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Subclinical Cardiac Dysfunctions in ß-Thalassemia Patients

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ABSTRACT

Background: Prediction of potential cardiac injury from iron overload in Thalassemia patients is necessary to assess the efficacy of the treatment regimes, particularly the chelation therapy and to propose any modification.

Aim: Early detection of preclinical markers of left and right ventricular dysfunction in patients with suspected myocardial iron overload especially in the absence of clinical signs of cardiac failure by echocardiography.

Patients and Methods: Thirty six Thalassemia patients were included in the study with another 36 matched healthy control persons. M-mode, two-dimensional echo, and echodoppler were performed to both.

Results: Pulmonary artery systolic pressure (PASP), Left atrial diameter (LAD), Right ventricular diameter (RVD), Left ventricular end-diastolic diameter (LVEDD), Left ventricular end-systolic diameter (LVESD) and Ejection fraction (EF) were significantly higher in patients than controls. Also, RVD, LVEDD and LVESD were lower in thalassemia major than in thalassemia intermedia patients. Moreover, hemoglobin level correlated negatively with EF and fraction shortening (FS) and also, Serum ferritin correlated negatively with LVESD and LVEDD.

Conclusion: Echocardiography remains a valuable tool in the cardiovascular function assessment. It is particularly suited to assess both systolic and diastolic functions and pulmonary pressure so it should be included in the follow-up scheme of thalassemic patients.

Key Words: *ß-Thalassemia – Systolic functions – Diastolic functions – Pulmonary pressure – Echocardiography.*

INTRODUCTION

The complications that occur with ß-thalassemia major or intermedia are related to over stimulation of the bone marrow, ineffective erythropoiesis, and iron overload from regular blood transfusions. Iron is deposited in visceral organs (mainly the heart, liver, and endocrine glands), and most patient deaths are caused by cardiac complications **[1,2,3]**.

In patients with various types of ß-Thalassemia, mortality and morbidity vary according to the severity of the disease and the quality of care provided. Severe cases of ß-Thalassemia major are fatal if not treated. Heart failure due to severe anemia or iron overload is a common cause of death in affected persons **[2,4-6]**. Iron overload interferes in the cardiomyocytes' capacity to catalyze the formation of deleterious oxygen free radicals. The quantification of myocardial iron content is not generally easy and only T2* Cardiovascular magnetic resonance (CMR) has allowed a reliable estimation in a large number of ß-Thalassemia major patients **[7]**.

Before the availability of iron chelation therapy, the majority of transfused ß-Thalassemia major patients died, usually in the second and third decade of life, from cardiac failure that was due to iron overload **[4]**. In Thalassemia intermedia the increased gastro-intestinal absorption of iron, which is much higher than that in normal individuals is most likely due to a paradoxical suppression of Hepcidin **[8]**.

The iron induced cardiac toxicity is often complicated by arrhythmias such as extra atrial and ventricular beats, paroxysmal atrial tachycardia, flutter or fibrillation. The high output state may also be related to the incidence of arrhythmias to a lesser extent. Life threatening ventricular tachycardia is rare and often associated with reduced LV function. Short runs of non specific ventricular tachycardia are quite common and are more common with elevated cardiac iron **[2,5]**.

In patients with high output state, the heart's systolic function index and ejection fraction

(EF) is expected to be higher than in normal subjects. Thus, for TM patients, it has been recommended that a normal LVEF should be above 60% **[9]** and the degree of cardiac output (CO) increase should be taken into account when assessing EF in each individual patient **[3,10]**.

PATIENTS AND METHODS

This study was conducted on 36 patients with thalassemia major and intermedia who were attending the Clinical Hematology Unit of Assiut University Hospital during the year 2010. The standard evaluation consisted of a thorough medical history and physical examination, electrocardiography, chest radiographs, and echocardiography. Thirty-six age- and sex-matched control subjects were randomly selected; they were non-smokers and had no evidence of anemia or liver, respiratory, or cardiovascular disease. Informed consents were taken from all subjects.

Complete M-mode, 2-dimensional, and Doppler (pulsed-wave, continuous wave, and color) echocardiography was performed at rest. Cardiac dimensions were measured according to the recommendations of the American Society of Echocardiography (ASE).

Statistical analysis:

Statistical analysis was performed using the SPSS 9.0 statistical software Package. Continuous variables were expressed as mean±SD. Categorical variables were expressed as numbers and percentages. *p*-value $p>0.05$ was considered statistically insignificant, $p<0.05$ was considered statistically significant, $p<0.001$ was considered statistically highly significant. Paired-samples and independent-samples student t tests were used to compare variables between patients and controls or between patient groups. Bivariate Pearson correlation was used to investigate potential relations between variables.

RESULTS

The clinical characteristics and demographic data of the patients and controls are represented in Table (1), while laboratory data as regards peripheral blood counts and some hepatic biochemical results are presented in Table (2). Electrocardiographic (ECG) findings of the studied patients are: Twenty patients (55.6%) had ECG abnormalities as left ventricular hypertrophy was detected in 15 patients (41.7% of total), left axis deviation (LAD) and LVH in two patients (5.6%), right axis deviation (RAD) with right bundle branch block (RBBB) in another 2 patients (5.6%) and P-pulmonale and RAD in one patient (2.8%), while 16 patients (44.4%) had normal ECG findings.

Table (1): Characteristics of 36 thalassemia patients and 36 controls.

Parameters	Patients	Controls	*p*-value
Gender:			
Male	25 (69.4%)	19 (52.8%)	
Female	11 (30.6%)	17 (47.2%)	
Age (years)	22±11	25±7	
Pattern:			
Thalssemia major	17 (47.2%)		
Thalassemia intermedia	19 (52.8%)		
Positive family history	14 (38.9%)		
Splenectomy	14 (38.9%)		
Positive hepatitis C virus	5 (13.9%)		
Frequent blood transfusion	27 (75%)		
Therapy:			
Deferoprone	13 (36.1%)		
Deferoxamine	8 (22.2%)		
No treatment	15 (41.7%)		
Serum ferritin	985.4±853.7	89.8±30	<0.001***

*=$p<0.05$, ***=$p<0.001$

Table (2): Peripheral hemogram and liver functions in thalassemic patients and controls.

Parameter	Patients (n=36)	Control (n=36)	Parameter	Patients (n=36)	Control (n=36)
Total Leucocytic Count (x10^9/L)	9.2±4.7***	6.3±2	Total Proteins (g/L)	73.3±6 *	76.6±5
Hemoglobin (g/dl)	7.7±1.7***	13±1	Albumin (g/L)	40±4.5*	42±2.6
Platelets Count (x10^9/L)	468±268***	271±102	Total bilirubin (umol/L)	47.6±32.7***	11±4
Reticulocytic Count %	8.0±6***	1±.6	Indirect bilirubin (umol/l)	33±29***	8±5
			Direct bilirubin (umol/l)	14.5± 10.4***	2.9±1.3
			AST (u/l)	29.1±29.6***	12±3.4
			ALT (u/l)	31.3±34.4***	12.6±3
			ALP (u/l)	91.3±68.0*	76±25

AST: Aspartase Transaminase. * : $p<0.05$.
ALT: Alanine Transaminase. *** : $p<0.001$
ALP: Alkaline Phosphatase.

The detected morphological changes by echocardiography in thalassemic patients was mitral valve incompetence in 9 patients (25%) 4 of them (11%) had mild form and 5 patients (14%) had trace incompetence, while tricusped valve incompetence was found in 14 patients (38.9%) 2 of them (5.6%) had moderate, 4 (11.1%) had mild and 8 patients (22.2%) had trace incompetence. Mitral valve prolapse was found in 2 patients (5.6%) pericardial effusion in one (2.8%) and hypokinesia was observed also in one patient (2.8%). Patients with pulmonary hypertension were 11 (30.6%); one patient had diastolic dysfunction (2.8%).

Comparison between thalassemic patients and their controls as regards conventional echocardiographic parameters are presented in Table (3), while Table (4) and Fig. (1) show echocardiographic parameters in relation to both serum ferritin and hemoglobin levels of the studied thalassemic patients.

Table (3): Echocardiographic parameters in 36 thalassemic patients and 36 controls

Parameters	Patients	Controls	*p*-value
PASP (mmHg)	28.7±10.4	16±2	<0.001***
RVD (cm)	1.6±0.5	1.24±0.4	<0.05*
LA D (cm)	3.1±0.6	2.8±0.2	<0.05*
LVEDD (cm)	5±0.7	4±0.4	<0.001***
LVESD (cm)	3±0.6	2.7±0.3	<0.001***
LVEF (%)	64.8±7	60.8±2.5	<0.05*
LVFS (%)	35.5±5.3	33.5±5	
PWD (cm)	0.9±0.16	0.8±.13	
IVSD (cm)	0.9±0.18	0.8±.13	

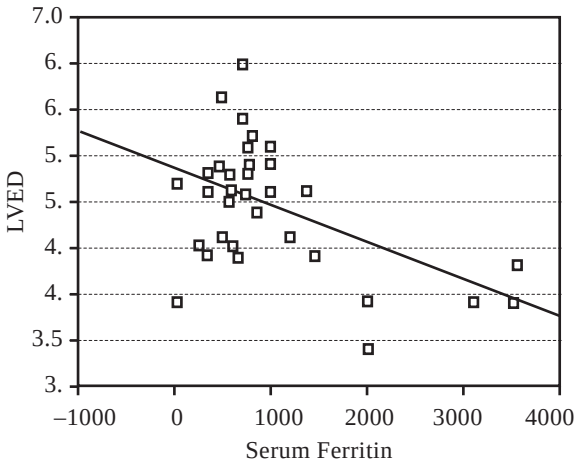
RVD : Right Ventricular Diameter.
LAD : Left Atrial Diameter.
LVEDD : Left Ventricular End Diastolic Diameter.
LVESD : Left Ventricular End Systolic Diameter.
LVEF : Left Ventricular Ejection Fraction.
LVFS. : Left Ventricular Fractional Shortening.
PWD : Diastolic Posterior Wall Thickness.
IVSD : Diastolic Interventricular Septal Thickness.
$p<0.05$: Significant*.
$p<0.001$: Highly Significant***.

Table (4): Echocardiographic parameters in correlation with serum ferritin and hemoglobin levels in 36 thalassemia patients.

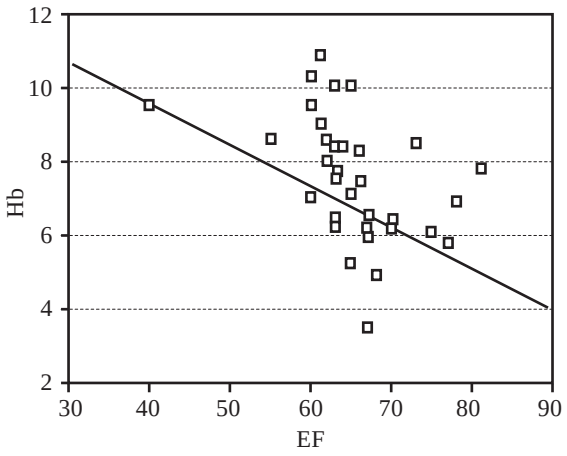
Parameters	Serum Ferritin		Hemoglobin level	
	r	*p*-value	*r*	*p*-value
PASP (mmHg)	0.091	NS	0.050	NS
RVD (cm)	–0.162	NS	0.050	NS
LA (cm)	–0.153	NS	0.080	NS
LVEDD (cm)	–0.494	<0.01*	–0.021	NS
LVESD (cm)	–0.368	<0.05*	0.188	NS
EF (%)	0.153	NS	–0.461	<0.01*
FS (%)	0.044	NS	–0.443	<0.01*
LVPWD (cm)	–0.065	NS	0.049	NS
IVSD (cm)	–0.142	NS	0.124	NS

RVD : Right ventricular diameter.
LAD : Left atrial diameter.
LVEDD : Left ventricular end diastolic diameter.
LVESD : Left ventricular end systolic diameter.
LVEF : Left ventricular ejection fraction.
LVFS : Left ventricular fractional shortening.
PWD : Diastolic posterior wall thickness.
IVSD : Diastolic interventricular septal thickness.
$p<0.05$: Significant*.
$p<0.001$: Highly significant***.
LAD : Left axis deviation.
LVH : Left ventricular hypertrophy.
RAD : Right axis deviation.
RBBB : Right bundle branch block.
PP : *p*-pulmonale

Fig. (1)



Negative correlation between serum ferritin and left ventricular end diastolic diameter (LVEDD) r=–0.494, p<0.01*.



Negative correlation between Hemoglobin (Hb) and ejection fraction (EF) r=–0.461, p=<0.01*.

DISCUSSION

Cardiac complications are still the most common cause of death in patients with thalassemia major. Iron overload causes severe and permanent cardiac damage even more than untreated anemia. Cardiac complications due to iron overload are recurrent pericarditis, heart block, ectopic ventricular beats, ventricular tachycardia, ventricular fibrillation, cardiomegaly, left ventricular (LV) dysfunction and finally heart failure resistant to any therapeutic measures **[2,3]**.

In the current study, pericarditis, was present in 2.8% of patients a figure which is less than that reported by Aessopos and his colleagues **[11]** as they stated that pericarditis was present in 8.1%; the difference may be explained by the larger sample of patients in their study. The pathogenesis of pericarditis was unclear; a likely cause was increased susceptibility to viral infection due to anemia, iron overload, and splenectomy in some patients.

As regards valvular lesions, the current study showed that valvular incompetence was recorded as trace, mild or moderate degrees. These results are in agreement with Aessopos and his colleagues **[11]**. The hyperkinetic state due to the high output, iron overloads, cardiac chamber dilatation and primarily elastic tissue abnormalities have been suggested as the responsible pathogenic mechanisms **[12]**. Although the hemodynamic consequences of these valvular abnormalities are not usually significant, they may have an additive effect when associated with other pathogenic mechanisms in the development of heart disease.

Pulmonary hypertension and right ventricular dysfunction are important components of cardiac dysfunction in *ß*-Thalassaemia. Right ventricular diameter (RVD) and pulmonary artery systolic pressure (PASP) were significantly higher in patients compared to controls with positive correlation between PASP and RVD. These results are concordant to the results obtained by both Aessopos and his colleagues **[11]** and Atichartakarn et al. **[13]**; they suggested that pulmonary hypertension is secondary to increased pulmonary vascular resistance due to a chronic low-grade hypercoagulable condition associated with thalassemia major. Pulmonary hypertension may be reversible with correction of anemia, iron chelation therapy, aspirin use and anticoagulation with warfarin. Blood transfusion to prevent pulmonary hypertension in thalassemia intermedia is currently a subject of much debate.

Also, in the current study, left ventricular end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) were significantly higher in patients with *ß*-thalassemia in relation to controls with negative correlation between LVEDD and patient's hemoglobin level. These results are coinciding with those of Aessopos et al. **[14]** and Ebru et al. **[15]**. Also, Left ventric-

ular ejection fraction (LVEF) showed statistically significant higher levels in ß-thalassemia patients than in controls with negative correlation with patient's hemoglobin levels and left ventricular fractional shortening (LVFS) which are similar to the findings of Stakos et al. **[15]**. In patients with high output state due to anemia, the heart's systolic function index and ejection fraction (EF) are expected to be higher than in normal subjects. Thus, for ß-thalassemia patients, even well transfused, it has been recommended that a normal LVEF should be above 60% **[9]** and the degree of cardiac output increase should be taken into account when assessing EF in each individual patient **[10]**. In those ß-thalassemia patients who are poorly transfused the increased cardiac output will be greater. On the other hand, Hahalis et al. **[17]** reported that their patients exhibited insignificant differences in LVEF in relation to controls, while Ebru et al. **[15]** reported that ejection fraction in their patients group was less than in control group that may be due to higher mean hemoglobin level (12±1.3 g/dl) in their ß-thalassemia patients which is not associated with increased cardiac output compared to our patients group who had lower mean hemoglobin level.

Thalassemia intermedia is a clinical definition applied to patients whose clinical phenotype is milder than that of thalassemia major. Criteria used to define thalassemia intermedia include age at presentation, hemoglobin or fetal hemoglobin levels and transfusion independence. Nevertheless, because of several factors that interact in the disease expression on molecular basis, the ß-genotype alone is not predictive of the phenotype in all cases. Although benign, the clinical course of thalassemia intermedia is characterized by several complications that can be prevented by an accurate follow-up **[18]**. In the current study, there is positive correlation between serum ferritin and PASP, EF and FS with negative correlation between serum ferritin level and left atrial diameter (LAD), right ventricular diameter (RVD), LVESD, diastolic interventricular septal thickness (IVSD) and LVEDD which are similar to that reported by Aessopos et al. **[14]**. These findings may be explained by that ß-thalassemia major patients are universally kept on an intensive transfusion regimen to maintain their hemoglobin level close to normal allowing an adequate tissue oxygen delivery. Patients with thalassemia intermedia, in contrast, remained without transfusions due to their less severe molecular defect, a fact that leads to a lower overall hemoglobin level. The resulting chronic hemolysis and ineffective erythropoiesis lead to chronic tissue hypoxia.

In conclusion: Prediction of potential cardiac injury from iron overload in thalassemia major patients is considered necessary in order to assess the efficacy of the treatment regimes, particularly the chelation therapy and to propose any modification. Echocardiography remains an indispensable tool in the cardiovascular assessment of patients, it provides many insights into cardiovascular function, and its use allows improved management of patients.

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