



ARTERIAL STIFFNESS AND CARDIAC REMODELING IN PATIENTS WITH BETA-THALASSEMIA MAJOR

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Iron overload in patients with beta-thalassemia major may result in systolic and diastolic dysfunction of the left ventricle. Although myocardial parenchymal damage occurs secondary to iron overload, atherogenic vascular complications have also been described in beta-thalassemic patients, which have been attributed to an increase in lipid peroxidation products. We enrolled thirty four patients with beta-thalassemia major (20 male and 14 female) aged 30.9±7.9 years. Left ventricular (LV) mass and systolic and diastolic function were assessed echocardiographically. Referring to the left ventricular mass and relative wall thickness (RWT), we defined four types of left ventricular remodeling: normal geometry (normal LV mass, RWT≤0.42), concentric remodeling (normal LV mass, RWT>0.42), concentric hypertrophy (increased LV mass, RWT>0.42), eccentric hypertrophy (increased LV mass, RWT≤0.42). We used tissue Doppler echocardiography for the evaluation of systolic and diastolic function. Artery stiffness was assessed by the cardio ankle vascular index (CAVI). Although the LV systolic function was apparently normal, there was a high percentage of LV remodeling 35.2%. Average LV mass indexed by body surface area was higher than normal, 106.5 ± 21.4g/m² in men and 94.7±22.5g/m² in women. R-CAVI index was 6.21± 0.85 and L-CAVI index was 6.39± 0.77. Both stiffness index correlated positively with indexed LV mass in men and women (p<0.05) and left ventricular remodeling (p<0.05). Also both stiffness index and left ventricular remodeling correlated positively with elevated LV fillig pressures (p<0.05). Nonetheless, no significant correlation existed between ferritin level and artery stiffness or left ventricular remodeling. Iron overload increases arterial stiffness and generates left ventricular remodeling in patients with β-thalassemia major, which leads to cardiac mechanical dysfunction

Keywords: beta-thalassemia major, iron overload, arterial stiffness, left ventricular remodeling

INTRODUCTION

Beta thalassemia major, autosomal recessive disease, is a blood disorder that reduces the production of hemoglobin. In beta thalassemia, there is a mutation affecting both beta globin chains leading to a lower level of hemoglobin and severe anemia. Many people with thalassemia major have severe symptoms requiring frequent blood transfusions to replenish their red blood cell supply. In time, an influx of iron-containing hemoglobin from chronic blood transfusions can lead to an accumulation of iron in the body, resulting liver, heart, and hormone problems.

Iron overload in patients with beta-thalassemia major can lead to systolic and diastolic dysfunction of the left ventricle.^{1,2} Vascular complications have also been described, among these patients and have been attributed to an increase in lipid peroxidation products³, but the mechanism of atherogenesis remains

controversial. Iron chelation with desferrioxamine in adults with coronary artery disease improves endothelium-dependent vasodilation⁴, which suggests that iron contributes to impaired nitric oxide function in atherosclerosis. Cheung YF et al have shown the first proof of improved arterial function in beta-thalassaemia patients who had received deferasirox for iron chelation⁵. Despite iron chelation, their body iron load remains significantly higher than normal. In vitro studies have shown disturbances of human vascular endothelial cell function⁶. Other structural changes involved are calcification⁷ and disruption of elastic tissue of arteries⁸, causing alteration of arterial stiffness. Arterial stiffness is related to vascular impedance and to the afterload of the left ventricle⁹. These changes in patients with β-thalassemia major can cause left ventricular remodeling, which leads to cardiac mechanical dysfunction. Up to now, however, no studies have yet been performed to correlate arterial stiffness and cardiac remodeling in patients with β-thalassemia major. In the present study we

additionally assessed the relationship between the index of vascular function, cardiac remodeling and serum ferritin level.

MATERIAL AND METHODS

Patients with β -thalassemia major, over 18 years old, were recruited from the Hematological Institute of Bucharest. Patients with severe heart failure or systemic hypertension were excluded. All subjects signed written informed consent before inclusion into the study.

The attempt procedures was performed within 1 week from transfusion in order to minimize any potential influence of anemia on the assessment of results. Body weight and height were measured, and body surface area was calculated accordingly. Assessments of left ventricular (LV) function and arterial stiffness were performed sequentially, as described below. Venous blood was then withdrawn from all subjects for measurement of hemoglobin, fasting glucose, and total cholesterol levels. We used the last values of serum ferritin level.

Echocardiographic Examination

Transthoracic echocardiography was performed using a Aloka Prosound Alpha 7 ultrasound machine. Left ventricular (LV) mass and systolic and diastolic function were assessed echo-cardiographically. We used standard parasternal short-axis view just below the tips of mitral valve leaflets for measurements of LV systolic and end-diastolic dimensions (LVEDD), left atrium size and thickness of interventricular septum (IVSd) and posterior LV wall (PWd) at diastole¹⁰. Left ventricular mass were calculated according to standard formula.¹¹ We measured left ventricular ejection fraction using the Simpson technique¹². Pulsed-wave Doppler examination was performed to obtain the following indexes of LV diastolic function²: peak mitral inflow velocities at early (E) and late (A) diastole, early deceleration time. Also we used tissue Doppler echocardiography for the evaluation of LV systolic and diastolic function: S' septal wave for the evaluation LV longitudinal systolic function, E' and A' wave for the evaluation of LV diastolic function.

Left ventricular mass and remodeling

Left ventricular (LV) mass and relative wall thickness (RWT) were calculated using the following equations: LV mass (g) = $0.8\{1.04[(LVEDD + IVSd + PWd)^3 - LVEDD^3]\} + 0.6$, $RWT = 2 * PWd / LVEDD$ ¹¹. LV mass indexed to body surface area (g/m^2) was calculated.

Referring to the left ventricular mass (Table 1) and RWT, we defined four types of ventricular remodeling: normal geometry (normal LV mass, $RWT \leq 0.42$), concentric remodeling (normal LV mass, $RWT > 0.42$), concentric hypertrophy (increased LV mass, $RWT > 0.42$), eccentric hypertrophy (increased LV mass, $RWT \leq 0.42$)¹³ (Figure 1)

	Female	Male
Reference Range	43-95	49-115
Mildly Abnormal	96-108	116-131
Moderately Abnormal	109-121	132-148
Severely Abnormal	≥ 122	≥ 149

Table 1. Reference ranges and partition values for LV Mass Indexed To BSA (g/m^2)

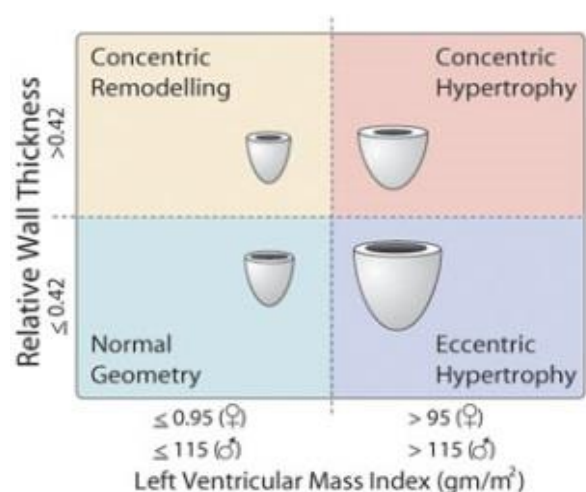


Figure 1. Types of ventricular remodeling

Left ventricular filling pressure

Tissue Doppler echocardiography of the mitral annulus during diastole has been proposed as a new method for the assessment of the cardiac function. Combining transmitral flow velocity with annular velocity (E/E') has been proposed as a tool for the assessment of LV filling pressures¹⁴. It is preferable to use the average E' velocity obtained from the septal and lateral sides of the mitral annulus for the prediction of LV filling pressures. Because septal E' is usually lower than lateral E' velocity, the E/E' ratio using septal signals is usually higher than the ratio derived from lateral E'. Using the septal E/E' ratio, a ratio < 8 is usually associated with normal LV filling pressures, whereas a ratio > 15 is associated with increased filling pressures.¹⁵ When the value is between 8 and 15, other echocardiographic indices should be used. In the range of E/E' of 8 to 15, other parameters must be applied (prior investigations pointed out the direct relationship between left atrial size and the filling pressures of the left ventricle¹⁶).

Measurement of Arterial Stiffness

Artery stiffness was assessed by the cardio ankle vascular index (CAVI). CAVI is an index reflecting the stiffness of the artery from the heart to ankles. As arteriosclerosis progresses, the CAVI value becomes higher. It is known that a decrease of the aorta elasticity causes onset of heart disease and is a factor determining the prognosis. CAVI is calculated based on the stiffness parameter β which is measured by carotid echography and represents the natural vascular stiffness independent of blood pressure. The stiffness parameter β is an index to diagnose different degrees of sclerosis of the carotid artery, from the diametrical variation and blood pressure measured by ultrasonic echography. Under the stable physiological condition, there is an exponential relation between intravascular pressure and diameter. Substitute the natural logarithm of systolic-diastolic pressure ratio ($\ln P_s/P_d$) and the arterial wall extensibility ($\Delta D/D$) for intravascular pressure and diameter. This straight slope is β . The higher the value, the lower the extensibility, that is, the stiffer the artery. We used vascular screening system 'VaSera' Fukuda Denshi, to measure index CAVI and we obtained two values: R-CAVI (right) and L-CAVI (left).

Statistical Analysis

Data are presented as mean \pm SD unless otherwise stated. Data on echocardiography and arterial stiffness were analyzed online. Pearson correlation analysis was used to assess for possible relationships between indexed LV mass or LV remodelling and arterial stiffness, between elevated LV filling pressure and arterial stiffness, between serum ferritin level and arterial stiffness. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using SPSS Version 20.0 (SPSS, Inc).

RESULTS AND DISCUSSIONS

We enrolled thirty four patients with beta-thalassemia major (20 male and 14 female), aged 30.9 \pm 7.9 years. 38,2% of patients had diabetes or impaired oral glucose tolerance. The demographic data, biochemistry, and hematologic profile of patients are summarized in Table 2.

Age (years)	30,9 \pm 7,9
Weight (kg)	56,4 \pm 9,4
Height (cm)	163,2 \pm 9,8
Haemoglobin (g/dl)	9,5 \pm 0,7
Serum ferritine (pmol/l)	944,2 \pm 746
Blood transfusion/year (U)	31,1 \pm 8,7
Years of chelator therapy	21,3 \pm 7,2
diabetes or impaired oral glucose tolerance	38,2%

Table 2. Demographic data, biochemistry and hematologic profile

Echocardiographic Findings

The parameters of left ventricular systolic and diastolic function are summarized in Table 2. All patients had normal left ventricular ejection fraction (LVEF) and normal mitral annular plane systolic excursion (MAPSE). Although the LV systolic function was apparently normal, 6 patients (17,6%) presented longitudinal systolic dysfunction by the means of S'septal evaluation. Only 14.7% of patients had diastolic dysfunction, but 44,1% of patients had elevated LV filling pressures (Table 3).

LVEF %, N \geq 60%	65,5 \pm 6,4
MAPSE(mm) N \geq 12mm	15,4 \pm 1,9
S'septal (cm/s), N \geq 7,5cm/s	7,8 \pm 1,4
% pts with S'septal <7,5 cm/s	17,6%
E (m/s)	1,05 \pm 0,16
E' (cm/s)	10,2 \pm 2,5
E/E' N<8	10,8 \pm 3,2
E/A, N 1-2	1,64 \pm 0,64
TdE, N 140-180ms	174 \pm 32,9

Table 3. Echocardiographic LV systolic and diastolic function

Left ventricular mass and arterial stiffness

Average LV mass indexed by body surface area was higher than normal, 106.5 \pm 21,4 g / m² in men and 94.7 \pm 22.5 g/m² in women. Both arterial stiffness index was higher than normal, R-CAVI index was 6.21 \pm 0.85 and L-CAVI index was 6.39 \pm 0.77 (Table 4)

LVDD(mm)	49,9 \pm 4,5
LV mass (g)	163,3 \pm 44,6
LV mass index (g/m ²)	101,6 \pm 22,3
LV mass index male(g/m ²)	106.5 \pm 21,4
LV mass index female(g/m ²)	94.7 \pm 22.5
R-CAVI	6,21 \pm 0,85
L-CAVI	6,39 \pm 0,77

Table 4. LV mass data and CAVI

Both arterial stiffness index correlated positively with LV mass, indexed to body surface area, in men and in women ($p < 0.05$) (Figure 2)

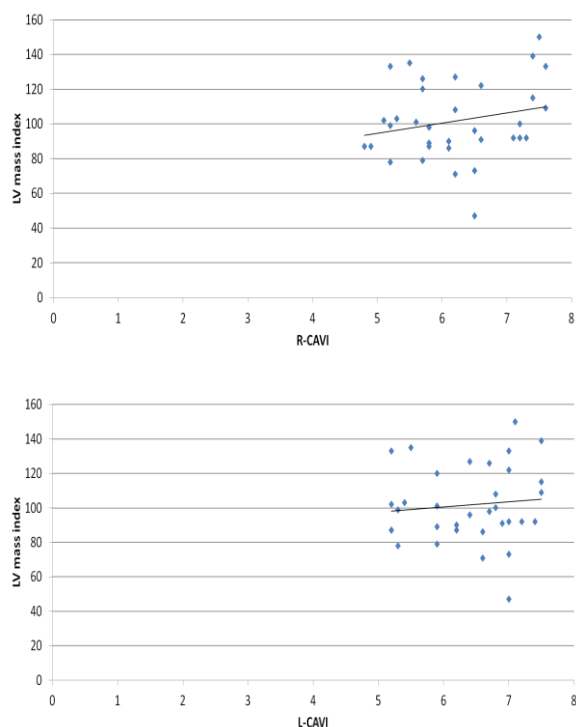


Figure 2. Scatter plots showing a positive correlation between both CAVI index and indexed left ventricular mass

Left ventricular remodeling and arterial stiffness

Although the LV systolic function was apparently normal, there was a high percentage of LV remodeling 35.2%, from which, 4 (11.7%) patients with concentric hypertrophy and 8 (23.5%) patients with eccentric hypertrophy. Both arterial stiffness index correlated positively with left ventricular remodeling (R-CAVI, $p=0.026$; L-CAVI, $p=0.05$).

Left ventricular fillig pressure, ferritin level, average haemoglobin and arterial stiffness

Both arterial stiffness index correlated positively with elevated LV fillig pressure (R-CAVI, $p=0.026$; L-CAVI, $p=0.042$). Also left ventricular remodeling correlated positively with elevated LV fillig pressure ($p=0.01$). We observed a slight correlation between average haemoglobin and arterial stiffness (R-CAVI, $p=0.07$; L-CAVI $p=0.053$) Nonetheless, no significant correlation existed between ferritin level and artery stiffness or left ventricular remodeling.

This study demonstrates increased arterial stiffness in patients with β -thalassemia major. This phenomena may occur even in the absence of cardiac dysfunction (all our patients had normal LV ejection fraction). Arterial endothelial dysfunction, corelated with arterial wall alteration, contributes to the overall increase in systemic arterial stiffness¹⁷.

Although congestive heart failure is the main cause of death in patients with β -thalassemia major, congestive heart failure due to an ischemic cause is uncommon. Their low levels of low-density lipoprotein cholesterol plasma¹⁸

could confer protection against atherogenetic risk and could explain the rather uncommon atherosclerotic complications despite the iron deposits in arteries.

Also, this study shows that in young adults with beta thalassemia major, without heart failure symptoms and normal ejection fraction, there are abnormalities of the left ventricular morfology and in systolic and diastolic function. In patients with β -thalassemia major iron overload can generates left ventricular remodelling, with LV mass higher than normal. There was a high percentage of patients with LV remodeling (35.2%), and about a quarter of patients developed the most severe form of cardiac remodeling, eccentric remodeling. We suggest that the LV remodeling that was observed in this patients may represent the first sign in the failure of the LV, and, for this reason, the strategy of treatment with chelating agents should be reconsidered.

Although all patients have normal left ventricular ejection fraction, some patients can present longitudinal systolic dysfunction, evaluated with tissue Doppler. Our study also shows a decrease in left ventricular performance, due to an increase in afterload, caused by an increase in arterial stiffness. Enrolling patients with a average age around 30 years, might be a responsible factor for the detection of changes in LV systolic function. This article demonstrates that arterial stiffness index correlated positively with indexed left ventricular mass and left ventricular remodelling.

Reports concerning left ventricular diastolic function in patients with β thalassaemia are somehow conflicting. In 1991, Spirito and colleagues reported a restrictive pattern of transmitral flow in a group of young adults with normal systolic function and no alteration in left ventricular compliance in the early stages of the disease¹⁹. In contrast, no alteration in left ventricular compliance was reported in the early stage of the disease by Kremastinos and associates^{20,21}. The restrictive pattern previously reported was explained by increased volume overload caused by the hyperdynamic state²⁰. A strongly restrictive pattern of transmitral flow was reported only in the final stages of the disease, similar with the final stages of dilated cardiomyopathies. The results of Ghaemian et al., study indicate that the 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 therapy²². In our study arterial stiffness index correlated positively with elevated left ventricular fillig pressures

Serum ferritin level does not correlate with the degree of arterial stiffness. A poor correlation between liver iron storage and serum ferritin level has been shown in patients receiving iron chelator²³. Bosi et al., found a weak but significant correlation between left ventricular ejection fraction and serum ferritin concentration, in the terms where patients with a high ferritin concentration (>2500 ng/ml) had a lower ejection fraction than patients

with a low ferritin concentration (<1000 ng/ml)²⁴. In 1994 Olivieri and colleagues, in a prospective clinical study,²⁵ found that the cardiovascular prognosis in thalassaemic patients was excellent if serum ferritin concentrations were maintained below 2500ng/ml. This value has been considered a “safe” concentration²⁵. Our study confirms this assumption, demonstrating the importance of a low ferritin concentration for the preservation of left ventricular mechanics. The high average age of our patients is another confirmation of a significant improvement not simply related to the quality of life. This probably reflects a more aggressive treatment with a low level of ferritin concentration in our study population. We suggest that a serum ferritin value of less than 1000 ng/ml should be considered the ideal goal of any therapeutic schedule. Starting this therapeutic approach in the early stages and maintaining good compliance has been documented before²⁵.

The traditional predictor of iron overload, serum ferritin, increases linearly with the number of blood transfusions and it is closely correlated with the liver iron content²⁶. Nevertheless, serum ferritin provides a simple mean for monitoring the iron chelation therapy. Liver iron concentration, on the other hand, requires an invasive procedure (liver biopsy) and it is also poorly correlated with myocardial iron content.

The development of an MRI based non-invasive method to measure tissue iron accumulation²⁷ establishing the T2* parameter, transformed the ability to adequately stratify the risk in thalassaemic patient population. Cardiac T2* has been proven to have a predictable relationship to physical iron content (study on autopsy hearts)²⁸. Increasing iron content, as shown by low T2* is associated with increasingly impaired ventricular function^{29,30}. There was a demonstrable 'dose-response', where higher T2* values were associated with decreasing risks of heart failure. Within the thalassaemia population there is a group (approximately 40%) with normal left ventricular (LV) function by conventional testing (EF), but severe iron loading, demonstrated by a low T2* (<10 ms)³⁰. These individuals pose a high risk of developing cardiac complications. Unfortunately, the availability of magnetic resonance scanners is limited and access prohibitively expensive in many populations. Clinicians may therefore need to rely on clinical judgment and, more hopefully, the use of echocardiography to help in the management of these patients.

A potential limitation to this study is the possible confounding influence of anemia. Furthermore, the fact that stiffness index, assessment which is independent of hemoglobin level, correlates significantly with PWV strengthens the evidence of a genuine increase in systemic arterial stiffness. The relevance of our findings in the pathogenesis of cardiac failure in thalassaemia becomes obvious when the heart and arterial system are considered from a mechanical perspective.

CONCLUSIONS

Iron overload increases arterial stiffness and generates left ventricular remodeling in patients with β -thalassaemia major, which leads to cardiac mechanical dysfunction. We suggest that left ventricular remodeling that was observed may represent the first step in the failure of the LV. Apart from rigorous iron chelation, interventions targeting to improve arterial dysfunction may perhaps delay deterioration of cardiac function on long-terms.

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