



## Echocardiographic Findings in Thalassemia Major: A Case Report and Literature Review

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### ARTICLE INFO

#### Article Type:

Case Report

#### Article History:

Received: 12 May 2012

Accepted: 28 July 2012

ePublished: 8 Sep 2012

#### Keywords:

Thalassemia Major

Pulmonary Hypertension

Right Ventricular Dysfunction

### ABSTRACT

We introduce a 28-year-old woman with Thalassemia major whose clinical assessment, including two-dimensional Doppler echocardiography demonstrated severe left ventricular hypertrophy with severe biventricular enlargement and systolic dysfunction as well as severe diastolic dysfunction. We hereby address these issues from an echocardiographic point of view.

### Introduction

Beta-Thalassemia or Thalassemia Major (TM) is a genetic hematological disorder which is caused by reduction in synthesis of  $\beta$ -globin chain. Its main manifestations are chronic anemia with growth retardation, bone marrow expansion, extramedullary hematopoiesis, splenomegaly, greater intestinal iron absorption and hypercoagulability.<sup>1</sup> These patients are prone to having repeated blood transfusions which in turns would lead to iron deposition in the heart ultimately causing severe cardiac complications. Cardiovascular complications are still considered as the main cause of mortality and morbidity in these patients despite novel recent advances in chelation therapy. Structure and function of the heart could immensely be affected by iron deposition. According to the literature, patients with TM develop ventricular systolic and diastolic dysfunction which may eventually lead to congestive heart failure (CHF).<sup>1,2</sup>

### Case Report

The patient was a 28-year-old female who was receiving periodic transfusions with intermittent chelation therapy and came to our clinic with complaint of dyspnea on exertion (DOE) in the past two years. By the time of her referral, the patient's DOE had exacerbated and reached NYHA functional class III-IV. She was fully-evaluated and ultimately diagnosed with cardiomyopathy caused by severe Iron overload. Two-dimensional (2D) conventional, pulse Doppler transthoracic echocardiography was performed with commercial GE Vivid 7 system (Horten,

Norway) equipped with an M3S multi-frequency harmonic phased array transducer. The images were taken with the subject at rest, lying in the lateral supine position at the end of expiration. An ECG was superimposed on the images, and end-diastole was considered the peak R-wave of the ECG. The LV global systolic function was evaluated via the Modified biplane Simpson method for calculating the left ventricular ejection fraction (LVEF) by measuring the end-diastolic and end-systolic volumes in the 2D images. LV septal and posterior walls thickness were studied as well. The presence of valvular diseases, both the left and right atrial areas and volumes were evaluated via the apical four-chamber view.

The studied LV diastolic function parameters included early diastolic wave (E wave), late diastolic wave (A wave), deceleration time of E wave (DT), isovolumic relaxation time (IVRT) and E wave to A wave (E/A) ratio and Tissue Doppler imaging study. Additionally, the ratio of color M-mode flow propagation velocity to early diastolic transmitral flow velocity (E/Vp) has been introduced as a preload-independent value for estimating LV filling pressures. An E/Vp of >1.5 is highly specific and sensitive for estimating pulmonary capillary wedge pressure (PCWP) and left ventricular end-diastolic pressure. The tricuspid valve velocity in systole as an index of pulmonary artery pressure was measured using tricuspid velocity jet in modified Bernoulli equation  $\{\Delta P_{RV-RA} = 4(V_{TR})^2\}$ .<sup>3</sup>

Severe LV systolic dysfunction with a LVEF of about 20% was detected in echocardiographic study which was

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associated with significantly further LV wall thickness in posterior wall and interventricular septum; mitral regurgitation up to moderate degree was observed as well. The patient's echocardiographic data are presented in Table 1. A restrictive filling pattern in both ventricles with both ventricular systolic dysfunction were evident in this patient, also a lower right ventricular function without correlation with pulmonary artery pressures ( $\approx 35$  mmHg) was found. Significant right ventricular dysfunction was defined as free wall TDI peak systolic velocity (Sm) less than 11 cm/sec and tricuspid annular plane systolic excursion (TAPSE) less than 16 mm; these parameters were 7 cm/sec and 11 mm respectively in our patient.

Diastolic function study showed a significantly higher E wave (2 m/sec), higher E/A ratio, shorter deceleration time of E wave and shorter IVRT (50 ms) all indicating severe diastolic dysfunction (Figure 1). The ratio of E wave velocity of the mitral to the tissue Doppler of the septal mitral annulus (E/e'-ratio) was significantly higher in this patient ( $\approx 25$ ; Table 1). Finally, the left and right atrial areas and volumes were significantly higher; Vp = 25 cm/sec and E/Vp = 8 (Figure 2).

### Discussion

In this case study, higher early diastolic filling of LV and high E/A ratio were suggestive of restrictive diastolic pattern and consequently stiff LV wall. These findings are in keeping with another study by Yaprak *et al.*<sup>4</sup> who demonstrated that  $\beta$ -TM patients ( $n = 63$ ) had significantly higher E wave, E/A ratio, and lower A wave velocity, indicating restrictive pattern in 54% in the study population. Similarly, it has been reported that transmitral diastolic filling measured by Doppler in patients with  $\beta$ -TM ( $n = 32$ , none of them had heart failure) demonstrates a restrictive pattern.<sup>5</sup> This was also in line with a previous report indicating that high E/A ratio is considered as the most common finding in patients with TM.<sup>6</sup>

Iron overload is blamed to facilitate the impaired diastolic function through stiffening myocardial wall and similar to others myocardial diseases it undergoes a stage of diastolic

dysfunction before development of systolic dysfunction.<sup>7</sup> According to the previously reported studies, mean pre-transfusion hemoglobin concentration of 9.5 gm/dl in the  $\beta$ -TM is associated with an increased dimension of LV cavity and LV volume in systole and diastole as well as LV wall thickness. The increase of the volume load in these patients could be explained by Frank Starling mechanism as it is due to the increase in heart rate; this has been observed in similar patients with the increment of LV volume in chronic anemia.<sup>8</sup>

In this case study, the decreased DT time of E wave was mostly related to the amplitude of the E wave which is caused by the impaired relaxation of LV. The IVRT was also shortened which is the reflection of the impaired LV relaxation pattern most probably caused by iron overload stiffness of LV wall. Furthermore, IVRT was positively correlated with the E/Vp ratio. However, E/Vp was consistently correlated with indirect indicators of LV filling pressure with high specificity and sensitivity.

In our case, TDI peak systolic velocity (Sm) and diastolic parameter (E/Em ratio) were significantly abnormal. Marci *et al.* reported a significant association between baseline systolic velocity (Sm)  $< 7.9$  cm/s and cardiac complications ( $P < 0.05$ ). They also concluded that systolic velocity is inversely related to NT-proBNP plasmatic levels ( $P < 0.001$ ).<sup>9</sup>

Biventricular dilated cardiomyopathy is still considered as the leading cause of mortality in patients with beta-thalassemia major. A restrictive type of left ventricular cardiomyopathy or pulmonary hypertension could be seen in some patients. Surprisingly, pulmonary arterial hypertension is the main cause of heart failure in beta-thalassemia intermedia rather than thalassemia major. Pulmonary diffusion defect, hypoxia and possibly airway obstruction due to iron overload are blamed as the causes of pulmonary hypertension in the  $\beta$ -TM patients; however, as mentioned earlier, the incidence of cor pulmonale as a cause of right heart failure seems to be much lower than previously believed.<sup>2</sup>

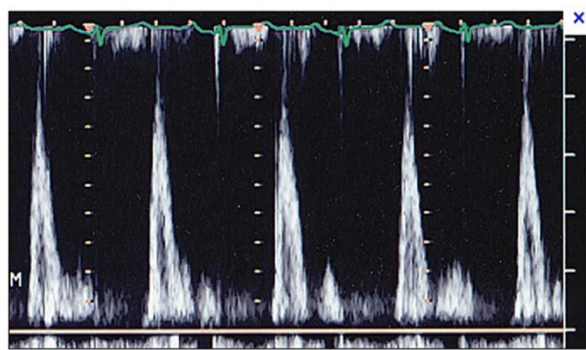


Figure 1. Mitral inflow Doppler velocity

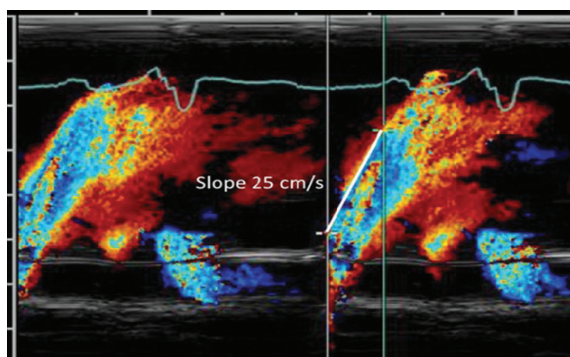


Figure 2. Color M-mode flow propagation velocity

**Table 1.** Patient's demographic and echocardiographic data

Demographic Data	
Age	56 (years)
Body surface area (Kg/M2)	1.76
Heart rate (bpm)	75
NHYA	3
QRS duration	160 msec
Echocardiographic data	
Mitral regurgitation	Up to moderate
LVEDD (mm/m2)	42
LVESD (mm/m2)	36
LVEDV (mL/m2)	187
LVESV (mL/m2)	163
LV sphericity index	1.69
LVEF (%)	20
Peak S (cm/s)	4
Peak E (cm/s)	4
E/E0 ratio	25

*Ethical issues:* The local ethics committee of Tabriz University of Medical Sciences approved the study.

*Conflict of interests:* The authors declare no conflicts of interest.

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