PMid:16339650.
8. Anderson LJ, Wonke B, Prescott E, Holden S, Walker JM, Pennell DJ. Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in beta-thalassaemia. The Lancet. 2002;360(9332):516-20. http://dx.doi.org/10.1016/S0140-6736(02)09740-4.
9. Kremastinos D, Farmakis D, Aessopos A, Hahalis G, Hamodraka E, Tsiapras D, *et al*. Beta-thalassemia cardiomyopathy: history, present considerations, and future perspectives. Circulation Heart failure. 2010;3(3):451. http://dx.doi.org/10.1161/CIRCHEARTFAILURE.109.913863; PMid:20484195.
10. Davis BA, O'Sullivan C, Jarritt PH, Porter JB. Value of sequential monitoring of left ventricular ejection fraction in the management of thalassemia major. Blood. 2004;104(1):263-9. http://dx.doi.org/10.1182/blood-2003-08-2841; PMid:15001468.
11. Vogel M, Anderson L, Holden S, Deanfield J, Pennell D, Walker J. Tissue Doppler echocardiography in patients with thalassaemia detects early myocardial dysfunction related to myocardial iron overload. European heart journal. 2003; 24(1):113-9. http://dx.doi.org/10.1016/S0195-668X(02)00381-0.
12. Chiara BD, Crivellaro W, Sara R, Ruffini L, Parolini M, Fesslovà V, *et al*. Early detection of cardiac dysfunction in thalassemic patients by radionuclide angiography and heart rate variability analysis. European journal of haematology. 2005;74(6):517-22. http://dx.doi.org/10.1111/j.1600-0609.2005.00434.x; PMid:15876256.
13. Anderson LJ, Westwood MA, Holden S, Davis B, Prescott E, Wonke B, *et al*. Myocardial iron clearance during reversal of siderotic cardiomyopathy with intravenous desferrioxamine: a prospective study using T2* cardiovascular magnetic resonance. British journal of haematology. 2004;127(3):348-55. http://dx.doi.org/10.1111/j.1365-2141.2004.05202.x; PMid:15491298.
14. Kremastinos DT, Tsetsos GA, Tsiapras DP, Karavolias GK, Ladis VA, Kattamis CA. Heart failure in beta thalassemia: a 5-year follow-up study. The American journal of medicine. 2001;111(5):349-54. http://dx.doi.org/10.1016/S0002-9343(01)00879-8.
15. Karimi M, Khanlari M, Rachmilewitz EA. Cerebrovascular accident in β-thalassemia major (β-TM) and β-thalassemia intermedia (β-TI). American journal of hematology. 2008;83(1):77-9. http://dx.doi.org/10.1002/ajh.20938; PMid:17696211.
16. Koide Y, Yotsukura M, Ando H, Aoki S, Suzuki T, Sakata K, *et al*. Usefulness of P-wave dispersion in standard twelve-lead electrocardiography to predict transition from paroxysmal to persistent atrial fibrillation. The American journal of cardiology. 2008;102(5):573-7. http://dx.doi.org/10.1016/j.amjcard.2008.04.065; PMid:18721514.
17. Platonov P, Carlson J, Ingemansson M, Roijer A, Hansson A, Chireikin L, *et al*. Detection of inter-atrial conduction defects with unfiltered signal-averaged P-wave ECG in patients with lone atrial fibrillation. Europace. 2000;2(1):32-41.

http://dx.doi.org/10.1053/eupc.1999.0072; PMid:11227584.

18. Ma X, Zhang X, Guo W. Factors to predict recurrence of atrial fibrillation in patients with hypertension. Clinical cardiology. 2009;32(5):264-8. http://dx.doi.org/10.1002/clc.20449; PMid:19452484.
19. Russo V, Ammendola E, De Crescenzo I, Docimo L, Santangelo L, Calabrò R. Severe obesity and P-wave dispersion: the effect of surgically induced weight loss. Obesity surgery. 2008;18(1):90-6. http://dx.doi.org/10.1007/s11695-007-9340-7; PMid:18080825.
20. Yazici M, Ozdemir K, Altunkeser BB, Kayrak M, Duzenli MA, Vatankulu MA, *et al*. The effect of diabetes mellitus on the P-wave dispersion. Circulation Journal. 2007;71(6):880-3. http://dx.doi.org/10.1253/circj.71.880; PMid:17526984.
21. Yasar AS, Bilen E, Bilge M, Ipek G, Ipek E, Kirbas O. P-Wave Duration and Dispersion in Patients with Metabolic Syndrome. Pacing and clinical electrophysiology. 2009;32(9):1168-72. http://dx.doi.org/10.1111/j.1540-8159.2009.02460.x; PMid:19719494.
22. Ozdemir O. P-wave durations as a predictor for atrial fibrillation development in patients with hypertrophic cardiomyopathy. International journal of cardiology. 2004;94(2):163-6. http://dx.doi.org/10.1016/j.ijcard.2003.01.001; PMid:15093974.
23. Baykan M, Çelik S, Erdöl C, Durmus I, Örem C, Küçükosmanoglu M, *et al*. Effects of P-wave Dispersion on Atrial Fibrillation in Patients with Acute Anterior Wall Myocardial Infarction. Annals of Noninvasive Electrocardiology. 2003;8(2):101-6. http://dx.doi.org/10.1046/j.1542-474X.2003.08202.x; PMid:12848789.
24. Guray U, Guray Y, Yýlmaz MB, Mecit B, Sasmaz H, Korknaz S, *et al*. Evaluation of P wave duration and P wave dispersion in adult patients with secundum atrial septal defect during normal sinus rhythm. International journal of cardiology. 2003;91(1):75-9. http://dx.doi.org/10.1016/S0167-5273(02)00598-3.
25. Nisli K, Taner Y, Naci O, Zafer S, Zeynep K, Aygun D, *et al*. Electrocardiographic markers for the early detection of cardiac disease in patients with beta-thalassemia major. Jornal de pediatria. 2010;86(2):159-62. http://dx.doi.org/10.2223/JPED.1982; PMid:20361126.
26. Ghadiri Anari A, Ghiliyan R, Rezaeian G. P-wave Dispersion in Patients with Major Thalassemia. Iranian journal of Pediatric Hematology Oncology. 2012;2(2):67-71.
27. Russo V, Rago A, Pannone B, Papa AA, Mayer MC, Spasiano A, *et al*. Atrial fibrillation and beta thalassemia major: the predictive role of the 12-lead electrocardiogram analysis. Indian pacing and electrophysiology journal. 2014;14(3):121. http://dx.doi.org/10.1016/S0972-6292(16)30753-7.
28. Acar K, Kayrak M, Gul EE, Abdulhalikov T, Ozbek O, Uçar R. Cardiac iron load and novel P-wave measurements in Patients with Thalassemia Major: The role of P index and Interatrial Block. European Journal of General Medicine. 2012;9(1).???
29. Dilaveris PE, Gialafos EJ, Andrikopoulos GK, Richter DJ, Papanikolaou V, Poralis K, *et al*. Clinical and electrocardiographic predictors of recurrent atrial fibrillation. Pacing and Clinical Electrophysiology. 2000;23(3):352-8. http://dx.doi.org/10.1111/j.1540-8159.2000.tb06761.x; PMid:10750136.
30. Taher A, Isma'eel H, Mehio G, Bignamini D, Kattamis A, Rachmilewitz EA, *et al*. Prevalence of thromboembolic events among 8,860 patients with thalassaemia major and intermedia in the Mediterranean area and Iran. Thromb Haemost. 2006;96(4):488-91. http://dx.doi.org/10.1160/th06-05-0267.

Cite this article : Amirghofran S, Amir Aslani, Zakerinia M. Investigation of P-Wave Dispersion in Adult Patients with Beta-Thalassemia Major. Journal of Cardiovascular Disease Research. 2016;7(3):116-9.