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LEFT VENTRICULAR DIASTOLIC ABNORMALITIES IN CHILDREN WITH β-THALASSEMIA MAJOR: A DOOPLER ECHOCARDIOGRAPHIC STUDY*

*Işın Yaprak MD**, Sadık Akşit MD***, Can Öztürk MD****, Ali R. Bakiler MD**
*Coşkun Dorak MD****, Meral Türker MD****

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Left ventricular filling patterns were assessed by Doppler echocardiography in 63 β-thalassemia major patients, aged for to 21 years, with no clinical evidence of congestive heart failure and 63 age- and sex-matched normal controls. The patients with β-thalassemia major were divided into three age groups, namely four to nine years (6.8 ± 1.5 years), 10-15 years (12.1 ± 1.6 years) and older than 15 years (17.3 ± 1.7 years). They were compared with age- and sex-matched normal controls in respects of Doopler diastolic indices. The ratio between the early and late (atrial) peaks of flow velocity was higher and peak flow velocity in late diastole was significantly lower in patients with β-thalassemia major as compared to controls in all three age groups ($p < .001$). As compared with the controls, peak early diastolic flow velocity was also significantly higher in the thalassemics aged 10 to 15 years (92 ± 16 vs 80 ± 12 cm/s, $P < .01$) and in those older than 15 years (95 ± 16 vs 79 ± 13 cm/s, $p < .001$). Restrictive left ventricular diastolic abnormalities were detected in a total of 34 (54%) patients with β-thalassemia major, whereas left ventricular systolic abnormalities were identified only eight (13%) of them. None of the patients without left ventricular diastolic abnormalities showed left ventricular systolic abnormalities. There was not any significant correlation between the hematologic parameters, such as mean serum ferritin, maximum serum ferritin and the number of blood units transfused, and left ventricular Doopler diastolic indices ($p > .05$). From the data presented here, we therefore conclude that left ventricular diastolic abnormalities develop in patients with β-thalassemia major in the early phase of the disease and before the apearance of systolic abnormalities, when clinical symptoms of congestive heart failure are absent.
Key words: β-thalassemia major, Doopler, echocardiography, left ventricular filling.

Congestive heart failure is the most frequent cause of death in patients with β-thalassemia major[1,2]. It has been reported in many studies that initial cardiac dysfunction can be determined in β-thalassemia major patients without clinical manifestations of heart failure by using the conventional echocardiographic/Doppler technique[3-9].

* From the Department of Pediatrics, Social Security Tepecik Teaching Hospital, İzmir.
** Associate Professor of Pediatrics, Social Security Tepecik Teaching Hospital.
*** Pediatrician, Ege University Faculty of Medicine, Bornova, İzmir.
**** Pediatrician, Social Security Tepecik Teaching Hospital.

Doppler echocardiography has been extensively used to assess left ventricular diastolic filling in patients with β-thalassemia major; however, these studies are rather conflicting[10-14]. Although some studies reported that left ventricular diastolic function was not altered in thalassemic patients[10, 11], more recent studies demonstrated that diastolic left ventricular filling abnormalities developed in the early phase of the disease in β-thalassemia major patients[12-14]. However, most of these studies were performed in adult thalassemics and, to our knowledge, there is no detailed study in the literature assessing left ventricular filling in thalassemic children in their first decade of life.

In the present study, our purpose was to investigate the left ventricular filling pattern, using Doppler echocardiography, in three different age groups of patients with β-thalassemia major who had no clinical evidence of heart failure.

Material and Methods

Sixty-three patients with β-thalassemia major without clinical signs of cardiac failure were studied by echocardiography. The patients were in the range of four to 21 years (mean, 12 ± 4 years), and 30 of them (48%) were male. None of the patients was treated with cardioactive medication. Each patient was receiving a transfusion every three to four weeks to maintain hemoglobin levels greater than 10 g/dl. Transfusion therapy had been started before the age of two years in all patients. The mean (± SD) onset of iron chelation therapy was 5.3 ± 2.5 years. For the last five years, all patients in our clinic with thalassemia major have been receiving subcutaneous deforaxime five days a week. Deferoxamine was given to each patient by subcutaneous infusion with an infusion pump for eight to 12 hours during the night at a dose of 25-50 mg/kg body weight. Prior to the last five years, the patients had received intramuscular deferoxamine three to five days a week with variable compliance.

The mean serum ferritin value in each patient was derived as the mean of six values obtained at two-month intervals during the last year. Maximum ferritin value was obtained in each patient as the highest value since the onset of transfusion therapy. Cardiac evaluation was performed 48 hours after the last transfusion, and hemoglobin levels were determined before and after transfusion in all patients.

Sixty-three age- and sex-matched normal subjects with no clinical, electrocardiographic, or echocardiographic evidence of cardiovascular disease were selected as the control group.

A Hewlett-Packard Sonos 1000 ultrasound sytem was used for the study. Two dimensional, M-mode, and Doopler echocardiographic assessments were performed using mechanical and phased-array sector scanners with 2.5-, 3.75- or 5.0-MHz transducers. Long-axis and parasternal short-axis views at the

midventricular level were used to derive the following M-mode measurements according to the criteria of the American Society of Echocardiography: left ventricular end-systolic (LVDS) and end-diastolic (LVDD) dimensions, left atrial systolic dimension (LAD), and end-systolic and end-diastolic thicknesses of interventricular septum (IVSs and IVSd) and left ventricular posterior wall (LVPWs and LVPWd)[15]. Left ventricular percentage of fractional shortening (FS) was calculated as follows: [(LVDD-LVDS)/LVDD] x 100.

A complete pulsed-wave, continuous-wave, and Doppler examinations were performed. The lowest wall filter settings were used to record flow velocities. Doppler signal, ECG lead II, and phonocardiogram were recorded on videotape simultaneously with speeds of 25, 50, and 100 mm/second.

The Doppler transmitral flow velocity profile was obtained from the apical four chamber view. In each subject, mean values were obtained by averaging at least two beats during inspiration and two beats during expiration for four to six cardiac cycles.

Peak flow velocities of the left ventricular inflow in early diastole (E) and late diastole with atrial contraction (A) were measured from the baseline to the maximum flow velocity. An E/A flow velocity ratio was calculated from each cardiac cycle. Deceleration time (DT) was measured as the distance (time) between the projection of the peak E velocity on the baseline and the point where the EF slope encounters the baseline, and the rate of deceleration of flow velocity (DR) in early diastole as the EF slope. Isovolumetric relaxation time (IVRT) was measured as the time from the onset of the aortic component of the second heart sound to the onset of diastolic flow velocity[8, 16].

Each patient and control underwent a conventional two-dimensional and transmitral Doppler flow evaluation on the same day. The echocardiographic study was performed by the same person (A.R.B.) in all patients, and Doppler tracings of patients and controls were coded. The measurements were obtained by another person (C.Ö.), who had no knowledge of the identity of the subjects. Arterial blood pressure was measured in all patients and controls at the time of the echocardiographic examination, and was within the normal range in all subjects.

Data were given as mean ± SD. Differences between study and control groups were compared using Student's t and Mann-Whitney U tests as appropriate. The relationship between hematologic data and echocardiographic findings was investigated with correlation analysis. Plus/minus two standard deviation values were calculated for echocardiographic/Doppler indices form the measurements of age- and sex-matched normal controls. If one or more Doppler variable exceeded two SD limits, the left ventricular filling pattern was accepted to be abnormal. A FS value of less than 28 percent was accepted to be evidence of left ventricular systolic abnormality. A P value of less than 0.05 was considered statistically significant.

Results

Clinical Findings

Twenty-six patients were four to nine years of age (6.8 ± 1.5 years), 23 patients 10 to 15 years (12.1 ± 1.6 years), and 14 patients older than 15 years (17.3 ± 1.7). The mean (SD) age of all the patients and controls was 12 ± 4 years. None of the patients with β-thalassemia major had clinical symptoms or signs of congestive heart failure. Thirty-three (52%) patients had a splenectomy. The hematologic profile of patients is shown in Table I. At the time of the examination, hemoglobin levels ranged from 11 to 14 g/dl (mean, 12.6 ± 0.7 g/dl). Patient and control groups were comparable with respect to systolic and diastolic blood pressure and heart rate.

Table I: Hematologic Data in Patients with β-Thalassemia Major in Three Different Age Groups*

	Age Groups (yr)			
	4-9 (n = 26)	10-15 (n = 23)	> 15 (n = 14)	Total (n = 63)
Transfusion, units/yr	22 ± 5 (14-35)	28 ± 6 (15-40)	26 ± 6 (16-36)	25 ± 6 (14-40)
Mean serum ferritin, ng/ml	3376 ± 1048 (1680-4700)	4277 ± 1468 (2340-7230)	4248 ± 1585 (2154-9340)	4884 ± 1825 (1680-9340)
Maximum serum ferritin, ng/ml	3878 ± 1226 (1845-6874)	5223 ± 1869 (2800-9340)	6195 ± 1732 (3600-8580)	4884 ± 1825 (1845-9340)
Pretransfusion hemoglobin, g/dl	9.3 ± 0.7 (8.1-10.6)	9.3 ± 0.6 (8.2-10.7)	9.6 ± 0.5 (8.7-10.6)	9.4 ± 0.6 (8.1-10.7)
Posttransfusion hemoglobin, g/dl	13.3 ± 0.8 (12.1-15.4)	12.9 ± 0.5 (12.2-14.0)	12.6 ± 0.6 (11.7-13.8)	13.0 ± 0.7 (11.7-15.4)

* The values are mean ± SD (range).

Doppler/Echo Findings

The echocardiographic measurements concerning left ventricular end-systolic and end-diastolic diameters, left atrial dimension, and the thickness of left ventricular posterior wall and interventricular septum were not different in thalassemic patients and controls. However, left ventricular FS in patients with β-thalassemia major was significantly less than that in the controls in the age groups of 10-15 years (34 ± 7% vs 39 ± 5%, $p < 0.05$) and older than 15 years (34 ± 4% vs 40 ± 5%, $p < .05$). In a total of eight (13%) patients with β-thalassemia major, fractional shortening of the left ventricle was less than 28 percent.

Left ventricular filling patterns differed substantially in the patients and controls (Tables II, III and IV). While peak flow velocity in early diastole (E) was not different in the thalassemics and controls aged four to nine years (94 ± 14 vs 92 ± 13 cm/s, $p > 0.05$), it was significantly higher in the thalassemic patients aged 10

to 15 years and older than 15 years than those in the control groups (92 ± 16 vs 80 ± 12 cm/s, $p < .01$ and 95 ± 16 vs 79 ± 13 cm/s, $p < .001$, respectively). Also, peak late diastolic flow velocity (A) was significantly lower ($p < .001$), and the ratio between the early and late peaks of flow velocity (E/A) was significantly higher ($p < .001$) in patients with β-thalassemia major than in the controls in all three age groups. Although the duration of isovolumetric relaxation time was shorter and the rate of deceleration of flow velocity after the early diastolic peak was higher in patients as compared with controls, they did not reach a statistical significance in any of the three age groups ($p > .05$). Flow velocity deceleration time was also comparable in thalassemic patients and controls ($p > .05$). Of the 63 patients with β-thalassemia major, 34 (54%) had left ventricular diastolic abnormalities, while only eight (13%) showed systolic abnormality (Table V). None of the thalassemic patients with a normal left ventricular diastolic filling pattern had a left ventricular systolic abnormality.

Table II: Echocardiographic/Doppler Data in 26 Patients with β-Thalassemia Major Aged 4-9 Years and 26 Age- and Sex-Matched Normal Controls (Mean ± SD)

Echo/Doppler Indices	Patients	Controls	P Value	Patients with Abnormal Indices, n (%)
M-mode				
LVDD (mm)	34 ± 5	33 ± 4	NS	1 (4)
LVDS (mm)	21 ± 3	20 ± 3	NS	1 (4)
FS (5)	38 ± 7	39 ± 6	NS	0 (0)
IVSs thickness (mm)	10 ± 2	11 ± 2	NS	1 (4)
IVSd thickness (mm)	6 ± 1	6 ± 1	NS	0 (0)
LVPWs thickness (mm)	10 ± 2	11 ± 2	NS	0 (0)
LVPWd thickness (mm)	6 ± 1	6 ± 1	NS	0 (0)
Doppler				
E (cm/s)	94 ± 14	92 ± 13	NS	1 (4)
A (cm/s)	43 ± 11	56 ± 9	< .001	8 (31)
E/A	2.20 ± 0.67	1.64 ± 0.21	< .001	10 (38)
DT (miliseconds)	116 ± 42	117 ± 22	NS	3 (12)
DR (cm/s^2)	643 ± 166	622 ± 164	NS	3 (12)
IVRT (miliseconds)	23 ± 12	28 ± 13	NS	2 (8)

LVDD : left ventriculardiastolic diameter.
LVDS : left ventricular systolic diameter.
FS : fractional shortening.
IVSs : interventricular septum systolic thickness.
VSd : interventricular septum diastolic thickness.
LVPWs : left ventricular posterior wall systolic thickness.
LVPWd : left ventricular posterior wall diastolic thickness.
LAD : left atrial systolic diameter.
E : peak early diastolic flow velocity.
A : peak late diastolic flow velocity.
E/A : ratio of peak flow velocity in early diastole to peak flow velocity in late diastole.
DT : flow velocity deceleration time.
DR : rate of deceleration.
IVRT : isovolumetric relaxation time.

Table III: Echocardiographic/Doppler Data in 23 Patients with β-Thalassemia Major Agend 10-15 Years and 23 Age- and Sex-Matched Normal Controls (Mean ± SD)

Echo/Doppler Indices	Patients	Controls	P Value	Patients with Abnormal Indices, n (%)
M-mode				
LVDD (mm)	39 ± 5	39 ± 4	NS	1 (4)
LVDS (mm)	26 ± 5	NS	2 (9)	
FS (%)	34 ± 7	39 ± 5	< .05	7 (30)
IVSs thickness (mm)	11 ± 2	12 ± 3	NS	1 (4)
IVSd thickness (mm)	7 ± 2	7 ± 1	NS	1 (4)
LVPWs thickness (mm)	12 ± 2	12 ± 3	NS	0 (0)
LVPWd thickness (mm)	7 ± 2	7 ± 1	NS	0 (0)
Doppler				
E (cm/s)	92 ± 16	80 ± 12	< .01	6 (26)
A (cm/s)	38 ± 9	48 ± 9	< .001	3 (13)
E/A	2.42 ± 0.63	1.67 ± 0.30	< .001	14 (61)
DT (miliseconds)	131 ± 41	134 ± 29	NS	4 (17)
DR (cm/s^2)	632 ± 179	573 ± 167	NS	5 (21)
IVRT (miliseconds)	35 ± 16	44 ± 18	NS	2 (9)

Abbreviations: See Table II.

Table IV: Echocardiographic/Doppler Data in 14 Patients with β-Thalassemia Major Older Than 15 Years and 14 Age- and Sex-Matched Normal Controls (Mean ± SD)

Echo/Doppler Indices	Patients	Controls	P Value	Patients with Abnormal Indices, n (%)
M-mode				
LVDD (mm)	44 ± 4	43 ± 2	NS	1 (7)
LVDS (mm)	29 ± 4	26 ± 4	NS	1 (7)
FS (%)	34 ± 4	40 ± 5	< .05	1 (7)
IVSs thickness (mm)	14 ± 3	14 ± 3	NS	0 (0)
IVDd thickness (mm)	8 ± 2	8 ± 1	NS	1 (7)
LVPWs thickness (mm)	14 ± 3	13 ± 2	NS	1 (7)
LVPWd thickness (mm)	8 ± 2	8 ± 1	NS	1 (7)
Doppler				
E (cm/s)	95 ± 16	79 ± 13	< .001	5 (36)
A (cm/s)	35 ± 8	46 ± 11	< .001	2 (14)
E/A	2.70 ± 0.76	1.72 ± 0.33	< .001	8 (57)
DT (miliseconds)	135 ± 34	138 ± 33	NS	1 (7)
DR (cm/s^2)	613 ± 142	558 ± 182	NS	3 (21)
IVRT (miliseconds)	38 ± 14	45 ± 11	NS	4 (29)

Abbreviations: See Table II.

Table V: Comparison of Systolic and Diastolic Indices of Left Ventricle in Patients with β-Thalassemia Major*

	Diastolic Indices		
Systolic Indices	Normal	Abnormal	Total
Normal	29 (46)	26 (41)	55 (87)
Abnormal	–	8 (13)	8 (13)
Total	29 (46)	34 (54)	63 (100)

* The values express number (%) of the patients.

There was no statistically significant correlation between hematologic data (mean serum ferritin, maximum serum ferritin, pretransfusion hemoglobin, number of blood units received) and left ventricular systolic (FS%) or diastolic (E, A, E/A, DT, DR, IVRT) indices ($p > .05$).

Discussion

Most of the previous authors investigated systolic and diastolic functions of the left ventricle in adult thalassemics. To our knowledge, there is no detailed study in the literature assessing both systolic and diastolic left ventricular functions in children with β-thalassemia major in their first decade of life.

Normal values are available for cardiac chamber dimensions measured from the two dimensional echocardiogram in adults. However, well-established normal data for cardiac chamber dimensions and Doppler diastolic indices from infancy to adulthood are not yet available. To minimize the influence of age on the Doppler diastolic indices, we divided thalassemic patients into three age groups, and compared them with age- and sex-matched normal controls.

Our study demonstrated that, in normal controls, peak early and late diastolic flow velocities and rate of deceleration of flow velocity after the early diastolic peak progressively decreased and flow velocity deceleration time and isovolumetric relaxation time progressively increased as the age of the child increased. However, while peak early diastolic flow velocity remained high in all three age groups of thalassemic children, the rate of deceleration increased with an increasing age as compared with controls. Peak late diastolic flow velocity was lower in the thalassemics than in the controls in all three age groups. This led to, in combination with higher peak early diastolic flow velocity in the thalassemics compared with controls, a greater E/A ratio in patients.

The Doppler data in our patients suggest a left ventricular restrictive abnormality characterized by increased filling in early diastole and impaired filling in late diastole, with an abnormal Doppler waveform of steeper slope of the early diastolic flow-velocity peak and decreased height of the late peak. These results are in accordance with Spirito et al.[12] who also detected restrictive diastolic abnormalities of the left ventricle in patients with β-thalassemia major, even in the early stage of the disease when iron overload had not yet caused systolic dysfunction.

When individual patient analysis was performed, in a total of 34 (54%) patients, one or more Doppler diastolic indices were beyond ± two SD limits obtained from the normal controls. The most common diastolic abnormalities were the increased ratio between early and late peaks of flow velocity and decreased late flow velocity. The E/A ratio was found to be abnormal even at an earlier stage of the disease [in 10 (38%) patients aged 4 to 9 years].

Our study also demonstrated that left ventricular systolic function in patients with β-thalassemia major was well-preserved, and became abnormal only after diastolic functions deteriorated. These results are also in accordance with the recent reports[12-14]. There were a total of eight (13%) patients with a FS value of less than 28 percent in our study.

Left ventricular and atrial dimensions and the thicknesses of IVS and LVPW were not different in thalassemic patients and controls. These findings are also in accordance with the previous studies[12-14]. Kremastinos et al.[11] also reported that these parameters become abnormal in thalassemic patients only after the clinical symptoms of congestive heart failure appear.

The pathogenesis of cardiac complications in β-thalassemia major is not yet clear. Many investigators blamed iron as the cause of cardiac abnormalities and reported that early and appropriate treatment with deferoxamine delayed cardiac complications[17-19]. Lewis et al.[6] did not determine any differences in left ventricular systolic performance between patients with β-thalassemia major and intermedia, and reported that clinical cardiac failure was the consequence of volume overload and abnormal cardiac compliance. Özbarlas et al.[20] also reported that restrictive diastolic abnormalities of the left ventricle developed in thalassemic patients when systolic functions were normal and that systolic and diastolic functions of the left ventricle were found to be comparable in the patients with thalassemia major and intermedia.

In the present study, there were not any significant correlations between hematologic data and left ventricular systolic and diastolic indices. This is in accordance with the studies of Kremastinos et al.[10, 11, 13] in which they also reported that iron overload is not the causative factor in the development of congestive heart failure but possibly only a predisposing factor in combination with others.

In conclusion, left ventricular diastolic abnormalities develop in patients with β-thalassemia major in an early stage of the disease when symptoms of congestive heart failure are absent and systolic functions are normal.

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