ORIGINAL RESEARCH

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The relation of fragmented QRS with tissue Doppler derived parameters in patients with b-thalassaemia major

Abstract

Purpose: The most important complication encountered in patients with b-thalassaemia major is degenerative fibrosis developing as a result of iron accumulation in myocardial tissue. Dysfunction pursues this accumulation. Recently, presence of fragmented QRS (fQRS) in ECG has been regarded as a predictor of myocardial fibrosis. We aimed in our study to investigate the frequency with which fQRS develops in patients with b-thalassaemia major and to disclose the correlation between fQRS frequency and Doppler-derived indices.

Methods: The patients with b-thalassaemia major (n=66; mean age: 23±6 years) and healthy controls (n=30; mean age: 23±4 years) were included. fQRS pattern was described as presence of RSR' manifested as existence of additional R wave and notching in either R or S waves in ECG recordings. 2D, M-mode, conventional Doppler, tissue Doppler echocardiography parameters were assessed. Mean serum ferritin levels over past 5 years were also calculated.

Results: When compared to those in control group, fQRS was more frequent in b-thalassaemia major group, indicating statistical significance (p = 0.001). While E/Em and ferritin level exhibited statistically significant increase in thalassaemia patients with fQRS (p < 0.05), the mean Em and Sm values were found to be significantly low (p < 0.05).

Conclusions: fQRS was frequently observed in the patients with b-thalassaemia major, which was of statistical significance. Tissue Doppler-derived diastolic and systolic indices in thalassaemia cases with fQRS showed statistically significant impairment compared to those without fQRS. In conclusion, fQRS may represent a novel noninvasive marker for cardiac involvement in patients with b-thalassaemia major.

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The most important complication in patients with b-thalassaemia major is cardiac dysfunction due to accumulation of iron in myocardial cells [1]. Heart failure holds the topmost position among the mortality reasons in patients with b-thalassaemia major [2]. 50% of the cases with thalassaemia major are complicated with manifest heart failure, for which reason early diagnosis may prove helpful in the treatment [3,4].

Recently, existence of fragmented QRS (fQRS) in ECG strips has been regarded as a predictor of myocardial fibrosis [5]. That fQRS proved to be a novel marker pointing out possible existence of myocardial scar was documented in the patients with coronary arterial disease [6].

Various number of parameters related to conventional Doppler echocardiography was used during investigations on the cardiac functioning in the patients with b-thalassaemia until now [7]. We used in our study the tissue Doppler imaging modality which has less technical limitations compared to conventional Doppler echocardiography.

What we aimed in this study was to disclose relationship between tissue Doppler echocardiography-derived indices and frequency of fQRS, a possibly novel indicator that may be used in the early identification of cardiac involvement in patients with b-thalassaemia major.

Methods

Study Group

A total of 96 patients were evaluated in this study who were further assigned into two subgroups as b-thalassaemia major group (n=66; mean age: 23 ± 6 years) and control group (n=30; mean age: 23 ± 4 years). Length, body surface area, blood pressure and pulse rates were recorded for each patient in the population. The exclusion criteria encompassed presence of systolic heart failure (Ejection fraction <50%), chronic atrial fibrillation, valvular heart disease, significant pulmonary hypertension (pulmonary artery systolic pressure > 50 mmHg), renal failure, cardiac medications usage and pregnancy, as well as some ECG findings like typical bundle-branch block pattern (QRS ≥ 120 ms) and incomplete right bundle-branch block. All of the patients with thalassaemia had already been on chelation therapy by oral route or subcutaneous route, or a combination of them and splenectomy had already been undertaken in diseased patients. All of the thalassaemic patients had been undergoing blood transfusion every 2-3 weeks since 1 to 3 years of age. Moreover, the mean ferritin level regarding prior 5 years in thalassaemia group was calculated. Written informed consent was obtained prior to enrollment from all of the participants. The Institutional Ethics Committee approved the study protocol

and study was conducted in accordance with the Declaration of Helsinki.

Measurement of fragmented QRS

The fQRS was defined on the routine 12-lead ECG (filter range 0.15 to 100 Hz; 25 mm/s, 10 mm/mV) as various QRS morphologies with different RSR' patterns, including the presence of an additional R wave (R') or notching in the nadir of the R wave or the S wave, or the presence of >1 R' (fragmentation) in 2 contiguous leads (figure 1). Typical bundle-branch block pattern (QRS ≥ 120 ms) and incomplete right bundle-branch block were excluded from the study. The ECG was analyzed by 2 independent readers blinded to the echocardiographic findings. The presence of fQRS in ≥ 2 contiguous lead was termed as "fQRS".

Echocardiographic data

The echocardiographic evaluations were performed following a period of rest lasting 15 minutes. In an attempt to prevent possible effects likely to be exerted by anemia in thalassaemia group, the evaluation was undertaken within a week after blood transfusion. All the population was undertaken screening via 2D echocardiography, conventional Doppler and tissue Doppler imaging. Images were acquired in the left lateral decubitus position using a Vingmed System Vivid 7 (GE Vingmed Ultrasound, Horten, Norway) with a standard 2D transducer. Left ventricular filling was evaluated by pulse wave Doppler, from the apical four chamber view, with the sample volume positioned at the tips of mitral valve. Velocities in early (E) and late (A) diastole were recorded, as well as E/A ratio, IVRT and deceleration time (DT) of E-wave. TDI utilizes modified wall filter and reduced gain in order to display myocardial velocity while avoiding blood flow detection. From four chamber view, the TDI sample volume was placed sequentially at septal and lateral sides of valvular ring. The mean values of early (Em) diastolic, late (Am) diastolic and systolic (Sm) myocardial velocities were calculated in cm/s. Furthermore, the E/Em ratio was also calculated. All measurements were obtained during end expiration, at a sweep speed of 50 m/sec. Left ventricular ejection fraction was also calculated from M-mode echocardiography. The pulmonary artery pressure was estimated from the tricuspid velocity by use of Bernoulli equation.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ SD and categorical variables are expressed as percentage. The level of signifi-

FIGURE 1. Fragmented QRS in a patient. Note notching in R wave in lead I, II, aVL, and aVF (arrows).

cance was accepted to be < 0.05 . To compare parametric continuous variables, Independent Student *t* test or Mann-Whitney U test were used. For categorical variables chi-square test or fisher-exact was used. When needed, Pearson and Spearman correlations tests were utilized so as to establish the correlation between the variables. Statistical analyses were performed using SPSS, version 17.0 for Windows.

Results

We echocardiographically analyzed 66 b-thalassaemia major patient and 30 normal subjects. There was no difference in terms of the age and the gender between two groups. Baseline clinical and hematological characteristics were compared in Table 1. Weight, height, body surface area were significantly smaller in the b-thalassaemia group. Systolic, diastolic, and mean blood pressures were lower in the b-thalassaemia group, while heart rate was slightly increased. The mean pre-transfusional hemoglobin concentration was 8.8 ± 1 g/dl, and the mean serum ferritin level was 3630 ± 1118 ng/ml. Chelation therapy had already been implemented in all patients through oral, subcutaneous routes or a combination of them. All patients had undergone splenectomy. As also depicted in Table 2, fQRS was observed significantly more frequently in the patients with b-thalassaemia (52% vs 17%, $p = 0.001$). While two dimensional echocardiography revealed significantly greater measurements related to the left atrium diameter, septal wall thickness and pulmonary artery pressure in the

group comprising thalassaemia patients compared to the control group, left ventricular ejection fraction was observed to be low, which reach the level of statistical significance. E/A ratios, IVRT and DT were similar between the groups. Em and Sm waves exhibited statistically significant decreases in tissue Doppler examination in the thalassaemia group, whereas E/Em ratio appeared to show statistically significant increase. The mean E/Em ratio and ferritin level were of statistically significant highness in the cases with fQRS ($p < 0.05$), Sm and Em levels were observed to exhibit statistically significant decrease ($p < 0.05$).

Discussion

We documented herein with this paper high incidence of fQRS in patients with b-thalassaemia major. Moreover, we identified that tissue Doppler-derived diastolic and systolic indices in the thalassaemia patients with fQRS showed greater impairment compared to those of the thalassaemia patients without fQRS, which was statistically significant.

The major etiologies in the mortality and morbidity of the patients with thalassaemia have been the cardiovascular diseases stemming from chronic anemia and related hemochromocytosis [8]. While dysfunction of the left ventricle arise from myocarditis and iron deposition in the heart, pulmonary iron deposition results in right ventricular dilatation and dysfunction secondary to resultant increase in the pulmonary arte-

TABLE 1. Demographic data related to the patients with b-thalassaemia major and control group.

Variable	Thalassaemia major (n= 66)	Control (n=30)	P
Age (years)	23 ± 6	23 ± 4	0.84
Sex (M/F)	39/27	18/12	0.93
Weight (kg)	51 ± 11	65 ± 13	<0.001
Height (m)	1.56 ± 0.10	1.69 ± 0.10	<0.001
BSA (m2)	1.53 ± 0.15	1.70 ± 0.21	<0.001
SBP (mm Hg)	100 ± 10	110 ± 14	<0.05
DBP (mm Hg)	65 ± 5	70 ± 6	<0.05
HR (beats/min)	84 ± 12	74 ± 14	<0.05
Serum ferritin (ng/ml) in mean	3630 ± 1118	87 ± 25	<0.001
Hemoglobin (g/dl)	8.8 ± 1	13.9 ± 2	<0.001
Splenectomy [n(%)]	66 (100)	-	
Iron chelating treatment (yes/no)	66/0	-	

BSA: body surface area, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate

riolar resistance [9]. However, congestive heart failure becomes evident only in the late periods in these patients [10].

Since congestive heart failure occupies the first rank for the mortality in the mentioned patients, early diagnosis of cardiac dysfunction may act as a guide in modifying the treatment [4,11]. Aggressive oral and parenteral iron chelation therapy can take role in delaying manifestation of heart failure, and even reverse it. It is for this reason that timely diagnosis of cardiac complications prior to their manifestation is crucial in the commencement of intensive chelation therapy. Kremastinos et al. reported in their study on young and adult thalassaemia patients that evaluation of diastolic functions of the heart by conventional Doppler echocardiography revealed similar parameters like E/A, IVRT and DT to those in the control group [12]. A study by Marci et al. documented similar E/A and DT values to those in the control group in the evaluation of diastolic functions of the heart via conventional Doppler echocardiography [13]. In accordance with the aforementioned data, we also did not identify any distinction with regard to conventional Doppler echocardiography findings between the groups. Moreover, we also included in our study the tissue Doppler imaging modality which is less attenuation dependent and does not necessitate a high pass filtering when compared to conventional Doppler echocardiography.

Magri et al. evaluated early cardiac diastolic functions in a study comprising younger thalassaemia patients, which revealed statistically significant decrease in Em and Sm values in thalassaemia patients [14]. A study by Parale et al. evaluating diastolic cardiac functions in pediatric thalassaemia patients documented that E/Em ratio exhibited statistically significant elevation in the thalassaemia group [15]. A study by Silvilairat et al. evaluating severity of iron deposition by tissue Doppler imaging in a pediatric patient population showed that E/Em ratio was calculated to be significantly elevated in the patients with mean ferritin level > 5000 ng/ml, whereas the amplitude of Sm wave was significantly decreased in the patients with ferritin level greater than 2500 ng/ml [16]. We identified in accordance with the previous studies that E/Em ratio showed statistically significance increase in the thalassaemia group compared with the control group in addition to Em ve Sm waves of statistically significant lower amplitude.

Magnetic resonance imaging can be implemented to estimate the amount of iron deposition in the myocardium at the time of examination. The mean serum ferritin level is highly correlated with the total amount of iron deposition in the organ and tissue, which finally leads to chronic fibrosis of the myocardium [17]. In this study, we measured the mean serum ferritin level of previous 5 years in order to better estimate the consequence of chronic iron myocardial accumulation.

TABLE 2. ECG and echocardiography related characteristics of the thalassaemia patients and normal controls.

Variable	Thalassaemia major (n= 66)	Control (n=30)	P
LAD (cm)	3.2 ± 0.4	2.8 ± 0.4	0.04
LVDD (cm)	4.1 ± 5.4	4.6 ± 4.1	0.74
LVSD (cm)	3.0 ± 5.1	2.9 ± 4.7	0.82
IVST (cm)	0.8 ± 0.07	0.8 ± 0.09	0.02
LVPT (cm)	0.8 ± 0.1	0.8 ± 0.08	0.73
LVEF (%)	61.0 ± 7.6	66 ± 4.5	<0.001
PAB (mm Hg)	28 ± 9	15 ± 3	<0.001
Conventional Doppler			
E/A	1.7 ± 0.2	1.6 ± 0.3	0.72
IVRT (msec)	78 ± 21	89 ± 19	0.58
EDEC (msec)	203 ± 45	197 ± 44	0.46
Tissue Doppler			
Em (cm/s)	10.3 ± 3.0	12.8 ± 2.0	<0.001
Am (cm/s)	7.8 ± 1.9	8.3 ± 2.1	0.64
E/Em	11.4 ± 3.9	6.6 ± 1.4	<0.001
Sm (cm/s)	6.1 ± 1.3	7.9 ± 1.4	<0.001
Fragmented QRS [n(%)]	34 (52)	5 (17)	0.001

LAD: left atrial diameter, LVDD: left ventricular diastolic diameter, LVSD: left ventricular systolic diameter, IVST: Interventricular septum thickness, LVPT: left ventricular posterior wall thickness, PAB: pulmonary artery pressure, IVRT: Isovolumetric relaxation time, EDEC: E deceleration time

Fragmented QRS complexes on a routine 12-lead electrocardiogram is suggested as novel another marker of depolarization abnormality and myocardial scar in patients with coronary artery disease [5,6,18]. It has been shown that the presence of fQRS in ≥ 2 contiguous leads predicts myocardial scar in patients with coronary artery disease. Thereby, fQRS is mainly an indicator of myocardial scar. Suggested mechanism of fQRS on ECG has been inferred from inhomogeneous activation of the ventricles due to myocardial scar [5]. Oeff et al. documented a

correlation between fQRS complexes and sustained monomorphic ventricular tachycardia [19]. A recent article pronounced fQRS complexes to be marker of Brugada syndrome and a predictor of ventricular fibrillation during follow-up [5]. In another study with regard to fQRS, Homsí et al. reported that fQRS indicated cardiac involvement in patients with sarcoidosis, which was identified via cardiac magnetic resonance imaging with Gadolinium-delayed enhancement [20]. Yüce et al. reported that fQRS was a predictor for severe mitral stenosis, decreased left ventricular ejection fraction, increased pulmonary artery pressure and poor functional capacity [21]. We found in our study that the frequency with which fQRS was present in thalassaemic patients was higher. While the mean E/Em value and ferritin levels were reported to be significantly higher in thalassaemia patient with fQRS compared with those without fQRS, Sm and Em values were found to be significantly low. We consider that myocardial iron accumulation and myocardial scarring induced by elevated ferritin levels gave rise to the development fQRS in ECG recordings.

In conclusion, it is likely that fQRS may stand for a novel indicator in the prediction of cardiac involvement in thalassaemia patients in the preclinical period. A simple and cost-effective method, this noninvasive indicator can possibly modify the chelation therapy. More randomized prospective studies have yet to be undertaken in order to evaluate further the prognostic significance of fQRS in thalassaemia patients.

Limitation

Our study was single-centre study with a relatively small sample size, and the lack of follow-up data that otherwise would have shown the significance of fQRS as a prognostic factor. **The definition of fQRS is qualitative, however for quantifying the fQRS on 12 lead ECG necessitates a specific software with an optimal low-pass filtering (100-150) (22). Fragmentation may be missed with a filter setting of 40 or 60 Hz.** Another important limitation of our study was that the mean fer-

TABLE 3. Change in ferritin level and tissue Doppler indices in accordance with accompanying fQRS in ECG.

Variable	fQRS(+)	fQRS(-)	P
Em (cm/s)	9.2 ± 2.1	10.9 ± 2.7	<0.05
Am (cm/s)	7.1 ± 1.1	7.2 ± 1.8	0.82
E/Em	13.5 ± 4.4	9.1 ± 1.9	<0.05
Sm (cm/s)	5.5 ± 1.4	6.8 ± 1.1	<0.05
Serum Ferritin (ng/ml)	4123 ± 1030	3089 ± 960	<0.05

ritin level of previous 5 years was used instead of MRI in order to visualize the iron load in the myocardium.

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