

# LEFT VENTRICULAR DIASTOLIC ABNORMALITIES IN $\beta$ -THALASSEMIA MAJOR WITH NORMAL SYSTOLIC FUNCTION

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## ABSTRACT

In order to identify left ventricular diastolic function in patients with beta-thalassemia major and normal systolic function by noninvasive M-mode and Doppler echocardiography, an analytic study was designed in a university hospital in Sari. We have studied 44 patients (23 men and 21 women), mean age  $15.48 \pm 2.16$  (range 12 to 20) and 43 age and sex matched control subjects. Peak flow velocity in early diastole increased in patients compared with controls ( $98 \pm 14$  vs.  $86 \pm 13$  cm/sec;  $p < 0.0001$ ), rate of deceleration of flow velocity was also increased ( $778 \pm 142$  vs.  $592 \pm 193$  cm/sec<sup>2</sup> and  $2.24 \pm 0.51$  vs.  $1.73 \pm 0.36$ , respectively;  $p < 0.0001$ ). Peak flow velocity during atrial contraction was not significantly different in patients and normal control subjects. Doppler diastolic indices had no correlation with age, serum ferritin levels and cumulative blood transfused in thalassemic patients. We concluded that left ventricular diastolic flow indices identified noninvasively by Doppler echocardiography in patients with thalassemia major are altered in an early phase, when systolic function is normal.

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**Keywords:** Thalassemia, Echocardiography, Left ventricular function.

## INTRODUCTION

In patients with thalassemia major, cardiac complications include pericarditis, arrhythmias and cardiomyopathies. Once congestive heart failure has developed, most patients die within one year.<sup>1-3</sup> The deposition of iron in the myocardium causes left ventricular dysfunction.<sup>1,3</sup> The attempts to improve the prognosis depend on the early identification of cardiac dysfunction that may be treated with large doses of iron chelating agents.<sup>4-6</sup> Left ventricular diastolic filling changes are now considered as being responsible for the symptoms before clinical deterioration in some patients.<sup>7-9</sup> Doppler echocardiography has been used to assess left ventricular diastolic filling in many cardiac diseases.<sup>10-13</sup> The aim of this study was to assess left ventricular diastolic fill-

ing in patients with thalassemia major who had no clinical symptoms of heart failure and normal left ventricular systolic function.

## MATERIAL AND METHODS

### Patients

44 patients were selected from 780 patients who are currently followed in the thalassemia clinic in our institution based on the following criteria: 1) Absence of symptoms of heart failure 2) serum Hb more than 10 g/dL 3) Normal electrocardiogram 4) Absence of cardiomegaly in chest radiography 5) Normal left ventricular cavity dimensions and systolic fractional shortening  $> 30\%$  as assessed by echocardiography. There were 23 boys and 21 girls ranging in age from 12 to 20 years

## Diastolic Abnormalities in $\beta$ -Thalassemia

**Table I.** Hematologic profile of 44 patients with thalassemia major.

	Age(yr)	Serum Hb (g/dL)	Transfusion Onset (mo)	Desferal Onset (yr)	Total Transfusion (mL)	Mean Serum Ferritin (mg/mL)
Mean $\pm$ SD	15.5 $\pm$ 2.1	12.25 $\pm$ 1.14	21.02 $\pm$ 22.16	5.78 $\pm$ 3.30	79649.43 $\pm$ 24913.42	2763.01 $\pm$ 1139.63
Range	12-20	10.2-15.7	1-96	1-13	21600-162000	200-500

(mean: 15.48 $\pm$ 2.16). Patients were receiving transfusions every 3-4 weeks to maintain Hb levels above 10 g/dL. The average cumulative transfusion loads were (79649.43 $\pm$ 24913.42). Of the 44 patients, 17 started iron chelation with deferoxamine before the age of 5 years and 27 patients started chelation after the age of 5 years. Deferoxamine dosage ranged from 25-50 mg/kg body wt. and was infused 3-6 days a week (Table I).

### Control group

43 age-matched and sex-matched normal subjects without any evidence of cardiovascular disease as assessed by clinical, electrocardiogram and echocardiography were selected as controls. The age range was 12-24 years (mean: 15.22 $\pm$ 2.18) and 21 were male.

### Echocardiography examination

M-mode and 2D and pulsed Doppler echocardiography studies were performed using a 750 Wing-Med ultrasound system. The ejection fraction and left ventricular systolic and diastolic dimensions were measured for systolic function.<sup>14</sup> The Doppler transmitral flow velocity profile was obtained from the apical four-chamber view. The following pulsed Doppler echocardiography indices were obtained:<sup>15-17</sup> Duration of the early diastolic flow velocity peak; peak of early diastolic flow velocity (E); rate of deceleration of flow velocity in early diastole (EF slope); flow velocity deceleration time (d.t.) measured as the distance between the peak of the E wave and the point where the EF slope encounters the baseline; peak flow velocity during atrial contraction (A); and ratio of the early and late peaks of flow velocity (E/A).

### Statistical analysis

Data were expressed as mean $\pm$ SD. Significance of the differences between the means was determined by using Student's t-test. A *p*-value of less than 0.05 was considered statistically significant.

## RESULTS

### Clinical findings

Hb level at the time of evaluation was 12.25 $\pm$ 1.14 g/dL ranging from 10.2 to 15.7 g/dL. Blood pressure and

heart rate were not significantly different in patients and controls (79 $\pm$ 6.6 and 79.12 $\pm$ 9.25 beats/min respectively).

### M-mode echocardiographic findings

The values of M-mode measurements are shown in Table II. Left ventricular diastolic dimension and systolic fractional shortening in the studied patients with thalassemia were within normal limits (<57 mm and >30%, respectively). Posterior free wall and left ventricular wall thickness were not significantly different in normal and patient groups.

### Doppler echocardiographic findings

Doppler echocardiographic findings in patients with thalassemia and normal controls are summarized in Table III.

The values of E and EF slope were significantly increased (*p*<0.0001) in patients with thalassemia compared with controls. The E/A ratio was also significantly higher in patients than controls (*p*<0.0001). This restrictive Doppler pattern of left ventricular filling is a sign of decreased left ventricular compliance<sup>18</sup> (Fig. 1).

Peak flow velocity during atrial contraction was not significantly different in patients and normal control subjects. Doppler diastolic indices had no correlation with age, serum ferritin levels and the cumulative blood transfused in thalassemic patients.

## DISCUSSION

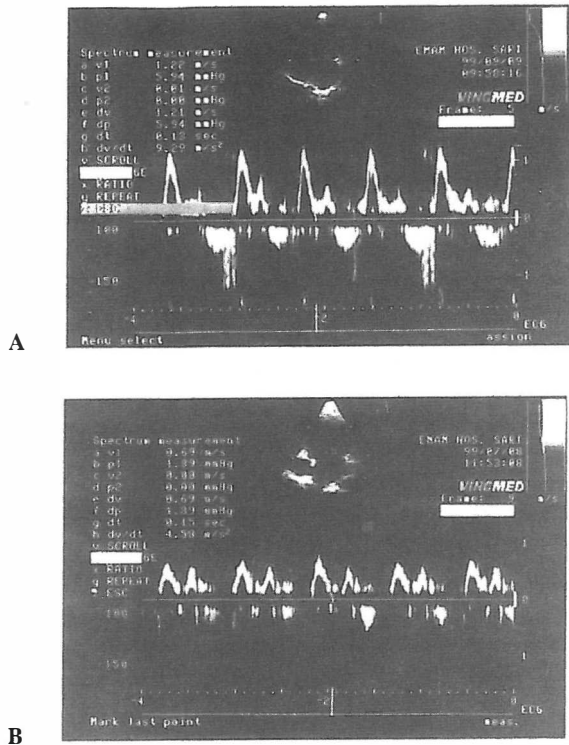
Cardiac problems are the most common cause of mortality and morbidity in patients with thalassemia

**Table II.** M-mode echocardiographic measurements in 44 patients with thalassemia major and in 43 normal control subjects.

Variables	Thalassemia		Normal	
	Mean	S.D.	Mean	S.D.
F.S.%	33.77	3.35	36.19	4.31
E.F.%	71.05	5.20	74.14	5.19
LVEDD (mm)	46.41	4.44	46.93	4.26
LVESD (mm)	30.32	3.15	29.16	3.73
P.W. (mm)	7.68	0.83	7.36	1.02

**Table III.** Doppler diastolic indices in 44 patients with thalassemia major and 43 normal control subjects.

Variable	Normal		Thalassemia	
	Mean	S.D.	Mean	S.D.
A(cm/sec)	50.73	8.24	45.55	10.59
E(cm/sec)	86.5	13.28	98.09	14.56
E/A	1.73	0.36	2.24	0.51
EF slope (cm/sec <sup>2</sup> )	592.19	104.08	778.16	142.48
Dt (msec)	145.81	26.67	126.14	19.44

**Fig. 1. A:** Abnormal Doppler transmitral in patient with thalassemia major. **Panel B:** Normal Doppler transmitral flow velocity.

major. In advanced stages these problems include left ventricular systolic dysfunction and reduced ejection fraction.<sup>13</sup> When cardiac impairment is clinically obvious, the disease is considered to be advanced.<sup>19</sup> So early detection of cardiac dysfunction is important to prevent myocardial damage. Doppler echocardiography is a noninvasive means for distinguishing normal from abnormal diastolic function in most study patients.<sup>17</sup>

In our study we used Doppler echocardiography in a group of patients with thalassemia major who were free of cardiac symptoms and had normal left ventricular systolic function. E, EF slope and the ratio between the early and late peak flow velocity were increased and flow velocity deceleration time was reduced in patients com-

pared with the normal group. These alterations are known as restrictive flow pattern.<sup>20,21</sup> Patients with such abnormalities may exhibit more severe impairment and decreased clinical functional class than those with reduction in left ventricular systolic performance.<sup>7,22</sup> Abnormalities in diastole appear earlier and may be used to differentiate different grades of myocardial dysfunction. When there is dysfunction in both diastole and systole the myocardial impairment is advanced and the prognosis is poor.<sup>23</sup> In this study left ventricular diastolic dysfunction was documented to occur earlier than systolic impairment. Deferoxamine has been known to protect the heart from damage induced by iron overload.<sup>6</sup> We compared diastolic indices in a subgroup of study patients who underwent optimal chelation treatment. In these patients, restrictive left ventricular filling was also identified. The results of this study indicate that measurement of diastolic filling parameters is a sensitive noninvasive method for identifying cardiac involvement in patients with thalassemia major when symptoms of heart failure are absent and systolic function is normal. This technique may be useful in providing a therapeutic guide to assess the efficacy of iron removal therapy.

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