

## **Echocardiographic Assessment of Cardiac Involvement in Patients with Thalassemia Major: Evidence of Abnormal Relaxation Pattern of the Left Ventricle in Children and Young Patients**

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### **Abstract**

**Background-** Cardiac involvement which leads to congestive heart failure (CHF) is a major cause of death in patients with thalassemia major due to hemosiderosis and chronic anemia. Although the left ventricular (LV) systolic function in patients with thalassemia major has been considerably studied, LV diastolic function has not been assessed adequately. In this current study we used Doppler echocardiography to assess LV function. The aim of our study is to investigate the consequences of chronic anemia and transfusional iron overload on the LV function, especially the diastolic filling pattern in patients with thalassemia major. We sought to test the hypothesis of measurement of myocardial performance index (MPI) and isovolumetric relaxation time (IVRT) in an early stage of the disease, when iron overload has not yet caused irreversible changes.

**Methods-** 65 patients with thalassemia major in New York Heart Association (NYHA) class I, II who have been treated with desferrioxamine with mean age of  $11 \pm 3$  years were randomly selected and assessed by Doppler echocardiography and the data were compared prospectively with those obtained in 48 age and sex-matched normal subjects.

**Results-** MPI was increased in thalassemic patients compared with normal control subjects ( $0.42 \pm 0.06$  vs.  $0.34 \pm 0.04$ , P value=0.015). IVRT was increased in patients vs. compared to controls ( $60 \pm 11$  msec vs.  $42 \pm 6$  msec, P value=0.020), indicating impaired relaxation in the early stage of LV diastolic dysfunction due to hemosiderosis. The peak velocity in late diastole (A) was increased in patients compared to controls ( $54 \pm 6$  cm/sec vs.  $38 \pm 4$  cm/sec, P value=0.034), while the ratio between the early and late peaks of flow velocity (E/A ratio) was reduced ( $1.3 \pm 0.2$  vs.  $1.8 \pm 0.3$ , P value=0.028). E deceleration time was increased in patients compared to controls ( $180 \pm 28$  msec vs.  $140 \pm 26$  msec, P value=0.044), whereas no difference was found in left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) in patients compared to controls (LVEF  $60 \pm 8$ , vs.  $64 \pm 6$ , P value 0.068) and (LVFS  $34 \pm 6$  vs.  $36 \pm 4$ , P value=0.072). Left ventricular end-diastolic volume (LVEDV) was increased in patients compared to controls ( $52 \pm 12$  cc/m<sup>2</sup> vs.  $38 \pm 8$  cc/m<sup>2</sup>, P value=0.012), indicating effects of chronic anemia on LV function.

**Conclusion-** The findings of this study also suggest that chelating therapy does not completely protect patients with thalassemia major from myocardial damage due to iron – related cardiac toxicity and there was no correlation between ferritin level and LV dysfunction. Evaluation of diastolic function and measurement of MPI and IVRT are simple and useful in early detection of LV dysfunction, especially in asymptomatic young patients in an early reversible stage of the disease when iron overload has not yet caused systolic dysfunction (*Iranian Heart Journal 2006; 7 (1): 31-36*).

**Key words:** myocardial performance index ■ isovolumic relaxation time ■ left ventricular end diastolic volume

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**P**ericarditis and chronic heart failure due to myocardial hemosiderosis usually occur during the second decade. The mechanisms of iron – mediated myocardial damage are related to the direct free iron effect on myocytes, increased oxidative damage to lipids and proteins and immune-mediated mechanisms.

Cardiac involvement which leads to CHF is a major cause of death in thalassemia major, with about 63.6%<sup>6</sup> due to secondary hemosiderosis and chronic anemia in two-thirds of these patients. CHF is due to the combination of systolic and diastolic dysfunction, but one-third of patients have diastolic dysfunction with preserved LV systolic function, especially in young patients.

Generally, the first manifestation in young patients is impaired LV filling pattern with evidence of abnormal relaxation pattern, while systolic function is normal and the patient is asymptomatic. There are reports<sup>5,6</sup> suggesting that if the diagnosis is made at this early stage and reversible phase, cardiac dysfunction improves after high-dose chelator therapy with desferioxamine, before substantial iron overload has occurred.

Myocardial Performance Index (MPI) is a new Doppler-derived index of combined systolic and diastolic function which is independent of heart rate, blood pressure and severity of mitral valve regurgitation and is simple, reproducible and reliable and correlates well with invasive measurements of systolic and diastolic function.<sup>4</sup>

IVRT appears to be the most accurate variable that is able to differentiate patients with early diastolic dysfunction from healthy subjects. This abnormal diastolic filling pattern could be explained by the existence of LV hypertrophy and therefore reduced LV compliance.<sup>2</sup>

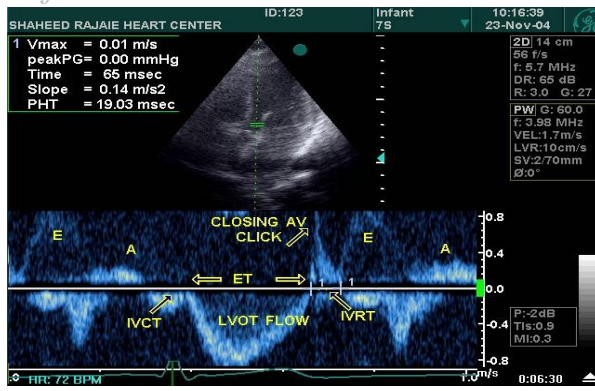
## Methods

The study group consisted of 65 randomly selected patients with thalassemia major referred to our department and compared prospectively with 48 age and sex-matched normal subjects. Heart failure was diagnosed according to NYHA criteria. Exclusion criteria were coexisting cardiac disease and NYHA functional class higher than II.

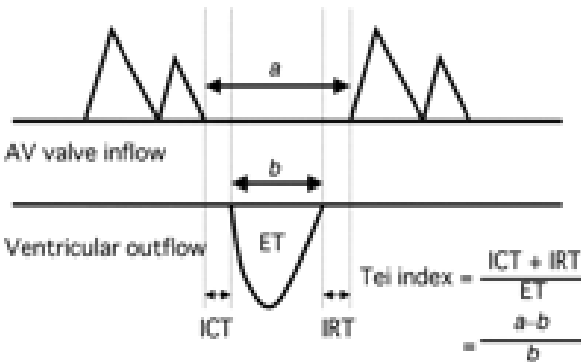
Patients' age ranged between 5 to 21 years (mean 11±3 years) and body surface areas were 0.6 to 1.45m<sup>2</sup> (mean 0.9±0.3m<sup>2</sup>). The frequency of blood transfusion varied from 2 to 5 weeks according to hemoglobin level, and iron chelating therapy with desferioxamine was modulated depending on serum ferritin level. Hemoglobin levels were 8 to 11.5 g/dL. In most patients, transfusion therapy had started before the age of one year. The follow up period ranged from 3 to 18 months. 2D, M-mode, color Doppler and continuous and pulse wave Doppler echocardiography was performed with Vivid 3 Ving-med system with a variable frequency transducer and peak E, peak A, E/A ratio and E deceleration time were measured.

The interval from R wave on ECG monitoring up to the onset of mitral opening was equal to the sum of isovolumic contraction time (IVCT), ejection time (ET) and isovolumic relaxation time (IVRT). Ejection time (ET) was measured as the time from LVOT opening to the closing click of the aortic valve. IVRT was measured as the time from the end of aortic flow to the beginning of the mitral inflow. The sum of IVCT and IVRT was obtained by subtraction of ET from total time.

The MPI measures the ratio of total isovolumic activity to the ET by this formula:  $MPI = IVCT + IVRT / ET$



A.



B.

Fig. 1 (A, B). Doppler echocardiographic view for measurement of MPI.

### Statistical analysis

Data are expressed as mean value  $\pm$  standard deviation (SD), differences between continuous variables were determined by using unpaired student's t test. A value of  $P < 0.05$  was considered statistically significant.

### Results

Patients with thalassemia major had greater LVEDD ( $4.6 \pm 0.5 \text{ cm}$  vs.  $3.4 \pm 0.3 \text{ cm}$ ,  $P$  value =  $0.016$ ) and LVEDV ( $52 \pm 12 \text{ cm}^3/\text{m}^2$  vs.  $38 \pm 8 \text{ cm}^3/\text{m}^2$ ,  $P$  value =  $0.012$ ) compared to healthy subjects whereas no difference was found in the LVEF ( $60 \pm 8$  VS.  $64 \pm 6$ ,  $P$  value =  $0/068$ ) and LVFS ( $34 \pm 6$  VS.  $36 \pm 4$ ,  $P$  value =  $0/072$ ).

The peak velocity in late diastole (peak A) was increased in patients compared with controls ( $54 \pm 6 \text{ cm/sec}$  vs.  $38 \pm 4 \text{ cm/sec}$ ,  $P$  value =  $0/034$ ) while the ratio between the early and late peak of flow velocity (E/A ratio) was reduced ( $1.3 \pm 0.2$  VS.  $1.8 \pm 0.3$ ,  $P$  value =  $0/028$ ).

E deceleration time was increased in patients compared to control subjects ( $180 \pm 28 \text{ msec}$  vs.  $140 \pm 26 \text{ msec}$ ,  $P$  value =  $0/044$ ).

IVRT was increased in patients compared with control subjects ( $60 \pm 11 \text{ msec}$  vs.  $42 \pm 6 \text{ msec}$ ,  $P$  value =  $0/020$ ).

MPI was significantly increased in patients compared with healthy subject ( $0.42 \pm 0.06$  vs  $0.34 \pm 0.04$ ,  $P$  value =  $0.015$ ).

There was no correlation between MPI and mean ferritin level in patients with thalassemia major ( $0.42 \pm 0.03$  in ferritin level under  $2000 \text{ ng/ml}$  vs.  $0.44 \pm 0.04$  in ferritin level upper  $2000 \text{ ng/ml}$ ,  $P$  value =  $0/085$ ).

Table I: Conventional 2-dimensional, M-mode echocardiography measurement in patients with thalassemia and control subjects (mean  $\pm$  SD).

Index	Thalassemic Patients No=65	Control subjects No=48	P value*
LVEDD	$4.6 \pm 0.5$	$3.4 \pm 0.3$	0/016
LVEDS	$2.9 \pm 0.4$	$2.1 \pm 0.3$	0/024
LVEDV	$52 \pm 12$	$38 \pm 8$	0/012
LVEDSV	$22 \pm 8$	$16 \pm 4$	0/032
LVFS	$34 \pm 6$	$36 \pm 4$	0/072
LVEF	$60 \pm 8$	$64 \pm 6$	0/068

\*Significant at the 0.05 level

Table II: Doppler LV diastolic parameters and time intervals in patients with thalassemia major and control subjects (Mean  $\pm$ SD)

Parameter	Patients No=65	Controls No= 48	P value*
Peak E (cm/sec)	$72 \pm 8$	$86 \pm 6$	0.054
Peak A (cm/sec)	$54 \pm 6$	$38 \pm 4$	0.034
E/A Ratio	$1.3 \pm 0.2$	$1.8 \pm 0.3$	0.028
E deceleration time (msec)	$180 \pm 28$	$140 \pm 26$	0.044
IVCT+ET+IVRT(msec)	$324 \pm 18$	$335 \pm 16$	0.084
ET (msec)	$225 \pm 18$	$234 \pm 14$	0.092
IVRT (msec)	$60 \pm 11$	$42 \pm 6$	0.020
MPI (Tei Index)	$0.42 \pm 0.06$	$0.34 \pm 0.04$	0.015

\*Significant at the 0.05 level

**Table III. Doppler LV diastolic indexes and time intervals in patients with thalassemia major according to the ferritin level ( mean  $\pm$  SD)**

Index	Ferritin level <2000 (ng/ml) No=38	Ferritin level >2000 (ng/ml) No=27	P value*
Peak E cm/sec	90 $\pm$ 8	92 $\pm$ 6	0/125
Peak A cm/sec	52 $\pm$ 8	54 $\pm$ 6	0/220
E/A Ratio	1.4 $\pm$ 0.3	1.3 $\pm$ 0.4	0/164
E deceleration time (msec)	180 $\pm$ 25	184 $\pm$ 18	0/320
IVCT + ET+ IVRT (msec)	325 $\pm$ 16	318 $\pm$ 24	0/188
ET (msec)	228 $\pm$ 14	220 $\pm$ 18	0/140
IVRT (msec)	62 $\pm$ 11	56 $\pm$ 8	0/095
Tei index (MPI)	0.42 $\pm$ 0.03	0.44 $\pm$ 0.04	0/085

\*Significant at the 0.05 level

## Discussion

Recently it has been documented that iron overload and chronic anemia are attributed to biventricular function, especially the diastolic filling pattern in patients with thalassemia major, and although LV systolic function has been considerably studied, LV diastolic function has not been assessed adequately.

There are reports<sup>5,6</sup> indicating that LV diastolic dysfunction may improve after high dose chelator therapy, thus the diagnosis should ideally be made at an early stage of LV diastolic dysfunction before substantial iron overload and the irreversible restrictive pattern of combined diastolic and systolic dysfunction has occurred.

Tei Chuwa et al (1995)<sup>3</sup> reported a non-invasive Doppler-derived interval index that incorporates both systolic and diastolic performance of the ventricles. However age and body size and severity of diastolic dysfunction affect the IVRT, but presence of increased IVRT is a strong and accurate variable in early stages of diastolic dysfunction that differentiates asymptomatic patients with early dysfunction from healthy subjects.<sup>2</sup>

Click et al.<sup>15</sup> showed that in symptomatic patients with secondary hemochromatosis, restrictive diastolic dysfunction (stage III,

IV) or decreased LV compliance pattern and markedly increased LA pressure results in shortened IVRT and greater initial transmitral gradient on high peak E velocity and increased E/A ratio and decreased E deceleration time. But in our study group, patients had no restrictive pattern and most of our patients were asymptomatic.

Olson et al<sup>17</sup> showed that iron is stored predominantly in the subepicardial layers, causing abnormal subepicardial motion observed in this study by measurement of IVRT, while LV systolic function remains unchanged, unlike a later stage of disease as the subendocardial layer is spared.

Appleton et al.<sup>18,19</sup> reported abnormalities of LV filling pattern associated with the relative degrees of abnormalities of myocardial relaxation and LV compliance.

## Conclusion

This study suggests that MPI, IVRT and diastolic inflow parameters are useful parameters in monitoring early ventricular dysfunction in young patients with thalassemia major while systolic parameters are preserved and not changed and patients are asymptomatic. Diagnosis should ideally be made at an early stage of ventricular dysfunction before substantial massive myocardial cell injury and irreversible changes have happened. Cardiac involvement in patients is multi-factorial and we need a reliable and safe method for early detection and monitoring of these patients.

Treatment of asymptomatic patients with subclinical LV dysfunction is still controversial. Oudit et al.<sup>11</sup> provide convincing evidence that L-type calcium channels (LVDCC) are a major pathway for entry of iron into cardiac myocytes. Many patients treated by calcium channel blockers may benefit from these drugs; however efficacy of the calcium channel blockers for iron overload will have to be proven in clinical trials.

**Study limitations**

This study was performed in childhood and adolescence and young adults, where disease is in its early stage and patients are asymptomatic. Age and body size strongly effect the IVRT and deceleration time in childhood and early adulthood. As diastolic function deteriorates, a transition from impaired relaxation to restrictive filling occurs. During this transition, mitral inflow pattern goes through a phase resembling a normal diastolic filling pattern referred to as the pseudo-normalized filling pattern and it represents a moderate stage of diastolic dysfunction and can be distinguished from a true normal pattern by measurement of IVRT and pulmonary vein flow velocities and tissue Doppler imaging<sup>5</sup> (TDI) to evaluate diastolic function by measuring mitral annulus velocity during diastole, reflecting the rate of changes in long axis dimension and LV volume.

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