DOI: 10.4274/tpa.46.05

Assessment of diastolic function in children and adolescents with beta-thalassemia major by tissue Doppler imaging

Taner Yavuz, Kemal Nişli*, Naci Öner**, Türkan Ertuğrul*, Zafer Şalcıoğlu ***, Gönül Aydoğan***, Zeynep Karakaş****, Ümrah Aydoğan*, Aygün Dindar*, Rukiye Eker Ömeroğlu*

Abant Izzet Baysal University, Izzet Baysal Medical Faculty, Department of Pediatrics, Bolu, Turkey
**Istanbul University, Istanbul Medical Faculty, Division of Pediatric Cardiology, İstanbul, Turkey*
***Trakya University Medical Faculty, Department of Pediatrics, Edirne, Turkey*
****Bakırköy Gynecology&Obstetrics and Pediatric Diseases Education and Reseach Hospital, Hematology-Oncology Clinic, İstanbul, Turkey*
*****Istanbul University, Istanbul Medical Faculty, Division of Pediatric Hematology-Oncology, İstanbul,Turkey*

Summary

Aim: The purpose of this study was to analyze myocardial diastolic function in patients with beta-thalassemia major before development of overt cardiomyopathy using pulsed wave tissue Doppler imaging and compare data with conventional Doppler echocardiography.

Material and Method: The study included 61 beta-thalassemia major subjects (age 4 to 20 years; mean age, 10.7±4.1 years; 32 females and 29 males) with normal left ventricular function and 52 healthy control subjects matched for age and sex. All participants underwent M-mode echocardiography and left ventricular systolic function was measured; diastolic function of the right and left ventricle was analysed using tissue Doppler imaging and conventional Doppler echocardiography. SPSS for Windows 13.0 sofware program were used for statistical analysis, and student's t-test were used to compare data. This study was approved by the ethics committee of the Istanbul Medical Faculty.

Results: Body surface area was significantly smaller in the patient group than in the control group (1.0±0.2 vs. 1.2±0.3 m^2, $p<0.01$). Transmitral early peak-E velocity (E) and E/A ratio was found to be significantly increased in patients in comparison to the controls ($p<0.01$ and $p=0.039$, respectively). Late peak-A velocity (A) of mitral valve and all Doppler velocities across the tricuspid valve did not differ between groups ($p>0.05$). In patients with beta-thalassemia major, the early diastolic (Em) velocities of the myocardium at the base of the left and right ventricle, at the middle segment of the left and right ventricle, and the interventricular septum were found to be higher than controls ($p<0.05$). We also found significantly higher late diastolic (Am) velocities at the base and middle segments of RV and higher Em/Am ratio at the base of the right ventricle and at the middle segments of the left ventricle, right ventricle and the interventricular septum compared with controls ($p<0.05$).

Conclusions: These findings obtained from young aged beta-thalassemia major patients with normal ventricular systolic function were believed to arise from high preload and hyperdynamic response to chronic anemia rather than true ventricular restriction. We suggest that long-term follow-up studies should be carried out in patients with beta-thalassemia major using tissue Doppler in order to evaluate the diagnostic accuracy of this imaging technique for the diagnosis of early stages of cardiac involvement. *(Turk Arch Ped 2011; 46: 27-32)*

Key words: Beta-thalassemia, cardiomyopathy, congestive heart failure, diastolic heart faliure, echocardiography, tissue Doppler imaging

Introduction

In patients with thalassemia major, the most common cause of death is heart failure resulting from iron accumulation secondary to repeated erythrocyte transfusions and increased iron absorption (1). Cardiomyopathy can be prevented if chelation therapy is started in time (2). However, the diagnosis generally delays because clinic signs and echocardiographic evidence of cardiomyopathy occur late and iron accumulation in the heart can not be predicted (3).

Address for Correspondence: Taner Yavuz MD, Abant Izzet Baysal University, Izzet Baysal Medical Faculty, Department of Pediatrics, Bolu, Turkey
E-mail: taneryavuz@yahoo.com **Received:** 01.03.2010 **Accepted:** 16.08.2010

Iron accumulation in thalassemia shows a patchy pattern. Therefore, regional wall motion disorders develop in the early phase of the disease, although general cardiac function is normal (4). Newly developed tissue Doppler imaging intended to demonstrate cardiac dysfunction in the early phase has started to be used in various patients groups and has been shown to be superior to conventional echocardiographic methods (5-9).

In our study, we intended to investigate cardiomyopathy by tissue Doppler imaging in children with beta-thalassemia major who had not yet developed heart failure and to compare results of tissue Doppler imaging with those of conventional Doppler.

Material and Method

Sixty one children with a diagnosis of beta thalassemia major treated with regular desferroxamine in the Division of Pediatric Hematology of Istanbul University Istanbul Medical Faculty and Pediatric Hematology Clinic of Bakırköy Education and Research Hospital and 52 healthy control subjects were included in the study. Patients files of the children with beta thalassemia major and healthy subjects were started to be screened for various data as retrospective cohort and screening was continued cross-sectionally with echocardiographic measurements. Study inclusion criteria were as follows: 1. Absence of signs of heart failure, 2. Shortening fraction or ejection fraction values within normal limits, 3. Normal electrocardiogram (ECG), 4. Absence of other systemic diseases or organ dysfunction, 5. Erythrocyte transfusion during the last 1-2 weeks.

M-mode and two dimensional echocardiographic examination was performed using specific imaging techniques recommended in the guidelines and using the age appropriate probe with the echocardiography device (Vivid-3 Expert, GE, USA) in supine position or slight left lateral decubitus position while breathing confortably (10-12). Cardiac measurements were done, systolic function was evaluated and recorded. Indicator values were calculated by dividing all measurement results into body surface area. Flow velocities of atrioventricular valves (E and A) were measured in apical four chamber position by placing Doppler sample volume in such a position that it will pass through the ends of atrioventricular valves. Flow rates on three consecutive heart beats from mitral valve for left ventricle and from tricuspid valve for right ventricle were measured and average value was taken to calculate E/A ratio. Left ventricular isovolemic relaxation time was calculated on apical five chamber imaging simultaneously with ECG.

All tissue Doppler recordings were done in apical four chamber position and with pulsed wave (PW) tissue Doppler technique. Myocardial movements of left ventricular free wall, interventricular septum and right ventricular free wall were examined. Myocardial flow velocities (Em and Am) were measured firstly at three basal points and then at the middle segment between each three points and the apex. Thus recordings were done from three different myocardial segments for each subject (13).

Statistical evaluation was done using SPSS 13.0 software. Student's t test was used for comparisions. $P<0.05$ was considered to be statistically significant.

This study was approved by the ethics committee of the Istanbul Medical Faculty.

Results

Mean age of 61 subjects comprising the thalassemia major group was 10.7 ± 4.1 years (ranges, 4 -20 years). Mean age of 52 subjects in the control group was 10.7±4.1 years (ranges, 4-19 years) ($p>0.05$). No significant difference was found between thalassemia major group (32 female, 29 male) and the control group (24 female, 28 male) in terms of gender distribution ($p>0.05$). Mean values for height, weight, body mass index, body surface area and diastolic blood pressure in thalassemia major group was found to be statistically significantly lower than the control group (Table 1). In thalassemia major group, mean Hb was 9.8±1.2 g/dL (7.5-12.7), serum ferritin level was 1945±861 ng/mL (375-4900), transfusion period was 9.8±4.2 years (3-19,2) and period of chelation therapy was 6.8±4.1 years (0.3-17.9). Splenectomy was performed in 22 of the subjects (36%) (Table 1).

Ratios of left ventricular lineer values measured by M-mode echocardiography to body surface area were found to be significantly higher in thalassemia major group compared to the control group (Table 2). In thalassemia major group, early trans-mitral flow velocity E and trans-mitral E/A ratio measured by PW Doppler as diastolic values were found to be significantly higher (Table 3). When myocardial velocities were compared by segments with pulsed wave tissue Doppler, Em of left ventricular basal and middle segment, Em/Am of left ventricular middle segment, Em and Em/Am of interventricular septum, Em and Am values of right ventricular basal segment were found to be significantly higher in thalassemia major group compared to the control group (Table 4).

Discussion

In 1964, Engle et al. (14) reported that heart failure was the main cause of death in thalassemia major and death generally occured during the first year after the diagnosis of heart failure. In the period before chelation therapy, mortality rate was 58% during the first 3 months after the diagnosis of heart failure (14). With recent modern therapy possibilities survival rate reached 50% for the five-year period after the diagnosis of heart failure (15). However, cardiac causes are still responsible for 71% of deaths in patients with thalassemia major (16). When conventional

findings of heart failure are observed on echocardiography, the prognosis of cardiomyopathy is frequently fatal (17). Recently, introduction of tissue Doppler for evaluation of diastolic function indicates that significant advances will be made in terms of early diagnosis of cardiomyopathy in patients with thalassemia major (18-22). In additon, usage of T2-star imaging method showing cardiac iron load has been the most important development for early diagnosis of risk of heart-related complications in recent years (23).

In our study, ratios of left ventricular wall thicknesses and diameters to body surface area and left ventricular mass index values (left ventricular M-mode measurements) were found to be significantly higher in the subjects with thalassemia major compared to healthy controls. These values should be divided into body surface areas and index values obtained should be compared. Body surface areas in patients with thalassemia are smaller compared to their peers (11). In literature, comparisons of left ventricular M-mode measurements in patients with thalassemia and in healthy controls have been made without measuring body surface areas of the patients or without considering body surface areas. Therefore, left ventricular M-mode measurements may give different results in these studies conducted in subjects who have not yet developed heart failure (22,24-28).

Table 1. General characteristics of thalassemia major group and control group

	Thalassemia major group (n=61)	Control group (n=52)	p
Age (yıl)	10.7±4.1	10.7±4.1	>0.05
(Age range)	(4-20)	(4-19)	
Gender (K/E)	32/29	24/28	>0.05
Height (cm)	131.6±0.2	144.1±0.2	<0.01
Weight (kg)	30.8±12.1	40.6±16.6	<0.01
Systolic blood pressure (mmHg)	108.8±10.3	111.5±8.6	>0.05
Diastolic blood pressure (mmHg)	62.7±8.1	66.5±7.7	0.012
Heart rate (dk)	87.6±11.1	84.4 ±15.6	>0.05
BMI (kg/m^2)	17.0±2.3	18.5±3.0	<0.01
BSA (m^2)	1.0±0.2	1.2±0.3	<0.01
Hb (g/dL)	9.8±1.2	-	-
Ferritin (ng/mL)	1945±861	-	-
Transfusion period (years)	9.8±4.2	-	-
Chelation period (years)	6.8±4.1	-	-
Splenectomy	22 (%36)	-	-

Values are given as mean ± standard deviation. BMI: Body mass index, BSA: Body surface area

Table 2. Left ventricular M-mode echocardiographic measurements in thalassemia major group and in control group

	Thalassemia major group (n = 61)	Control group (n = 52)	p
LVESD (mm)	27.0±4.0	27.0±3.7	>0.05
LVESD / BSA	26.5±4.0	22.6±4.9	<0.01
LVESD (mm)	42.6±5.6	42.1±5.1	>0.05
LVEDD / BSA	42.1±6.6	35.3±7.7	<0.01
IST (mm)	8.0±1.9	7.4±1.5	>0.05
IST / BSA	7.8±1.6	6.2±1.3	<0.01
PWT (mm)	6.4±1.3	6.4±1.4	>0.05
PWT / BSA	6.3±1.4	5.4±1.3	<0.01
EF (%)	65.0±4.0	64.9±3.8	>0.05
SF (%)	36.6±3.0	36.0±3.4	>0.05
LVM (g)	94.9±40.7	84.7±27.1	>0.05
LVM / BSA (g/m^2)	88.4±20.6	67.6±12.4	<0.01
LVM / Height $^{2.7}$ (g/m^2)	44.1±10.6	32.1±7.9	<0.01

Values are given as mean ± standard deviation. EF: Ejection fraction, SF: Shortening fraction, IST:Interventricular septum thickness, PWT: Left ventricular posterior wall thickness, LVEDD: Left ventricular end-diastolic diameter, LVM: Left ventricular mass, LVESD: Left ventricular end-systolic diameter, BSA: Body surface area

Index values higher than healthy controls though within normal limits may be explained by loading due to chronic anemia and increase in left ventricular mass index values due to small body surface areas (27).

In literature, contradictory results have been reported in studies in which trans-mitral measurements have been made with PW Doppler in patients with thalassemia major without signs of heart failure (22,24-29). "Restrictive" diastolic dysfunction was found in some studies conducted in thalassemia major patients having normal left ventricular systolic function without signs of heart failure (24,25). In other studies, "restrictive" dysfunction was not reported, although elevation in trans-mitral E wave or differences in other diastolic indicators were found (22,26-29). In our trans-mitral PW Doppler results, E value was found to be significantly higher and E/A ratio was found to be slightly significantly higher. In addition, A value was found to be higher, though not significantly. Although increases of E and E/A values in our study suggest "restrictive" dysfunction, simultaneous decrease in A value would be expected. However, it is very well known that results obtained from trans-mitral PW Doppler measurements may be erroneous. Differences in left ventricular and left atrial pressures affect mitral flow and trans-mitral PW Doppler measurements depend on pre-load. Specifically in relaxation type diastolic dysfunction, increase in left atrial pressure leads to pseudonormalization pattern and this pseudonormal appearance can be corrected by saline infusion (30). Hyperdynamic response developing due to chronic anemia in thalassemia patients affects the results of this measurement (31). Though patient groups are similar in above mentioned reports and in our study, differences in trans-mitral PW Doppler data can be explained by being affected by preload (22,27).

Studies conducted with PW Doppler in thalassemia patients until this time have predominantly examined left ventricular function (22,24,25,27-30). Very few studies have examined right ventricular diastolic function (32-34).

Table 3. Diastolic indexes measured at atrioventricular valves by pulsed wave Doppler

		Thalassemia major group (n=61)	Control group (n=52)	p
Trans-mitral				
	İVGZ (msn)	75.5±11.0	71.5±12.7	>0.05
	E (cm/sn)	100.7±13.2	87.8±11.8	<0.01
	A (cm/sn)	55.6±9.5	52.3±10.1	>0.05
	E/A (cm/sn)	1.8±0.3	1.7±0.3	0.039
Trans-triküspit				
	E (cm/sn)	65.2±10.6	64.5±15.2	>0.05
	A (cm/sn)	44.9±8.1	41.8±11.2	>0.05
	E/A (cm/sn)	1.5±0.2	1.6±0.3	>0.05

Values are given as mean±standard deviation. A: Atrial flow velocity, E: Early diastolic flow velocity, IVRT: Isovolemic relaxation time

The first Doppler study examining right ventricular diastolic function was performed by Hahalis et al. (32) in 2001. Investigators suggested that increase in deceleration time supported an actual right ventricular dysfunction. Although right heart failure was suggested to be secondary to pulmonary hypertension in previous studies (33,34), results of recently published reports support that right heart failure develops primarily (26,32). In post-mortem examination of cardiac hemochromatosis, both ventricles were shown to be involved equally (35). When muscle cells are exposed to iron toxicity, it would not be surprising to see that the first chamber affected is the right ventricle. Relatively less number of muscle cells may not maintain normal cardiac function. Degeneration of muscle cells and development of fibrotic tissue may lead to diastolic dysfunction and a more rapid dysfunction in the right ventricle which has a thin wall. When systolic dysfunction is added to diastolic dysfunction after a

Table 4. Diastolic flow velocities of myocardial segments measured by pulsed wave tissue Doppler (cm/sn)

		Thalassemia major group (n=61)	Control group (n=52)	p
Left ventricle				
Basal				
	LVB-Em	22.5±4.4	20.6±3.7	0.020
	LVB-Am	9.9±2.7	9.4±2.4	>0.05
	LVB-Em/Am	2.4±0.5	2.3±0.6	>0.05
Middle				
	LVM-Em	18.7±3.2	16.5±3.8	<0.01
	LVM-Am	5.9±1.6	6.1±1.6	>0.05
	LVM-Em/Am	3.3±0.7	2.8±0.7	<0.01
Septum				
Basal				
	IVSB-Em	13.9±2.4	14.1±2.1	>0.05
	IVSB-Am	6.9±1.5	7.2±1.6	>0.05
	IVSB-Em/Am	2.1±0.4	2.0±0.5	>0.05
Middle				
	IVSM-Em	12.7±2.1	11.8±1.8	0.027
	IVSM-Am	5.6±0.9	5.7±1.1	>0.05
	IVSM-Em/Am	2.3±0.5	2.1±0.5	0.032
Right ventricle				
Basal				
	RVB-Em	19.1±2.9	17.4±3.2	<0.01
	RVB-Am	13.2±3.3	11.3±2.9	<0.01
	RVB-Em/Am	1.5±0.4	1.6±0.4	>0.05
Middle				
	RVM-Em	16.6±3.3	14.9±3.5	0.010
	RVM-Am	10.3±2.9	9.3±2.0	0.046
	RVM-Em/Am	1.7±0.5	1.6±0.4	>0.05

Values are given as mean±standard deviation. Am: Myocardial atrial flow velocity, Em: Early myocardial flow velocity, IVSB: Interventricular septum basal, IVSM: Interventricular septum middle, LVB: left ventricular basal, LVM: left ventricular middle, RVB: Right ventricular basal, RVM: Right ventricular middle segment.

while, the patient may present with right heart failure alone. In thalassemia major patients, rate of clinical presentation with right heart failure alone can reach a significant level, though less frequently compared to left heart failure (15). Although results of trans-tricuspid measurements were found to be slightly higher compared to the control group in our study, the difference was not statistically significant. According to the results obtained by this method we can state that right ventricular diastolic function was found to be normal in our patient group. Pulsed wave Doppler echocardiography evaluates general diastolic function of ventricles. Preload volume and pressure changes and activation of adrenergic system can prevent recognition of myocardial diastolic dysfunction by causing pseudonormalization (31). In addition, segmental effects of iron toxicity may be diffuse enough to disturb general function.

Pulsed wave tissue Doppler complements other Doppler methods and is superior in some aspects. The most important superior porperties in clinical practice are as follows: the method is not affected by preload and provides segmantary analysis of myocardial function (36). Iron accumulation in thalassemia shows a patchy pattern and regional wall motion anomalies may develop before clinical findings occur in the early phase of the disease, although general cardiac function is normal (18). When we compared segmentary measurement results obtained by PW tissue Doppler in our study with the control group, we found the following: 1) Early diastolic flow velocities were higher in all segments except for septal basal segment, 2) Late diastolic flow velocity was significantly higher only in right ventricular segments, 3) Ratio of diastolic flow velocities (Em/Am) were found to be higher only in left ventricular and septal middle segments. Apical segment is relatively constant throughout the cardiac cycle, flow velocities are low and occasionally low-resolution and low-quality images are obtained. Although we made apical measurements, we excluded these data, since they could affect the reliability of the study (37,38).

In literature, we found few studies conducted in beta thalassemia patients which can be compared with our study (18-22). Specifically, tissue Doppler examination in the study performed by Vogel et al. (18) included segmentary measurements as in our study. Early diastolic flow velocities in thalassemia patients have been found to be lower in multiple segments compared to healthy controls. In the study evaluating cardiac iron load in young beta thalassemia major patients with T2-star imaging method performed by Magri et al. (19), tissue Doppler measurements determined diastolic dysfunction specifically in the septum and in the right ventricle which was compatible with the study performed by Vogel et al. (18). In the study performed by Hamdy et al. (20) evaluating right ventricular function, abnormal relaxation type diastolic dysfunction was found to be developed in children with beta thalassemia major. In another study performed by Silvilairat et al. (21) in children with beta thalassemia, left ventricular E/Em ratio and serum ferritin levels were found to be correlated. Contrary to these studies, early diastolic flow velocities were found to be higher in multiple segments in thalassemia patients compared to healthy controls in our study. The other tissue Doppler study was performed by Iarussi et al. (22) in beta thalassemia major patients with normal systolic function and no significant difference was found in diastolic flow velocities in comparison to healthy controls. The authors explained this result by the young mean age (22±6 years) of the patient group and iron accumulation being still in the early phase. Compatible with this study, diastolic blood flow velocities were not found to be decreased in thalassemia major patients compared to healthy controls and were even more higher in our study. Our study was performed in young aged patients (mean age) 10.7±4.1 years, ranges 4-20 years). While early diastolic flow velocities were found to be decreased in thalassemia patients compared to healthy controls in the study performed by M. Vogel et al. (18), this difference was not observed in the study performed by Iarussi et al. (22) in patients of a younger age group. The results of our study performed in patients of a much younger age group support the conclusion made by Iarussi et al. (20). Diastolic blood flow velocities measured by PW tissue Doppler can be found within normal limits or even higher in beta thalassemia patients who receive appropriate chelation therapy and have not yet developed systolic dysfunction. Our study showed that hyperdynamic response developing secondary to chronic anemia in young ages in beta thalassemia major patients played a relatively predominant role compared to iron cardiomyopathy and diastolic function was not yet developed in patients receiving regular chelation therapy.

We beleive that PW tissue Doppler can be used widely as a method of early diagnosis in beta thalassemia major patients as in many other diseases due to its convenience of administration and low cost.

Conflict of interest: None declared

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