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The importance of cardiac tomography in the evaluation of cardiac changes and coronary atherosclerosis in patients with betathalassemia major

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Abstract. Betathalassemic patients demonstrate an increased rate of extracardiac vascular complications, but very low prevalence for coronary artery disease. Computed tomography (CT) achieves excellent tissue characterization, with high spatial resolution and has developed as a gold standard for noninvasive angiography and calcium score assessment. **Methods.** We examined 7 patients with major beta-thalassemia and 7 patients who had an indication for cardiac CT for resting ECG changes, without symptoms of angina pectoris. We investigated the coronary atherosclerosis by assessing the coronary artery calcium (CAC) and arterial stiffness. Usual tests and echocardiography measurement were performed. Cardiac computed tomography determined left ventricular mass, left ventricular ejection fraction (LVEF), coronary calcium score and coronary anatomy. An analysis of myocardial density was also performed. Artery stiffness was assessed by the cardio ankle vascular index (CAVI). **Results.** Arterial stiffness index in betathalassemic group was higher than control group, R-CAVI index was 6.21 ± 0.49 vs 5.65 ± 0.37 and L-CAVI index was 6.21 ± 0.38 vs 5.71 ± 0.31 . The assessment of systolic function by echocardiography and cardiac CT examination in the 2 groups, shows that the LVEF in the betathalassemic group was significantly lower than in the control group, which means that some patients already had cardiomyopathy. LV myocardial mass was significantly higher in the group with beta-thalassemia, which is explained by the appearance of myocardial remodeling. The calcium score in patients with major beta-thalassemia was 0 and 8.5 ± 5.9 in the control group. Only 3 patients (42,8%) in the control group had a calcium score > 10 U. No atherosclerotic lesions were observed in patients with major beta-thalassemia, whereas the control group showed mild coronary atherosclerotic lesions. If myocardial density can be determined, calcium or iron deposits can be detected in the myocardium. In patients with beta-thalassemia, the density of the myocardium was higher, both in the left ventricle (49.29 ± 8.87 HU) and in the septum (56.71 ± 8.1 HU). Calculation of Pearson's correlation coefficient revealed a good association between CT and echocardiography, reproducibility of CT was significantly higher on an intra-observer level for LVEF and LV Mass. **Conclusions:** Patients with β -thalassemia major have a similar calcium score compared to control subjects, but they have an increase in arterial stiffness. However, zero frequency of coronary heart disease, denotes coronary protection mechanisms in thalassemia, so future research should focus on the anti-atherogenic potential of blood lipids at these patients. The ability of cardiac tomography to detect calcifications and changes in myocardial density should be valued, as it can be a good tool for establishing the diagnosis of cardiomyopathy by iron loading.

Keywords. Beta-thalassemia major, cardiac tomography, calcium score, arterial stiffness

Introduction

Beta-thalassemia major is an autosomal recessive disease caused by reduced synthesis of β -globin chains, with an excess of α -globin chains, leading to inefficient erythropoiesis and chronic hemolytic anemia [1]. In major beta-thalassemia, iron overload occurs in various organs and tissues, leading most frequently to cardiovascular complications. Iron overload increases arterial stiffness and generates left ventricular remodeling in patients with major β -thalassemia, which over time leads to the occurrence of mechanical cardiac dysfunction [2]. Vascular complications in these patients have been attributed to increased lipid peroxidation products, but the mechanism of atherogenesis remains controversial [3]. Iron chelators with deferoxamine in patients with coronary heart disease improve endothelium-dependent vasodilation, thus suggesting that iron contributes to nitric oxide dysfunction in atherosclerosis.

Computed tomography (CT) achieves excellent tissue characterization, with high spatial resolution and has developed as a gold standard for noninvasive angiography and calcium score assessment. Although less widely used for functional analysis, its ability to accurately assess left ventricular (LV) function has been known for many years [4] and is recommended when other imaging techniques, especially magnetic resonance are not available.

Materials and Methods

In the current study, we recruited patients from our institution, Elias University and Emergency Hospital Bucharest, 7 patients with major beta-thalassemia, who agreed to undergo a cardiac computed tomography evaluation. A control group was chosen, including 7 subjects without a diagnosis of beta-thalassemia, but who were suspected of having cardiovascular disease due to the fact that they had resting ECG changes, without angina pectoris. The subjects in the control group were chosen to correspond with the beta-thalassemic group, in terms of age, gender and cardiovascular risk factors. Body weight and height were measured, and body surface area was calculated accordingly. At the same time their evaluation with cardiac ultrasound, cardiac tomography and determination of arterial stiffness was performed. Biological samples were also collected, which included blood counts, fasting blood glucose, cholesterol, triglycerides, and serum ferritin.

Echocardiographic Examination

Transthoracic echocardiography was performed using an Aloka Prosound Alpha 7 ultrasound machine. We used standard parasternal short-axis for measurements of LV systolic and end-diastolic dimensions (LVEDD) and for the thickness of interventricular septum (IVSd) and posterior LV wall (PWd) at diastole. We measured left ventricular ejection fraction using the Simpson technique [5]. We also used tissue Doppler echocardiography for the evaluation of LV systolic function: S' septal wave for the evaluation LV longitudinal systolic function. Left ventricular (LV) mass and relative wall thickness (RWT) were calculated using the following equations: $LV\ mass\ (g) = 0.8 \{ 1.04 [(LVEDD + IVSd + PWd)^3 - LVEDD^3] \} + 0.6$, $RWT = 2 * PWd / LVEDD$ [6]. LV mass indexed to body surface area (g/m^2) was calculated.

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 in the elasticity of the aorta causes onset of heart disease and is a determining factor for the prognosis. CAVI is

calculated based on the stiffness parameter, which represents the natural vascular stiffness independent of blood pressure. We used vascular screening system 'VaSera' Fukuda Denshi, to measure index CAVI and we obtained two values: R-CAVI (right) and L-CAVI (left).

Measurement of cardiac CT parameters

All subjects were examined with a 128-MDCT scanner (Somatom Definition AS+, Siemens) with prospective ECG triggering during a single breath hold (typically 8 s). Data were obtained from the entire heart using acquisition. All scans were read by the same experienced readers (R.O.) for the presence and amount of coronary calcification using a workstation (Synego Via Workstation). Quantification of calcium score was calculated by the Agatston method.[7] The technique proposed by Agatston for producing a standardized reproducible score has remained the standard method to the present day. The Agatston score is calculated using both the area and a weighted value related to the density of calcification. Any structure with a density greater than 130 Hounsfield units (HU) and with an area of 1 mm² or greater is quantified as a calcified focus. Presence of coronary calcification (CAC) was defined as calcium score > 10 Agatston units, and severe CAC as calcium score > 400 AU. The density of a tissue is represented using the Hounsfield scale, with water having a value of zero Hounsfield units (HU), tissues denser than water having positive values, and tissues less dense than water having negative values.

Statistical Analysis

Data are presented as mean $\pm$ SD. The Pearson correlation index was used to evaluate the possible relationships between the data obtained on echocardiography and cardiac CT in betathalassemia group and the control group. Statistical significance was defined as $P < 0.05$. Statistical analyzes were performed using SPSS Version 20.0 (SPSS, Inc).

Results

We included 7 patients with beta- thalassemia major (4 male), aged 36.8 ± 5.5 years and 7 healthy control group (4 male) 37.1 ± 4.8 years old. Patient from control group had low suspicion of cardiovascular disease by having resting ECG changes, but without describing angina pectoris. The comparison between the study and the control group for age and gender showed no significant intergroup differences. The demographic data, biochemistry, and hematologic profile of patients are summarized in [Table 1](#).

Table 1. Demographic and biochemistry data of the study's patients and control group

	β-TM I	Control
Age (years)	36.8 $\pm$ 5.5	37.1 $\pm$ 4.8
Gender male/female	4/3	4/3
Weight (kg)	61 $\pm$ 12	78.7 $\pm$ 9.8
Height (cm)	162.8 $\pm$ 8.7	175.1 $\pm$ 10.1
Hemoglobin (g/dl)	9.8 $\pm$ 0.84	14.14 $\pm$ 1.16
Diabetes or impaired oral glucose tolerance	42.9%	0
Hypertension	14.3%	28.5%
Smokers	28.5%	57.1%

Family history of cardiovascular disease	14.3%	14.3%
Dislipidemia	28.5%	57.1%

Patients with beta-thalassemia were less likely to smoke and had less frequent hyperlipidemia and hypertension compared to the control group, but were associated diabetes or impaired oral glucose tolerance (42.9%).

The mean hemoglobin level of the patients was 9.8 ± 0.84 g/dl, while the mean hemoglobin level of the control group was 14.14 ± 1.16 g/dl ($p < 0.001$). This difference of values in hemoglobin levels will determine a hyperdynamic status, with increased cardiac output. This important aspect can affect the measures' interpretation for the ventricular function.

All patients with thalassemia were receiving oral iron chelators regularly (deferasirox) and they were compliant to treatment, but the mean serum ferritin in the thalassemic patients was high. It is an almost satisfactory value, the gold standard being below 1000 ng/ml, which shows the effectiveness of chelation treatment. Most of the patients had ferritin over 1000 ng/ml (57.1%). We observed that the patients are treated since preschool with iron chelators.

Table 2. Data for the betathalassemic patients

Hemoglobin (g/dl)	9.8 ± 0.84
Serum ferritin (ng/ml)	1220 ± 664.7
Blood transfusion(U)/year	41.1 ± 8.1
Years of chelator therapy (years)	25.1 ± 7.7

Arterial stiffness findings

Arterial stiffness index in betathalassemic group was higher than control group, R-CAVI index was 6.21 ± 0.49 vs 5.65 ± 0.37 and L-CAVI index was 6.21 ± 0.38 vs 5.71 ± 0.31 .

Table 3. CAVI data

	β-TM	Control	P value
R-CAVI	6.21 ± 0.49	5.65 ± 0.37	<0.05
L-CAVI	6.21 ± 0.38	5.71 ± 0.31	<0.05

Echocardiographic Findings

The assessment of systolic function by left ventricular ejection fraction (LVEF) in the 2 groups shows that the LVEF in the betathalassemic group was significantly lower than in the control group ($56.2 \pm 7.2\%$ vs. $60.5 \pm 3\%$, $p < 0.05$), which means that some patients already had cardiomyopathy. In contrast, myocardial mass was significantly higher in the group with beta-thalassemia (105.8 ± 22.4 g vs. 73.7 ± 12.8 g, $p < 0.05$), which is explained by the appearance of myocardial remodeling, as well as the early phase of cardiomyopathy by iron loading [8].

Evaluation of left ventricular systolic function by tissue Doppler imaging, using the septal S 'wave, shows a significant decrease in the study group compared to control group (0.7 ± 1.0 cm/s vs. 10 ± 1.7 cm/s, $p < 0.05$). No differences were observed analyzing the longitudinal systolic function parameter MAPSE (mitral annular plane systolic excursion).

Table 4. Echocardiographic LV systolic function betathalassemia group and control subjects.

	β -TM	Control	P value
LVEF %, $N \geq 60\%$	56.2 ± 7.2	60.5 ± 3	<0.05
MAPSE(mm) $N \geq 12$ mm	16 ± 3	15.4 ± 1.0	>0.05
S'septal (cm/s), $N \geq 7.5$ cm/s	7 ± 1.0	10.4 ± 1.7	<0.05

LVEF – left ventricle ejection fraction, S' septal - systolic myocardial velocities at the basal mitral annulus of the septal wall, mitral annular plane systolic excursion (MAPSE)

Cardiac CT findings

No complications occurred during CT imaging. No patient was excluded due to ECG triggering artifacts. All patients had a regular sinus rhythm with a mean HR of 62 ± 10 bpm (range: 53-76 bpm) during multislice CT. The time needed to complete CT examination took about 5 ± 3 min.

The ejection fraction assessed by cardiac CT examination was lower in the group with major thalassemia ($55.5 \pm 6.9\%$ vs. $60.2 \pm 3.3\%$, $p < 0.05$). In contrast, myocardial mass was significantly higher in the group with beta-thalassemia (109 ± 29.2 g vs. 76.1 ± 13.2 g, $p < 0.05$), fact also noted above in the echocardiographic evaluation.

The calcium score in patients with major beta-thalassemia was 0 and 8.5 ± 5.9 in the control group. Only 3 patients (42,8%) in the control group had a calcium score > 10 U. No atherosclerotic lesions were observed in patients with major beta-thalassemia, whereas the control group showed mild coronary atherosclerotic lesions. Zero frequencies of coronary atherosclerosis denote coronary protection mechanisms in thalassemia.

If myocardial density can be determined, calcium deposits or iron deposits can be detected. We determined the density of the myocardium in the left ventricle, but also in the intraventricular septum. In patients with beta-thalassemia, higher than normal values were obtained, both at the left ventricle level (49.2 ± 8.8 HU) and at the septum level (56.7 ± 8.1 HU). Intramyocardial calcifications were observed in 2 patients with beta-thalassemia.

Figure 1. Cardiac CT a) calcifications of the left atrium b) calculation of myocardial density

Echocardiographic vs CT findings

In this study we wanted to evaluate the reproducibility of the measurements obtained on ultrasound, compared to those obtained on cardiac tomography. Thus, we analyzed 14 patients by comparing the data from ultrasound with those from CT.

We compared the mean values and standard deviation for indexed LV mass and FEVS (Table 5).

Table 5. Comparison between echocardiographic and CT data

		Echo	CT	P value
indexed LV mass (g/m ²)	β-TM	105.8 ± 22.4	111 ± 27.6	<0.05
	control	73.7 ± 12.8	76.1 ± 13.2	<0.05
LVEF(%)	β-TM	56.2±7.2	55.57 ± 6.9	<0.05
	control	60.5±3	60.2 ± 3.3	<0.05

Calculation of Pearson's correlation coefficient (r) revealed a good association between CT and echocardiography (Figure 2). Reproducibility of CT was significantly higher on an intra-observer level for LVEF and LV Mass.

		LV mass CT
LV mass ECHO	Pearson Correlation	.976
	Sig. (2-tailed)	.000
	N	14
		FEVS CT
FEVS ECHO	Pearson Correlation	.900
	Sig. (2-tailed)	.000
	N	14

The graphs show minimal dispersion of the data and good correlation ($r > 0.9$) for LV end-diastolic mass and LV ejection fraction.

Figure 2. Correlation of LV end-diastolic mass and of LV ejection fraction (LVEF), echocardiography vs. CT.

Discussions

The main findings of this study were that the calcium score was similar between thalassemic patients and control subjects. Arterial stiffness was higher in beta-thalassemic patients, which suggests premature arterial aging in this group. [9,10] Coronary artery calcification participates in the development of atherosclerosis and is found exclusively in atherosclerotic lesions, not in the wall of the normal arterial vessel. Although calcifications appear in small amounts in atherosclerotic lesions in the second and third decades of age, they become more common in advanced coronary lesions over the years [11]. Therefore, the current report suggests a different rate of progression of coronary atherosclerosis and vascular aging in patients with major beta-thalassemia.

In patients with major beta-thalassemia, vascular disease is part of normal aging. Free radicals are the main factors that lead to decreased endothelial reactivity, intima proliferation, increased cell adhesion and vascular inflammation. However, many factors accelerate this process, including iron overload, circulating microparticles, circulating hemoglobin, chronic anemia and inflammatory cytokines. Vascular complications attributed to lipid peroxidation products have also been described, but the atherogenic mechanism remains controversial [12]. Insulin resistance and diabetes also increase vascular oxidative stress.

In vitro studies have shown disorders of vascular endothelial function [13]. Other structural changes involved are calcifications of the vascular endothelium and alteration of arterial elastic tissue, leading to impaired arterial stiffness [14,15]. Arterial stiffness affects the performance of the left ventricle, due to the unfavorable increase in systemic impedance and postload [16]. These changes in patients with major beta-thalassemia may cause LV remodeling which leads to mechanical cardiac dysfunction.

There is no consensus for routine diagnosis of systemic vascular disease. Flow-mediated vascular dilation, although a marker of endothelial function, is not well adapted to clinical practice. Intimate carotid thickness can be routinely performed, but no clear levels of risk or specific interventions have been established. In patients with major beta-thalassemia, with no signs of heart failure, with normal levels of cardiac iron load, documented by T2 *, an increase in aortic stiffness was observed, assessed by pulse rate (carotid-femoral), compared to subjects with normal control. Oxidized low-density lipoproteins correlates with vascular stiffness in thalassemia, but titration is not widely available [17]. Computed tomography angiography is recommended to evaluate vascular calcifications and aneurysms.

The high incidence of venous thromboembolic events and strokes in these patients, while coronary artery is not affected, suggests an atheroprotective lipid pattern with a proatherogenic environment. [18,19] Both venous thromboembolism and carotid atherosclerosis predict subsequent atherothrombotic episodes. [20] For example, increased carotid intima-media thickness (cIMT) increases the risk for future myocardial infarction [21]. These findings suggest that the severe arterial dysfunction in thalassemia may indicate an additional clinical vulnerability for venous thromboembolism. Hahalis and colleagues reported five extracardiac thrombotic episodes and no coronary heart disease events over a 20-year period. [9]

Specifically in beta-thalassemia major, about 1% rate of vascular episodes accounts for 3.3%–3.5% of total mortality, [22] contrasts the zero incidence of coronary artery disease in these patients, [23] and it is in accord with our results. The causes for such differential protection of the coronary tree are speculative [9,10,24], but so far no large study has addressed coronary atherosclerosis in thalassemic patients. Coronary artery calcification (CAC) is highly specific for atherosclerosis, has a close association with cardiovascular risk factors and enables a refined risk prediction beyond the one provided by the global risk assessment tools. [25]

Absence of coronary artery calcification on multidetector computed tomography in adults identifies individuals at low risk for cardiovascular disease and cardiovascular events. [25,26]

LV volume assessment obtained with CT was compared to the results based on echocardiography. Our results show a good correlation between CT and echocardiography. Only slight differences with no clinical impact were found between analyzed parameters. These differences may be caused by different respiratory phases related to different acquisition techniques. This can be because in maximum inspiration LV venous return is decreased, resulting in end diastolic volume reduction and consensual end systolic volume reduction preserving stroke volume. The lower intra- and inter-observer variability for left ventricular wall mass by tomography may be related to better definition of contours as a result of higher spatial resolution, which improves evaluation of the base slice.

If myocardial density can be determined, calcium or iron deposits can be detected. In patients with beta-thalassemia, the density of the myocardium was higher, both in the LV (49.29 ± 8.87 HU) and in the septum (56.71 ± 8.1 HU). Thus, spectral cardiac tomography can provide a wider range of tools for myocardial evaluation and to complete the standard MRI. A study of 19 patients with a clinical history of thalassemia were compared T2 * cardiac MRI with dual-energy cardiac CT and found that the values of iron deposits in the septal muscle were strongly correlated with the values obtained by T2*[27].

Despite good agreement with magnetic resonance (MR), CT is unlikely to become the preferred imaging investigation for LV functional assessment because of the radiation exposure and administration of contrast material. However, for patients with poor echocardiographic compliance, and contra-indications to MR, CT can offer a reliable alternative to assess ventricular function.

Clinical relevance of the study results

Because calcium scores and implicitly atherosclerosis correlate with arterial stiffness, we would have expected to find a higher frequency among thalassemic patients, but we must take into account the small number of patients examined. However, zero frequencies of coronary heart disease, denotes coronary protection mechanisms in thalassemia. Low-density and medium-density lipoprotein cholesterol particles have been shown to predominate in thalassemic patients. There is also an increased oxidative stress and very high plasma levels of lipoprotein-associated phospholipase A2 (Lp-PLA2)[24]. In addition it appears that elevated plasma Lp-PLA2 levels in the presence of an anti-atherogenic lipid profile may contribute to premature carotid atherosclerosis, and not coronary heart disease. [28]

Limitations

This was an observational, non-randomized investigation on a small number of healthy subjects and patients with major beta-thalassemia. A larger study with the appropriate sample size may have been able to detect significant differences in calcium score between study groups.

Conclusions

This paper showed that the patients with major beta-thalassemia have a similar calcium score compared to the control subjects, but however they showed an increase in arterial stiffness. Yet, zero frequency of coronary heart disease, denotes coronary protection mechanisms in thalassemia, so future research should focus on the anti-atherogenic potential of the blood lipids with these patients. The ability of cardiac tomography to detect calcifications

and changes in myocardial density should be valued, as it can be a good tool for establishing the diagnosis of cardiomyopathy by iron loading.

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