TECHNIUM
SOCIAL SCIENCES JOURNAL

Vol. 8, 2020

A new decade for social changes

ISSN 2668-7798

www.techniumscience.com

Technium Social Sciences Journal
Vol. 8, 670-684, June 2020
ISSN: 2668-7798
www.techniumscience.com

Predictive factors of heart failure in patients with betathalassemia major

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Abstract. Cardiomyopathy by loading the myocardium with iron is the cause of heart failure in patients with major beta-thalassemia. In these patients cardiac systolic function remains normal for a long time, but when signs of heart failure appear, death may occur in the first year, so it is necessary to identify parameters to predict the patient's progress and prognosis. Materials and methods. We enrolled 62 patients with beta-thalassemia major (30 men and 32 women), mean age 29.9 ± 7.3 years. 32.2% of patients had disorders of carbohydrate metabolism, 12.9% associated hypothyroidism, and the mean ferritin was 1060.9 ± 856.6 ng / ml. Patients were evaluated echocardiographically, using tissue doppler technique to assess systolic and diastolic function. Myocardial mass was calculated using standard formulas and the type of left ventricular remodelling (LV) was thus obtained. Depending on the ferritin level, choosing the threshold value of 1000ng / ml, a group subanalysis of the ultrasound parameters of cardiac systolic and diastolic function was performed. Results. All patients had LV ejection fraction above 50% (LVEF), but longitudinal LV systolic dysfunction was observed in 19.3% of patients. Also, in patients with serum ferritin values above 1000ng / ml, the parameters of longitudinal systolic function of LV are affected, paradoxically the average value of LVEF being higher in these patients. About a quarter of the patients had diastolic dysfunction, but 40.3% had elevated LV filling pressures. We noticed that the batch with ferritin over 1000 ng / ml associated increased LV filling pressures. The evaluation of the function of the right ventricle by tissue Doppler (S wave at the level of the RV free wall) was statistically significantly correlated with the hemoglobin value and we obtained pathological values (S RV <11.5 cm / s) especially in the group with ferritin over 1000ng / ml. We noticed the presence of morphological abnormalities of LV, by an increase in the myocardial mass and the appearance of LV remodelling. 31% of these patients showed severe forms, especially eccentric remodelling. It was observed that there is a risk of negative remodelling of the left ventricle in the group of those with ferritin above 1000ng/ml.
Conclusions. The study proves that the evaluation of the systolic and diastolic function of the left and right ventricle by tissue Doppler ultrasound is much more accurate in the early detection of myocardial dysfunction. Ferritin levels above 1000ng / ml have been associated with impaired cardiac function parameters. Also, the remodelling of the left ventricle observed in this group of patients may be the first sign of heart failure.

Keywords. Predictive factors, heart failure, patients with major beta-thalassemia

Technium Social Sciences Journal
Vol. 8, 670-684, June 2020
ISSN: 2668-7798
www.techniumscience.com

1.Introduction

Patients with major beta-thalassemia have severe hereditary anemia that requires lifelong transfusions to prolong survival and allow normal development [1]. Due to the absence of an effective physiological excretory pathway in humans, the undesirable consequence of these blood transfusions is iron overload, predominantly affecting the heart, liver and endocrine organs. Despite recent improvements in patient care, iron overload cardiomyopathy remains a leading cause of death, with a rate of approximately 70% in the patients with major beta-thalassemia in many centers. Although cardiac systolic function remains normal for a long time, when signs of heart failure appear, death can occur within the first year. [2. 3]. Early detection of iron-induced cardiac toxicity is therefore a key component of clinical management.

Iron overload in patients with major beta-thalassemia can lead to systolic and diastolic LV dysfunction [4]. In the case of iron overload, iron in its ferrous form (Fe^{2+}) enters the myocytes through voltage-dependent L-type calcium channels and through the divalent metal transporter 1 (DMT1). Myocardial iron loading is slower than liver loading, so myocardial dysfunction occurs later compared to the liver. Iron deposits initially occur in the ventricle myocardium, from the epicardium to the subendocardium, later in the atrial, affecting the conduction system, but not to the same extent as affecting the mechanical system. [5]

Iron is stored in myocytes in the form of ferritin, hemosiderin and free iron, the latter being also the most active. Unstable iron forms reactive oxygen species that transform ferrous iron into ferric iron generating toxic hydroxyl radicals. Antioxidant cellular properties are exceeded, resulting in membrane lipid peroxidation, cellular proteins and nucleic acids. In major beta-thalassemia, structural and quantitative changes occur in the β-globin chain. These changes lead to imbalance of the globin chain, which in turn affects both the intracellular and the extracellular oxidative environment. The resulting oxidative stress and the body's inability to adapt are largely responsible for the pathophysiology of myocardial structural changes.

Also, the increase of iron transport in myocytes through L-type calcium channels determines the alteration of the excitation-contraction duo involved in the appearance of systolic and diastolic ventricular dysfunction [6].

2. The pathogenesis of heart failure in patients with major beta-thalassemia

Two patterns of cardiac damage were identified by iron overload of myocytes: (1) dilated phenotype - with cardiac remodeling leading to left ventricular dilation and subsequent systolic dysfunction, with decreased ejection fraction, and (2) restrictive phenotype - with dysfunction restrictive diastolic type, by increasing filling pressures in the left ventricle, with preservation of the LV ejection fraction, but with the appearance of pulmonary hypertension and dysfunction and dilation of the right ventricle (RV). [7]

In the early stages of the disease, myocardial iron overload is expressed by diastolic ventricular dysfunction. A study that included 88 adolescent and adult patients showed restrictive diastolic dysfunction in only 8% of subjects, who also had elevated serum ferritin levels [8]. More recent studies that have used BNP as a marker have shown increased filling pressures of LV and diastolic dysfunction of LV in the early stages of the disease. If iron overload persists and no treatment with iron chelators is initiated, over 90% of the patients develop LV remodeling, which ultimately leads to LV dilation and LV ejection fraction decrease [9]. Only a small proportion of the patients, generally less than 10%, develop the restrictive form, with pulmonary hypertension and right ventricular dysfunction [10]. A retrospective study of 319 patients with β thalassemia demonstrated a progressive decrease in systolic RV function due to the increase in the myocardial iron load, following a pattern similar

Technium Social Sciences Journal
Vol. 8, 670-684, June 2020
ISSN: 2668-7798
www.techniumscience.com

to LV systolic function [11]. It should be noted that the signs of heart failure can be masked for a long time by the anemia induced hyperdynamic status,

In patients with beta-thalassemia, an impairment of arterial stiffness was observed due to lipid peroxidation products within disorders of vascular endothelial function. Arterial stiffness is correlated with vascular impedance and LV post-pregnancy, leading to remodeling of the left ventricle over time and impaired cardiac function [12].

3.Materials and methods

Patients over 18 years of age, with major beta-thalassemia, were recruited from the Hematology Institute of Bucharest. Patients with valvular heart failure or systemic hypertension were excluded. The procedures were performed in the first week after the transfusion, in order to reduce a possible influence of the anemia on the results. Height and weight were measured to calculate the body area. Patients were evaluated clinically, and venous blood was collected to measure hemoglobin, fasting blood glucose and serum ferritin. Resting electrocardiograms were performed and patients were evaluated echocardiographically.

Echocardiographic examination

Aloka Prosound Alpha 7 was used for transthoracic echocardiography. LV mass and LV systolic and diastolic function were evaluated echocardiographically. We used the short parasternal axis ultrasound window to measure LS systolic and end-diastolic diameter, AS diameter, SIV thickness, and LV posterior wall thickness. The LV mass was calculated according to the standard formula. We measured the LV ejection fraction according to the Simpson technique. We used pulsed Doppler ultrasound to obtain the following indices of LV diastolic function: E wave, A wave, and A wave deceleration time. We also used tissue Doppler echocardiography to evaluate LV systolic and diastolic function: S' septal wave measured at the base of the mitral ring for the evaluation of the longitudinal function of the LV, and E' and A' waves for the evaluation of the diastolic function of the LV. For the evaluation of RV systolic function we used as parameters TAPSE (longitudinal axis movement of the tricuspid ring in M mode) and evaluation by tissue Doppler of the S 'wave of the free wall of RV measured at the base of the tricuspid ring.

Mass and remodeling of the left ventricle

LV mass and relative wall thickness (RWT) were calculated according to the formula: LV mass = 0.8 {1.04 [([LVEDD + ILVd + PWd] 3-LVEDD3)]} + 0.6, RWT = 2 * PWd / LVEDD. LV mass was related to body surface area (g / m²).

Depending on the LV mass values (Table 1) and the relative thickness of the RWT wall, we defined 4 types of 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), and eccentric hypertrophy (increased LV mass, RWT≤0.42) (Figure 1).

Table 1. LV mass indexed to body surface (g/m2)

	Women	**Men**
Normal values	43-95	49-115
Easy change	96-108	116-131
Moderate change	109-121	132-148
Severe change	≥122	≥149

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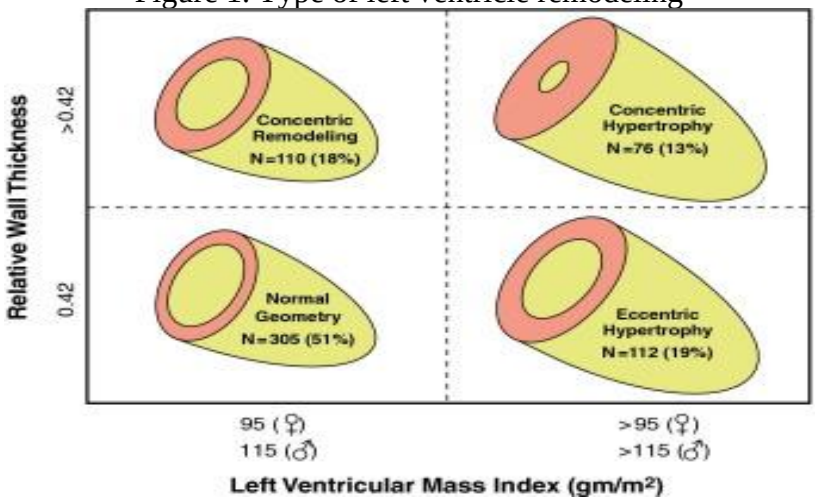
Figure 1. Type of left ventricle remodeling



LV filling pressure

Mitral ring tissue Doppler echocardiography measured during diastole has been proposed as a new method for assessing cardiac function. For the evaluation of LV filling pressures, we used the ratio between the rate of transmitral flow (E wave) and the speed of mitral ring evaluated by tissue Doppler (E '). It is preferable to use the average of the E-wave velocity, measured at the septum and the side wall of the mitral ring, to assess the filling pressures of the LV. Because septal E' is usually lower than lateral E', the E / E' ratio using septal velocity is generally higher than E / E' using lateral wall velocity. The septal I / O ratio <8 is usually associated with normal LV filling pressures, while a septal I / O ratio> 15 means increased filling pressures. When the value is between 8-15, other echocardiographic indices should be used (previous studies have shown the direct relationship between AS size and LV filling pressures).

Statistical analysis

Data are presented as mean ± standard deviation, unless otherwise specified. Echocardiography data were analyzed online. Pearson correlation analysis, T test, and odd ratio risk analysis were used to obtain correlations between various clinical, biochemical parameters, and echocardiographic data, to assess systolic and diastolic function. Regression curves were used to highlight the evolution of myocardial mass as a function of serum ferritin level. Thresholds of statistical significance were defined as statistically significant high at $p < 0.001$ and statistically significant low at $p < 0.05$. All statistics were analyzed using SPSS Version 20.0 (SPSS, Inc).

4. Results

We enrolled 62 patients with beta-thalassemia major (30 men and 32 women), mean age 29.9 ± 7.3 years. Patients did not show symptoms or clinical signs of heart failure at the time of examination. 32.2% of patients had diabetes or impaired oral glucose tolerance. 8 of the patients (12.9%) had associated hypothyroidism. Demographic data, biochemical analyzes and hematological profile are highlighted in Table 2.

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Vol. 8, 670-684, June 2020
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Table 2. Demographic, biochemical and hematological data

Age (years)	29,9±7,3
Average weight (kg) women	52,3±8.5
Men	63.3±8,2
Average height(cm) women	157.7±7.7
Men	169,9±6,8
Hemoglobin (g/dl)	9,48±0.75
Serum ferritin (ng/ml)	1060.9±856.6
Erythrocyte mass /year (U)	33,7±8,9
Chelator Treatment (years)	22,,7±7,6
Diabetes / altered glucose tolerance	322.2%
Hypothyroidism	12.9%

It is observed that the average hemoglobin is low (9.48 mg / dl), and only a quarter of the patients had pretransfusion hemoglobin over 10 g / dl, which will cause a hyperdynamic status, with increased cardiac output, affecting the echocardiographic measures of ventricular function. This is important for early detection of cardiac dysfunction, as the use of inappropriate benchmarks can mask myocardial dysfunction.

The average value of ferritin, about 1000 ng / ml, is an almost satisfactory value, the gold standard being below 1000 ng / ml, which shows us the effectiveness of chelation treatment. It should be noted that 58% of patients have serum ferritin below 1000 ng / ml and 87% below 2500 ng / ml. If we look at the difference between the age of the patients and the duration of the chelating treatment, we notice that the patients are treated since preschool with iron chelators.

Echocardiographic parameters

The parameters of systolic and diastolic LV function are highlighted in Table 3.

Table 3. Parameters of systolic and diastolic function

LVEF%, N ≥ 60%	64.3±5.9
MAPSE (mm) N≥12mm	15.8±2.2
LV S'septal wave (cm/s), N≥7.5cm/s	7.9±1.4
% patients with LV S' septal wave <7.5 cm/s	25.8%
E (m/s)	1.1±0.22
E'(cm/s)	10.2±2.5
E/E' N<8	11±3.3
E/A, N 1-2	1.64±0.64
TdE, N 140-180ms	179.2±37.3
TAPSE (mm) N≥21mm	26.7±4.3
RV S wave, N≥11.5cm/s	14.3±3
% patients with RV S wave <11.5cm/s	17.7%

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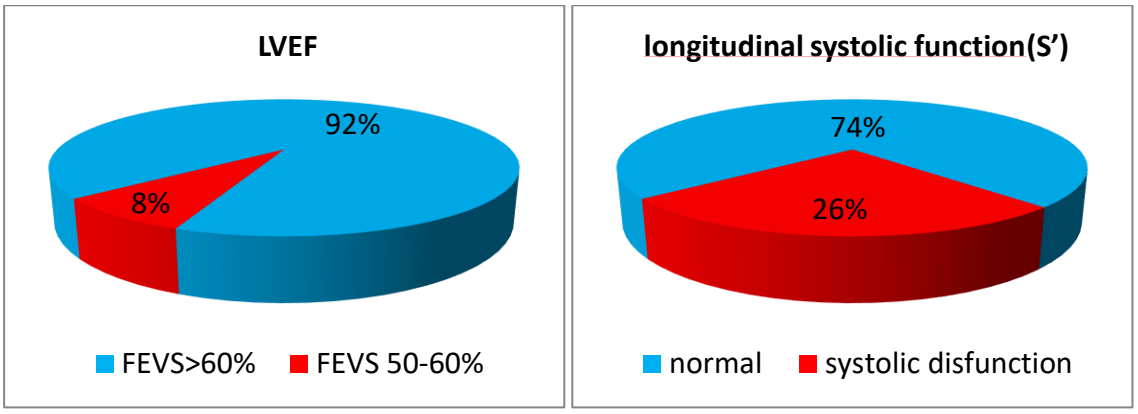
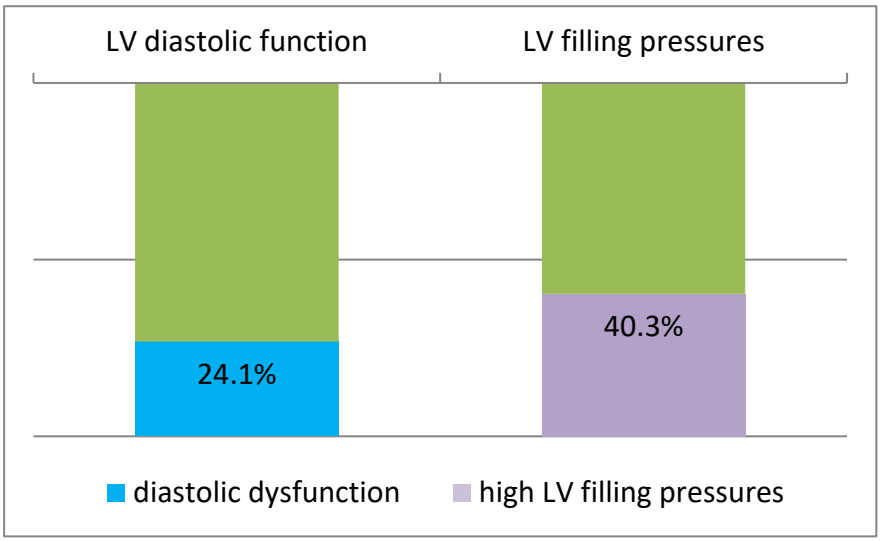
Vol. 8, 670-684, June 2020
ISSN: 2668-7798
www.techniumscience.com

All patients had LV ejection fraction above 50% (LVEF), but 5 patients had LLV between 50% -60%, suggesting mild systolic dysfunction. Also, 2 patients presented with a longitudinal dysfunction (measured by MAPSE <12mm). Longitudinal systolic LV dysfunction assessed by S 'septal velocity was observed in 16 patients (25.8%).



24.1% of the patients had diastolic disfunction, being evaluated by pulsating doppler at mitral valve, and 40.3% had increase LV filling pressures evaluated by tissue doppler at the level of the interventional septum.



Evaluating the systolic function of the right ventricle by TAPSE and S' wave parameters at the RV free wall, we observed that TAPSE has a low value in 2 patients, but 11 patients (17.7%) have a value below 11.5 cm / s and S' RV , suggesting impaired longitudinal function of the right ventricle.

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Ferritin, medium hemoglobin versus diabetes and hypothyroidism

There is a negative correlation between ferritin and hypothyroidism, which would suggest that elevated ferritin increases the risk of hypothyroidism, but the low number of patients provides poor statistical significance (p = 0.037). There is also a positive correlation between ferritin and hemoglobin levels and increased blood glucose levels, suggesting that iron deposits and anemia may influence diabetes (p <0.05, p <0.001).

		Diabetes /IGF	Hypothyroidism
Ferritin	Pearson Correlation	.146*	-.234*
	Sig. (2-tailed)	.024	.037
	N	62	62

		DZ/IGF	Hypothyroidism
Mean Hb	Pearson Correlation	.971*	.080
	Sig. (2-tailed)	.000	.536
	N	62	62

Anemia and systolic and diastolic function LV and RV

There is a negative correlation between mean hemoglobin levels and LVEF, which suggests that anemia initially causes a hyperkinetic status with an increase in ejection fraction if we analyze the whole group. If we analyze the other parameters of systolic function, we do not obtain statistically significant results. Also, diastolic function is not statistically significantly influenced by anemia.

		LV diastolic dysfunction	increased LV Filling Pressure
Mean Hb level	Pearson Correlation	.115	.227
	Sig. (2-tailed)	.373	.077
	N	62	62

		S LV	LVEF	MAPSE
Mean Hb level	Pearson Correlation	.047	-.102*	-.063
	Sig. (2-tailed)	.720	. 029	.628
	N	62	62	62

Regarding right ventricular function, there is a negative TAPSE correlation with the mean hemoglobin and a statistically significant high positive correlation (p <0.001) with the measurement of systolic function by tissue Doppler (S wave at the RV free wall)

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		TAPSE	Pathological RV S wave	Pulmonary hypertension
Mean Hb level	Pearson Correlation	-.318*	.412**	.130
	Sig. (2-tailed)	.012	.001	.314
		62	62	62

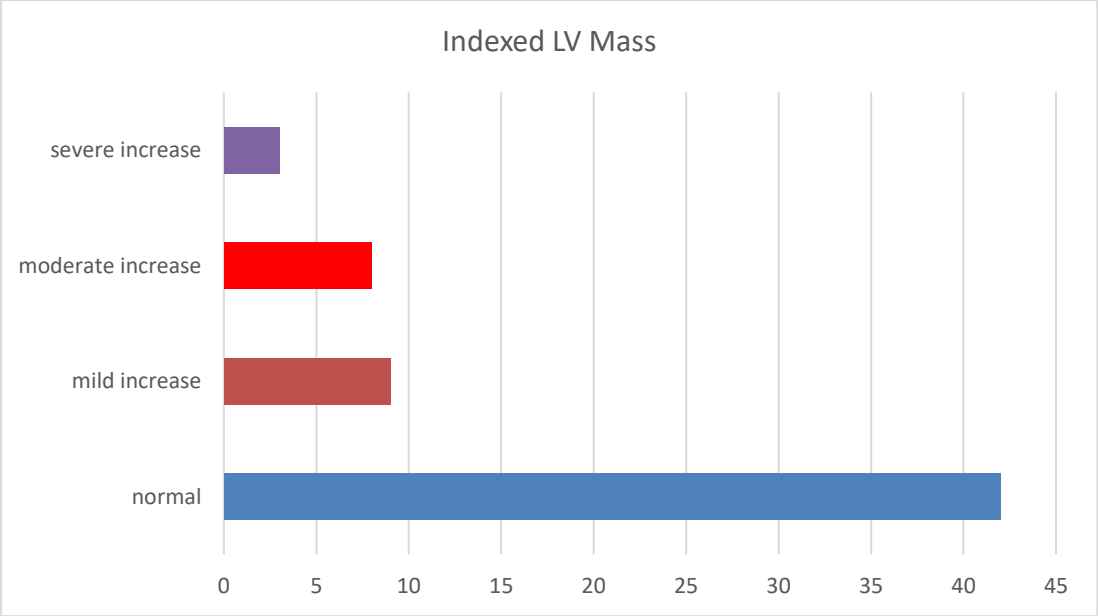
Left ventricular mass

The mean LV mass relative to body surface area was higher than the normal average, 103.8 ± 21.2 g / m² in men and 90.78 ± 19.6 g / m² in women, respectively.

Table 4. Left ventricular mass

LV Mass men(g)	179.9±40.9
indexed LV Mass men(g/m2)	103.8±21.2
LV Mass women (g)	136.5±28.4
indexed LV Mass women (g/m2)	90.78±19.6 g/m2

Depending on the results obtained after the calculation of the indexed myocardial mass on the body surface and by gender, 42 patients (67.7%) have myocardial mass within normal limits, the remaining 32.3% have increased myocardial mass.



Regarding the correlation between serum ferritin and indexed LV mass, there has been no proven statistical significanc. On the regression graphs there is an increase in myocardial mass with the increase of ferritin, and in men rather than women a decrease in

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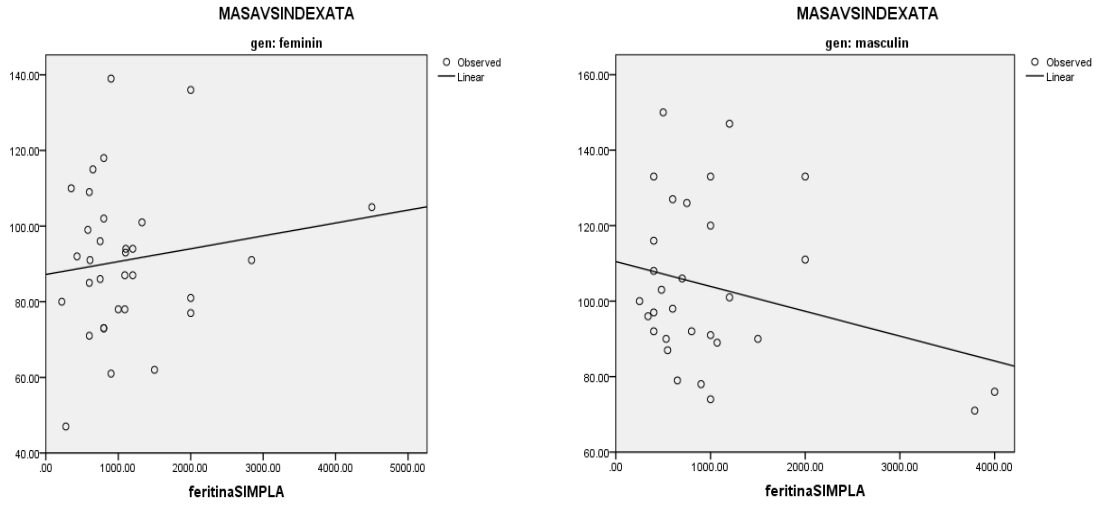
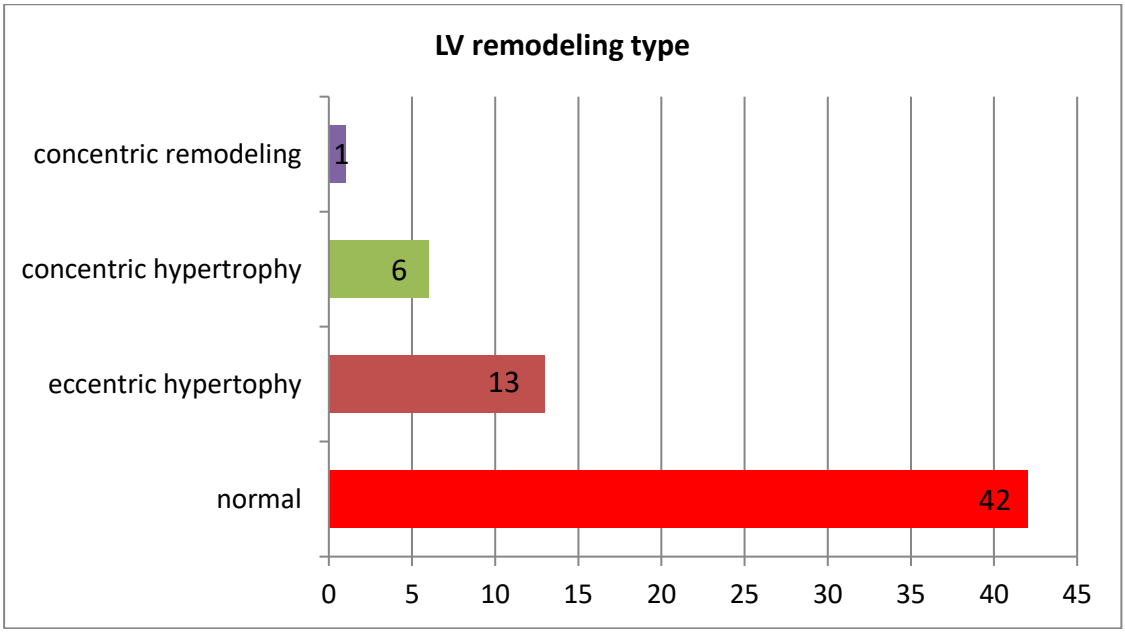
Vol. 8, 670-684, June 2020
ISSN: 2668-7798
www.techniumscience.com

myocardial mass. Moreover, it is known that myocardial changes are influenced by iron deposited in the myocardium (assessed imaging by the T*2 magnetic resonance technique), and less correlated with the level of serum ferritin, but, as we will show below the level of serum ferritin correlates with the remodeling of the left ventricle.



Left ventricular remodeling

There was an increased percentage of left ventricular remodeling 32.3%, of which, 6 patients (9.6%) had concentric hypertrophy and 13 patients (20.9%) eccentric hypertrophy. Thus, 31% of patients had severe cardiac remodeling by increasing the myocardial mass of the left ventricle.



Statistical analysis according to serum ferritin level

It is interesting to divide the lot according to the level of ferritin and we chose as threshold value 1000 ng/ml. Two groups are obtained: one of 36 patients with ferritin levels below 1000 ng/ml and a second one of 26 patients with ferritin levels above 1000ng/ml.

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Regarding the geometry of the left ventricle, it is observed that there is a risk of negative reshaping of the left ventricle in the group of those with increased ferritin, compared to those with ferritin levels below 1000 ng/ml (OR 1.53, 95%)

		LV geometry		
		Normal	abormal	Odd ratio
Ferritin levels(ng/ml)	<1000	19 73.1%	7 26.9%	
	≥1000	23 63.9%	13 36.1%	
		1.143	. 745	1.534

Evaluating the systolic LV function by measuring LVEF, it is observed that there are significant differences between the two groups, paradoxically LVEF is lower in those with serum ferritin below 1000 ng/ml.

Ferritin levels(ng/ml)		N	Mean	Std. Deviation	T	Sig. (2-tailed)
<1000	LVEF	36	63.94	6.66	65.000	.000
	MAPSE	36	15.8750	2.42421	39.291	.000
	LV septal S'wave	36	.0801	.01181	40.711	.000
≥ 1000	LVEF	26	65. 000	5.09	57.5	.000
	MAPSE	26	15.7692	1.98611	40.485	.000
	LV septal S'wave	26	.0770	.01789	21.955	.000

However, it is observed that the longitudinal systolic LV function correlates positively with low ferritin values. Both MAPSE and LV S' septal wave have higher values in the group of those with ferritin under 1000ng/ml (T- test). LV septal S'wave measured by tissue doppler, has pathological values (S septal<7. 5cm/s) in the group of those with ferritin over 1000 ng/ml (OR 2. 19, 95%).

		LV septal S'wave pathological (<7. 5cm/s)		Odds Ratio
		Normal	Pathological	
Ferritin levels(ng/ml)	<1000	29 80.6%	7 19.4%%	
	≥1000	17 65.4%%	9 34.6%%	
		1.178	.516	2.193

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At the level of the parameters that evaluate the diastolic function of the LV, there are no differences between the two groups,-however, if we evaluate the LV filling pressures, we notice that the batch with increased ferritin is associated with increased LV filling pressures (OR 1.69, 95%).

		LV Filling Pressures		
		increased pressures	normal pressures	Odds Ratio
Ferritin levels (ng/ml)	≥1000	17 47. 2%of the amount of	19 52.8%	
	<1000	9 34.6%	17 65. 4%of the amount of	
		1.365	0.807	1.69

At the level of the parameters that evaluate the RV systolic function it is observed that are there are differences between the two groups, the smaller the ferritin, the higher the TAPSE values.

Ferritin levels ng/ml		N	Mean	Std. Deviation	T	Sig. (2-tailed)
<1000	TAPSE	36	27.4444	4.60090	35.790	.000
	Svd	36	.1474	35.790	27.587	.000
≥ 1000	TAPSE	26	25.8846	27.587	32.100	.000
	Svd	26	.1378	32.100	23.881	.000

Evaluating the RV longitudinal systolic function by The Tissue Doppler, the RV Free Wall S wave has higher value in the group of those with low ferritin (T-test) and pathological values (RV S wave <11. 5cm/s) in the group of those with ferritin over 1000ng/dl (OR 1.86,95%).

		S wave RV (<11. 5cm/s)		Odds Ratio
		Normal	Pathological	
Ferritin levels(ng/ml)	<1000	31 86.1%	5 13.9%	
	≥1000	20 76.9%	6 23.1%	
		1.119	.602	1.86

5. Discussions

This study demonstrates that the changes in the structural and cardiac functions in patients with major beta-thalassemia occur before signs of heart failure and decreased left

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ventricular ejection fraction (all-our patients had LVEF over 50%). Although cardiac systolic function remains normal for a long time, when signs of heart failure appear, death may occur in the first year, therefore, assessing cardiac function by classical parameters is a method of assessing the patient at that moment in time, without being able to predict the evolution and patient prognosis. For this reason it is necessary to identify other more specific parameters, which highlight the impairment of diastolic and systolic function of the left and right ventricles before the patient becomes symptomatic.

The average hemoglobin level in our group was low (9.4 mg / dl), which will determine in the first phase a hyperdynamic status, with increased cardiac output, but over time, by maintaining hypoxemia, it becomes a risk factor in heart failure. To prevent heart failure, it is recommended to maintain a pretransfusion hemoglobin level of over 10g / dl [13], which in our group was achieved in a very small percentage (25%–of all patients). On the other hand, increasing the need for transfusions would increase iron deposits, which would have a long-term negative effect, so a balance must be found between hemoglobin and serum ferritin levels. About one-third of patients had diabetes or prediabetes, and 12.9% had hypothyroidism, risk factors for heart failure. Patients in our group were euthyroid under treatment and had relatively good blood sugar control, which gave them a better long-term prognosis.

Regarding the echocardiographic data, first, we noticed the presence of morphological LV abnormalities, by increasing myocardial mass and the appearance of LV remodeling. A large percentage of patients had LV remodeling (32.2%), 31% of them having severe forms of cardiac remodeling, especially eccentric remodeling. It was observed that there is a risk of left ventricle negative remodeling in the group of those with elevated ferritin, compared to those with ferritin below 1000 ng / ml. Understanding the pathophysiological mechanisms involved in the process of hypertrophy and cardiac remodeling is crucial for the development of new therapeutic plans, because reported mortality rates remain high in patients with remodeling and cardiac dysfunction [14]. In major beta-thalassemia, structural and quantitative changes occur in the β-globin chain, which in turn affects both the intracellular and extracellular oxidative environment. The resulting oxidative stress and the body's inability to adapt are largely responsible for the pathophysiology of myocardial structural changes. We suggest that LV remodeling seen in this group of patients may be the first sign of heart failure which should guide specific treatment. In addition to treatment with iron chelators, oxidative stress-reducing preparations and perhaps drugs already known to play a role in myocardial remodeling (conversion enzyme inhibitors and antialdosterone diuretics) could have a favorable effect even in those with normal LV ejection fraction. From our experience with the patients in this group, we can notice that the angiotensine-converting enzime inhibitors were poorly tolerated, due to the low values of blood pressures.

Although all patients had LV ejection fraction over 50%, a fairly high percentage (25.8%) had longitudinal systolic dysfunction, assessed by tissue Doppler ultrasound (S 'septal LV wave) and in M mode (MAPSE). There is a negative correlation between mean hemoglobin levels and LVEF, which suggests that anemia initially causes a hyperkinetic status with an increase in ejection fraction if we analyze the whole group. Also, in patients with elevated serum ferritin values above 1000ng / ml, the parameters of longitudinal systolic LV function (S' septal and MAPSE) are affected, paradoxically the mean value of LVEF being higher in these patients. Previously published data have shown that ejection fraction (LVEF) is increased in patients with major beta-thalassemia in whom no increase in myocardial iron load has been detected, even though serum ferritin is most likely due to chronic increased cardiac output associated with anemia [15 , 16]. This is important for early detection of cardiac dysfunction,

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as the use of inappropriate benchmarks can mask the diagnosis of underlying cardiomyopathy, and this can lead to delayed treatment and early onset of heart failure [17].

About a quarter of the patients had diastolic dysfunction, assessed by the parameters obtained by pulsed doppler at the mitral valve. Using tissue doppler in the LV septum, we detected increased LV filling pressures at a fairly high percentage in 40.3% of patients. At the level of the parameters that evaluate the diastolic function, we noticed that the group with ferritin over 1000 ng / ml associated increased LV filling pressures. Studies using the BNP as a marker have shown increased LV filling pressures and LV diastolic dysfunction in the early stages of the disease. [8]. Studies in the literature on diastolic LV function in patients with β-major thalassemia are somewhat contradictory. Spirito and colleagues reported a restrictive pattern of transmitral flow in a group of young adults with normal systolic function in the early stages of the disease [18]. In contrast, Kremastinos and associates reported non-alteration of LV compliance in the early stages of the disease. [19]. A severely restrictive pattern of transmittal flow has been reported in the final stage of the disease, similar to that of cardiomyopathies. The study by Ghaemian and associates indicates the measurement of diastolic filling parameters as a non-invasive method, with high sensitivity, for cardiac evaluation in patients with β-major thalassemia, without symptoms of heart failure and normal systolic function. [20]. At our end, we consider that the evaluation of LV filling pressures is a very good parameter to detect diastolic dysfunction at an early stage/ onset in these patients.

Evaluation of the right ventricular function by tissue Doppler (S' wave at the RV free wall) was statistically significantly correlated with hemoglobin value. It is also observed that the wave V' of right ventricle's free wall has higher value in the group of those with ferritin levels below 1000 ng/ml (T-test) and pathological values (S' RV <11.5cm / s) in the group of those with ferritin above 1000 ng/ ml.

The average value of ferritin in our group, approximately 1060 ng/ml, is a satisfactory value, which shows the effectiveness of chelation treatment. It should be noted that 58% of patients have serum ferritin below 1000 ng/ml and 87% below 2500 ng/ml. If we look at the difference between the age of the patients and the duration of the chelating treatment, we notice that the patients are treated with iron chelators since preschool. We also consider that a serum ferritin concentration of less than 1000 ng / ml should be considered a gold standard for any therapeutic program [21].

6. Conclusions

Although cardiac systolic function remains normal for a long time, iron overload cardiomyopathy remains the leading cause of death in patients with major beta-thalassemia. Our study proves that the evaluation of systolic and diastolic function of the left and right ventricles by tissue Doppler ultrasound is much more accurate in the early detection of myocardial dysfunction. Ferritin levels above 1000 ng / ml have been associated with impaired heart function parameters. Also, the remodeling of the left ventricle observed in this group of patients may be the first sign of heart failure. Early detection of iron-induced cardiac toxicity is therefore a key component of the treatment of patients with major beta-thalassemia.

Technium Social Sciences Journal
Vol. 8, 670-684, June 2020
ISSN: 2668-7798
www.techniumscience.com

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