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P-Wave and QT Dispersion in Children With βeta-Thalassemia

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Authors' contributions

This work was carried out in collaboration among all authors. Author MS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SEN and IB managed the analyses of the study. Author AZ managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: This study aimed at assessing P-wave and QT interval dispersion in children with β-thalassemia and to correlate them with various laboratory and echocardiographic data.
Methodology: Subjects comprised of 30 children with β-thalassemia major as the patient group. 30 healthy children matched for age and sex served as the control group. All patients were evaluated clinically as well as by echocardiography and 12 leads ECG. The type of study is prospective case control study.
Results: There was a statistically significant increase of Interventricular Septal end diastole (IVSd), Interventricular Septal end systole (IVSs), Left Ventricular Internal Diameter end diastole (LVIDd), Left Ventricular Internal Diameter end systole (LVIDs) and Left Ventricular Posterior Wall end diastole (LVPWd) in patients as compared to controls (Mean ±SD = 0.950±0.166, 0.863±0.103, 3.983±0.456, 2.947±0.535a nd 0.797±0.165 respectively) (P < 0.05). Moreover, there were a significant increase of LV mass (Mean ±SD = 107.267±26.736, P= 0.002) and LV mass index of the studied patients (Mean ±SD = 106.900±22.651, P = 0.005) compared to the controls. There were significant decrease of ejection fraction (EF%)(Mean ±SD = 60.373 ± 8.088, P = 0.032)and

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fractional shortening (FS%) (Mean ±SD = 29.495 ± 4.171, P = 0.026) of the studied patients compared to control group. Both P wave dispersion (PWd) (Mean ±SD = 33.667 ± 13.767, P = 0.029) and QT dispersion (QTd) (Mean ±SD = 53.000 ± 18.411, P = 0.001) were significantly higher in patients compared to controls. There was a significant positive correlation between PWd and serum ferritin (r =0.551, P-value= 0.002), LVIDd (r =0.406, P-value= 0.026), LVPWd (r =0.461, P-value= 0.010), LV mass (r =0.412, P-value= 0.024), and LV mass index(r = 0.379, P-value= 0.039). While, there were a significant positive correlations between QTd and serum ferritin (r =0.654, P-value <0.001), LVIDd (r = 0.388, P-value = 0.034), LV mass (r = 0.454, P-value = 0.012) and LV mass index (r = 0.456, P-value = 0.011).

Conclusion: P wave dispersion and QT dispersion were prolonged in children with β-thalassemia major denoting cardiac autonomic dysfunction with homogeneity disorders of atrial conduction and ventricular repolarization in these patients.

Keywords: Beta-thalassemia major; QT dispersion; P wave dispersion.

ABBREVIATIONS

AF	*: Atrial Fibrillation*
β-TM	*: β Thalassemia Major*
2-D echocardiography	*: 2 Dimensional echo-cardiography*
ECG	*: Electrocardiogram*
EF	*: Ejection Fraction*
FS	*: Fractional Shortening*
Hb	*: Haemoglobin*
HR	*: Heart Rate*
IVSd	*: Interventricular Septal end diastole*
IVSs	*: Interventricular Septal end systole*
LV	*: The Left Ventricle*
LVIDd	*: Left Ventricular Internal Diameter end diastole*
LVIDs	*: Left Ventricular Internal Diameter end systole*
LVPWd	*: Left Ventricular Posterior Wall end diastole*
MHz	*: Mega Hertz*
M Mode	*: Motion Mode*
PWd	*: P Wave dispersion*
QTd	*: QT dispersion*
SD	*: Standard Deviation*

1. INTRODUCTION

β Thalassemia major (β-TM) is an inherited autosomal recessive blood disease causing chronic hemolytic anemia necessitating periodic blood transfusion regimens to prevent complications [1]. Because of the hemolysis and repeated blood transfusion, β-TM is associated with iron overload. Cardiac iron overload is the most frequent cause of death from chronic transfusion therapy. Iron induced cardiac complications include recurrent pericarditis, various forms of arrhythmias, cardiomegaly with deteriorating left ventricular functions and ultimately refractory congestive heart failure [2,3].

The diagnosis of cardiac complication is often delayed by the unpredictability of cardiac iron deposition and late development of symptoms and echocardiographic abnormalities. The early diagnosis of iron induced cardiomyopathy with conventional echocardiography and stress radionuclide angiography has had limited success [4].

P-wave dispersion (PWD) is a non-invasive electrocardiographic marker for atrial remodelling and predictor for atrial fibrillation (AF) [5]. PWD has received increasing attention in broad range of clinical settings including cardiovascular and non-cardiovascular diseases [6]. PWD is a reliable test for the presymptomatic identification of cardiomyopathy and has a predictive value especially for paroxysmal atrial fibrillation [7].

QT dispersion (QTd) was proposed as an index of ventricular recovery times to distinguish myocardium that is homogenous from myocardium that display non-homogeneity in the repolarization time [8].

In thalassemic patients, it has been shown that ventricular wall thickening may be altered by pathological iron deposition. The iron deposition may affect the ventricular recovery time due to inhomogeneity in the repolarization time with altered QT interval and QTd [9].

Some studies evaluated the QTd and others evaluated PWD in patients with thalassemia major but the correlation between PWD and QTd in this group of patients and laboratory data as serum ferritin level and echocardiographic parameters as LV mass and LV mass index have not been evaluated.

Thus, the aim of this study was to evaluate both P-wave and QT interval dispersion in children with β-thalassemia and to correlate them with various laboratory and echocardiographic parameters for early detection of cardiac involvement in these patients.

2. SUBJECTS AND METHODS

This study included 30 children with transfusion dependent β-TM who were recruited from Pediatric Hematology Clinic, Pediatric Department, Tanta University Hospital, Egypt. 30 healthy children matched for age and sex were enrolled as a control group Over a period of one year from February 2018 to February 2019.The type of study is prospective case control study.

Inclusion criteria: Children less than 18 years with a confirmed diagnosis of β-TM for more than 3 years who were on regular blood transfusion and iron chelation therapy.

Exclusion criteria: Children with congenital or acquired heart disease, with arrhythmias, taking cardiac medications or medications that prolong QT interval, with renal or liver diseases, with endocrinal disease, with metabolic disorders, and with other types of thalassemia or hemoglobinopathies.

All children enrolled in this study were subjected to the following:

- Full history taking including: Duration of the disease, frequency of blood transfusion, history of splenectomy, type of iron chelating therapy and its regularity. Complete physical examination was performed.
- Laboratory investigations: Complete blood count, serum ferritin and hemoglobin electrophoresis were done.
- Twelve leads ECG: To determine P-wave and QT interval dispersion, and to evaluate occurrence of various arrhythmias.

a) P Wave dispersion (PWD): P max, P min and Pd were measured in all 12 leads in the surface ECG recording. P wave duration was measured manually using calipers and magnifying lens to improve accuracy. The P max was defined as the longest atrial conduction time measured from the 12 leads and the P min as the shortest atrial conduction time. P wave dispersion was defined as the difference between P max and P min [10].

b) QT dispersion (QTd): QT interval was measured in all leads from the beginning of QRS complex to the end of T wave, which was defined as the return to baseline. When U wave was present, the QT interval was measured to the nadir of the curve between T and U wave. Dispersion of QT was calculated as the difference between the longest and the shortest values measured in each of the ECG leads [11].

Echocardiographic examination: Echocardiographic examination was performed using Vivid 7 ultrasound machine (GE Medical System, Horten, Norway with 4S MHz and 3 MHz multi-frequency transducers) according to the criteria of the American Society of Echocardiography. Each patient enrolled in the study had echocardiographic measurements including M Mode, 2 dimensional (2-D) echocardiography, Doppler, and colour flow mode. The following echocardiographic parameters were measured: the left ventricle (LV) septal wall thickness, LV posterior wall thickness, LV end-systolic dimension (LV ESD) and LV end-diastolic dimension (LV EDD). LV fractional shortening (FS) and LV ejection fraction percentage (LVEF %) were also measured. LV mass (LVM) and LV mass index (LVMI) were calculated where [12]:

$$LV\ M = 0.8\ [1.04\ (LVIDd + IVSd + PWd)^3 - (LVID)^3] + 0.6.$$

2.1 Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using frequency and percentages. Quantitative data were described using mean and standard deviation (M±SD). The Kolmogorov Smirnov test was used to verify the normality of distribution. Chi square test was used to compare qualitative data between the two groups; while student's t test was used to compare quantitative data between the two groups. Correlation between PWD and QTd and

various laboratory and echocardiographic data was performed using Spearman correlation coefficient. Significance of the obtained results was judged at the 5% alpha level.

3. RESULTS

The demographic data of the β-TM patients and the healthy controls are summarized in Table 1. The mean age of the β-TM group was 9.430 ± 3.112 years and 60% were female, while the mean age of the control group was 9.633 ± 3.038 years. There was no significant difference between the two groups as regards to age and sex. The systolic and diastolic pressures values were comparable in both groups, but the heart rate was significantly higher in β-TM group compared to the control group. The serum ferritin level was significantly higher in the β-TM group compared to the control group (P <0.001). Hemoglobin level was significantly lower in the β-TM group compared to the control group (P <0.001).

Table 2 showed that PWD and QTd were significantly higher in children with thalassemia compared to the control group (P = 0.029, P = 0.001 respectively).

Table 3 summarizes the echo Doppler findings in both control and β-TM groups. The β-TM group showed significantly higher LV wall thickness, IVSd (0.950±0.166), IVSs (0.863±0.103), LV IDs (2.947±0.535), LVIDd (3.983±0.456), LVM (107.267±26.736) and LVMI (106.900±22.651) in children with β-TM compared to the control group. Moreover, there was a significant decrease of LV FS (29.495±4.171) and LVEF% (60.373±8.088) in patients group compared to the control group.

Interestingly, there was a strong positive correlation between both PWD and QTd and serum ferritin, LVIDd, LVPWd, LVM and LVMI Table 4.

4. DISCUSSION

The current study showed that there was significant increase of IVSd, IVSs, LVIDd, LVIDs and LVPWd in the studied patients as compared to controls. These results come in agreement with the study done by Bosi et al. This may be explained by long standing anemia leading to hypoxia, chamber dilatation and myocardial ion dysfunction, also regular blood transfusion leads to iron overload and the heart is the most severely affected organ [13].

Also, our study showed that there was significant increase of LVM and LVMI of the thalassemic patients compared to controls. These results come in agreement with the study done by Kremastinos et al. This may be explained by iron overload which results in iron deposition in a variety of parenchymal tissues including the heart. Free iron in the cells is highly toxic and stimulates formation of free radicals, which result

Table 1. Demographic characteristics of the studied groups

	Patients (n=30)	Control (n=30)	P-value
Age (Years)	9.430 ± 3.112	9.633 ± 3.038	0.836
Gender (male: female)	12-18 40.00	14 -16 46.67	0.670
HR (bpm)	106.3 ± 10.212	98.800 ± 11.409	0.031*
Systolic blood pressure(mmHg)	98.667 ± 9.371	104.000 ±12.421	0.114
Diastolic blood pressure(mmHg)	69.667 ± 8.087	71.333 ± 6.399	0.491
Hb (g/dl)	10.017 ± 0.666	12.067 ± 0.799	<0.001*
Serum ferritin (ng/ml)	2732.333 ± 1956.141	137.667 ± 55.247	<0.001*

HR: heart rate, Hb: hemoglobin

Table 2. P-wave dispersion and QT dispersion of the studied groups

	Patients(n=30)	Control (n=30)	P-value
P-wave dispersion(ms)	33.667 ± 13.767	25.333 ± 5.164	0.029*
QT dispersion(ms)	53.000 ± 18.411	33.333 ± 4.880	0.001*

Table 3. Echocardiographic findings in the studied groups

	Patients	Control	P-value
IVSd (cm)	0.950±0.166	0.780± 0.142	0.001*
IVSs (cm)	0.863±0.103	0.780± 0.077	0.009*
LVIDd (cm)	3.983±0.456	2.213± 0.385	<0.001*
LVIDs (cm)	2.947±0.535	1.927± 0.392	<0.001*
LVPWd (cm)	0.797±0.165	0.653± 0.083	0.003*
LV mass (gm)	107.267±26.736	84.267 ± 7.294	0.002*
LV mass index (gm/m2)	106.900±22.651	89.333 ± 5.627	0.005*
EF%	60.373 ± 8.088	65.510 ± 5.430	0.032*
FS%	29.495 ± 4.171	32.123 ± 1.930	0.026*

IVSd: Interventricular septal end diastole, IVSs: Interventricular septal end systole, LVIDd: Left ventricular internal diameter end diastole, LVIDs: Left ventricular internal diameter end systole, LVPWd: Left ventricular posterior wall end diastole, EF: Ejection fraction, FS: Fractional shortening

Table 4. Correlation between PWd and QTd and various laboratory and echocardiographic data

	P wave dispersion(ms)		QT dispersion(ms)	
	R	P-value	R	P-value
Hb (g/dl)	-0.191	0.312	-0.063	0.740
Serum ferritin (ng/ml)	0.551	0.002*	0.654	<0.001*
IVSd (cm)	0.325	0.079	0.277	0.138
IVSs (cm)	0.170	0.368	0.150	0.427
LVIDd(cm)	0.406	0.026*	0.388	0.034*
LVIDs (cm)	0.224	0.234	0.209	0.267
LVPWd(cm)	0.461	0.010*	0.299	0.109
LV mass (gm)	0.412	0.024*	0.454	0.012*
LV mass index (gm/m2)	0.379	0.039*	0.456	0.011*
EF%	-0.050	0.792	-0.219	0.244
FS%	-0.334	0.072	-0.135	0.477
Duration of disease (Years)	0.129	0.496	0.222	0.239

Hb: Hemoglobin, IVSd: Interventricular septal end diastole, IVSs: Interventricular septal end systole, LVIDd: Left ventricular internal diameter end diastole, LVIDs: Left ventricular internal diameter end systole, LVPWd: Left ventricular posterior wall end diastole, EF: Ejection fraction, FS: Fractional shortening

in peroxidative damage of membrane lipids and proteins provoking cellular injury [14]. Also, this can be explained by chronic anemia which leads to hypoxia and chamber dilatation in addition to iron-mediated cardiomyopathy, leading to increased LVEDd, IVSd, LVPWd, LV mass and LV mass index [15].

The present study showed that there was a significant decrease of LV systolic function in thalassemic patients compared to controls. These results come in agreement with the study done by Vaccari et al. This may be explained by cardiac iron deposition due to long-term transfusion, which causes formation of free radicals and impairment in the function report of the mitochondrial respiratory chain and sarcoplasmic reticulum, resulting in LV systolic dysfunction that may cause heart failure [15]. Additionally, increased intracellular ferrous iron inhibits the ryanodine sensitive calcium channels of the sarcoplasmic reticulum, which modulates calcium release, resulting in further reduction of cardiac function, conduction problems, and arrhythmia development [4].

In one report it was shown that the overall cardiovascular prognosis was good if the serum ferritin is below 2500 ng/dl; the low ferritin of < 1000 ng/dl was associated with normal LVEF%, while high level was associated with low LVEF%, serum ferritin of our patients was high (mean 2732.333 ± 1956.141). This explained the significant decrease of LV systolic function in our patients [16].

In our study there was significant increase of PWD of thalassemic children compared to controls. These results come in agreement with the study done by Russo et al. This may be

explained by myocardial iron deposition, leading to atrial remodelling such as chronically elevated atrial pressure, ischemia and metabolic stress resulting in slow conduction with inhomogeneous recovery, defining a substrate for AF [17]. Regional delays in atrial depolarization might produce a heterogeneous P-wave duration. This local hypothesis explaining the interlead variation in P-waves duration is called P wave dispersion [18].

The current study showed that there was significant increase of QTd in the patients with β-TM compared to controls. These results come in agreement with the study done by Kocharian et al. there was significant increase of QT dispersion in B-TM [19]. This may be explained by alteration of ventricular wall thickening by pathological iron deposition. The iron deposition may affect the ventricular recovery times due to inhomogeneity in the repolarization time with altered QT interval and QTd. Mittal [20] also in agreement with Noori NM et al. who showed that QTd was larger in case group than in control group. This study showed acceptable sensitivity and specificity of QTd in comparison to LVMI and suggests that standard ECG can be used for early diagnosis of cardiac involvement in asymptomatic patients with thalassemia major [21].

These results are not in agreement with the study done by Garadah et al. who showed that there was no significant increase of QTd in β-TM patients, as the serum ferritin in their β-TM patients was not too high to produce significant changes in QTd in contrast to our patients which have high serum ferritin [22].

In our study there was statistically significant positive correlations between PWD and serum ferritin. These results come in agreement with the study done by Ghadiri et al. This may be explained by impaired cardiomyocyte contractility, delayed electrical conduction and increased electrophysiological heterogeneities due to iron toxicity [23].

The current study showed that there was no significant correlation between PWD and EF% and FS%. These results are not in agreement with the study done by Bosi et al. which showed that cardiac systolic function was affected by increased PWd and this may be explained by dilatation of the atria and ventricles caused by iron overload resulting in arrhythmia, valvular dysfunction, pericarditis, thickening of the muscles and finally heart failure [13].

Also our study showed that there was statistically significant positive correlations between QT dispersion and serum ferritin, LVIDd, LV mass and LV mass index. These results come in agreement with the study done by Faruqi et al., which showed that there was a positive linear correlation between QTd and serum ferritin levels. This may be explained by impaired cardiomyocyte contractility, delayed electrical conduction and increased electrophysiological heterogeneities due to iron toxicity [24] and in agreement with the study done by Azarkeivan et al. who explained this by chronic hypoxia due to chronic anemia and iron overload [25].

Also these results come in agreement with the study done by Ulger et al. which demonstrated an association between increased QTd with echocardiographic measurements such as LV mass and LV mass index in patients with thalassemia and showed increased level of these indices. This may be explained by iron overload, chronic anemia and LV hypertrophy [26].

5. CONCLUSION

PWD and QTd were prolonged in children with β-thalassemia major, denoting cardiac autonomic dysfunction with homogeneity disorders of atrial conduction and ventricular repolarization in these patients. PWD and QTd strongly correlated to serum ferritin and echocardiographic data of cardiac involvement in these patients with β-TM.

6. LIMITATIONS OF THE STUDY

Expensive cost of Holter ECG which allows 24 hours monitoring of the patients to detect any abnormality in the ECG.

CONSENT AND ETHICAL APPROVAL

Written informed consent was obtained from all parents or guardians of the children. The study was approved by the Ethical Committee of Faculty of Medicine, Tanta University. Permission number is 32010/12/17.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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