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Klinik Araştırma

Assessment of Left Ventricular Volume and Function in Patients with β Thalassemia Major

Beta Talasemi Major Tanılı Hastalarda Sol Ventriküler Volüm ve Fonksiyon Değerlendirilmesi

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ABSTRACT

Objective: *Long-term blood transfusion therapy in patients with thalassemia extravascular hemolysis and increased intestinal absorption lead to excessive storage of iron. Therefore hemosiderosis may develop in several organs especially in the heart.*

Material and Method: *Eighty-five patients with thalassemia major with a mean age of 13±7 years who used chelation therapy and 85 healthy children were included in this study.*

Results: *When the study group was clasiffied into two subgroups according to serum ferritin levels (ferritin>2500, and ferritin<2500) there was no significant difference between sıstolic, and diastolic cardiac functions. When we compared the Doppler echocardiographic findings of study and control groups we found decreased diastolic functions and increased LV mass indices in patients with thalassemia major.*

Conclusion: *As a result it has been found that in patients with thalassemia major cardiac geometry was distorted, right, ad left diastolic functions were impaired as detected with tissue Doppler examination.*

Keywords: *cardiology, hemosiderozis, pediatrci cardiology, thalassemia*

ÖZ

Amaç: *Talasemi majorlu hastalarda uzun süreli transfüzyon tedavisi, ekstravazal hemoliz ve demirin artmış intestinal absorbsiyonu aşırı demir yüküne yol açar. Bunun sonucunda birçok organda, özellikle kalpte hemosideroz gelişir.*

Gereç ve Yöntem: *Hastanemizde izlenen, ortalama yaş grubu 13±7 yaş grubundaki tümü şelatör tedavi almış olan 85 hastamızda ekokardiyografi ve MR T2* ile kardiyak sistolik ve diyastolik fonksiyonlar değerlendirildi.*

Bulgular: *Ferritin değerlerine göre (ferritinin 2.500 altındaki ve üstündekiler), kardiyak MR T2* (20'nin altı ve üstündekiler) değerlerine göre gruplandırıldığında kardiyak fonksiyonlarda (sistolik ve diyastolik) anlamlı bir farklılık saptanılmadı. Talasemili hastalar ile kontrol grubu karşılaştırıldığında doku Doppler ile sol ventrikül diyastolik fonksiyonlarında azalma ve sol ventrikül kas kitle (LV mass) endeksinde anlamlı artış saptanmıştır.*

Sonuç: *Çalışmamızda, talasemili hastalarda kardiyak geometrinin bozulduğu ve doku Doppler incelemede sağ ve sol diyastolik fonksiyonların azaldığı saptanmıştır.*

Anahtar kelimeler: *kardiyoloji, aşırı demir yükü, pediyatrik kardiyoloji, talasemi*

INTRODUCTION

Cardiac complications are significant causes of mortality and morbidty in patients with thalassemia major. Increased cardiac output with increased ventricular contractility and ventricular dilatation due to chronic hemolytic anemia, and excessive storage of iron are major causes of the cardiac dysfunction [1,3]. Tissue hypoxia due to inadequate blood transfusions, pulmonary vascular endothelial damage due to increased cardiac output, frequent pulmonary infections and extramedullary hematopoiesis can lead to

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restriction of ventricular wall motion and also lead to development of cardiomyopathies. Typical findings of advanced stage-cardiomyopathies which are related to excessive storage of iron are peripheric edema, arrhytmias and congestive cardiac failure symptoms that show high rates of mortality [4]. Altough there are many improvements about transfusion and chelation techniques, some patients die because of transfusion therapy which causes excessive storage of iron in myocardium, heart failure and dysfunction of other organs. Early diagnosis and treatment of cardiomyopathy which is the major cause of mortality is very important.

Beta-thalassemia major has both cardiac and vascular complications due to the iron overload. One of the most important iron overload may involve the heart and these patients may have left ventricular dysfunction. One of the main reasons of vascular pathology is impaired nitric oxide metabolism in vascular tissue with esuing iron overload. The other one is calcification and secondary impairment of the arterial wall. Due to these changes ventricular afterload and vascular resistance related to arterial stiffness develop. All of these changes lead to cardiac remodeling with resultant cardiac dysfunction. Up to now, however, no studies have yet been performed to correlate arterial stiffness with cardiac remodeling in patients with thalassemia major. In the present study we additionally assessed the relationship between the index of vascular function, cardiac remodeling and serum ferritin [5].

The positive signs may be detected only at the late stages with the conventional echocardiographic (echo) methods, That's why echocardiography may be useful in the earlier detection of cardiac dysfunction in patients with high risk of cardiac hemosiderosis. Tissue Doppler echo and radionuclide angiography reveal regional wall motion abnormalities even in the early stages. MR-T2*, due to its ability to evaluate the iron load as well as the structure and function of the heart stimultaneously; i addition of its being noninvasive, sensitive and specific, is superior to (but more expensive than) other modalities [6].

In previous studies several parameters were used to detect early cardiac dysfunctions. Ferritin levels, cardiac MR T2* index, heart rate changes detected on 24- hour rhythm monitoring with Holter, cardiac geometry demonstrated with echocardiography, systolic and diastolic functions revealed with tissue Doppler were evaluated [7].

MATERIAL and METHODS

The asymptomatic patients with TM and normal left ventricular (LV) global systolic function were evaluated by M-mode echocardiography. In the study group, 85 children (< 18 years) with TM were evaluated by conventional echocardiography and pulsed-wave tissue Doppler imaging (PW-TDI). Also, cardiac geometry was revealed with echocardiography.

In our study also ferritin levels, cardiac MR T2* index and cardiac geometric changes were evaluated in the study group and early cardiac dysfunction was revealed. The ethics committee of our institution approved this study.

Chelation Therapy: All patients were followed up in the pediatric hematology clinic. The patients were transfused with 8 to 15 mL/kg body weight of packed red blood cells every 2 to 5 weeks for maintaining the pretransfusion hemoglobin level between 9 to 10.5 g/dL. In this study aged 85 patients with thalassemia (mean age: 13.2±7 years) were discussed with 85 healty children who were at similar age, gender and body surface areas. Cardiac evaluation of the study group were done 5-7 days after transfussion to prevent patients from being harmed because of excessive blood volume. We classified study groups according to their ferritin levels and cardiac MR T2* levels, and discussed their cardiac functions.

FINDINGS

The comparsion between study and control group as for age, gender and BSA showed no significant intergroup differences. Echocardiographic findings revealed normal left ventricular systolic functions (EF, KF) in the study group and tissue Doppler findings showed decreased left ventricular diastolic functions (increased A velocity and decreased E/A rate)

Table 1. Comparison demographic data and cardiac parameters study and Control Subjects.

	Study group n:85 49/36 (female/male)	Control group n:85 49/36 (female/male)	P
Age	13,22±7,07	13,06±6,92	0,87
Bsa	1,3±0,41	1,35±0,45	0,63
Hr	92,79±16,2	83,89±20,01	0,002
QTc	432,2±19,09	394,14±18,8	0,021
İvsd	8,66±1,78	7,18±1,13	0,0001
Lvdd	43,47±6,91	41,54±6,65	0,065
Lvds	27,14±4,39	25,72±4,87	0,047
Lvpwd	7,38±1,88	5,88±1,13	0,0001
Lvedv	88,35±32,46	79,59±28,49	0,063
Ejection fraction	67,74±4,62	69,25±5,02	0,043
DLVe	1.5±0,34	1,71±0,19	0,0001
DLVa	0,7±0,18	0,56±13	0,0001
Dlv e/a	1.5±0,34	1,71±0,19	0,0001
Cardiac output	5,43±2,07	4,37±1,36	0,0001

BSA: body surface area, İVSd: interventricular septum diastolic diameter, LVDd: left ventricular diastolic diameter, LVDs: left ventricular systolic diameter, Lvpwd: left ventricular posterior wall diastolic diameter, LVmass: left ventricular mass index, DLVe: Doppler tissue imaging left ventricular E wave velocity, Dlva: Doppler tissue imaging left vetricular A wave velocity, DLVe/a: Doppler tissue imaging left ventricular E/A wave velocity range

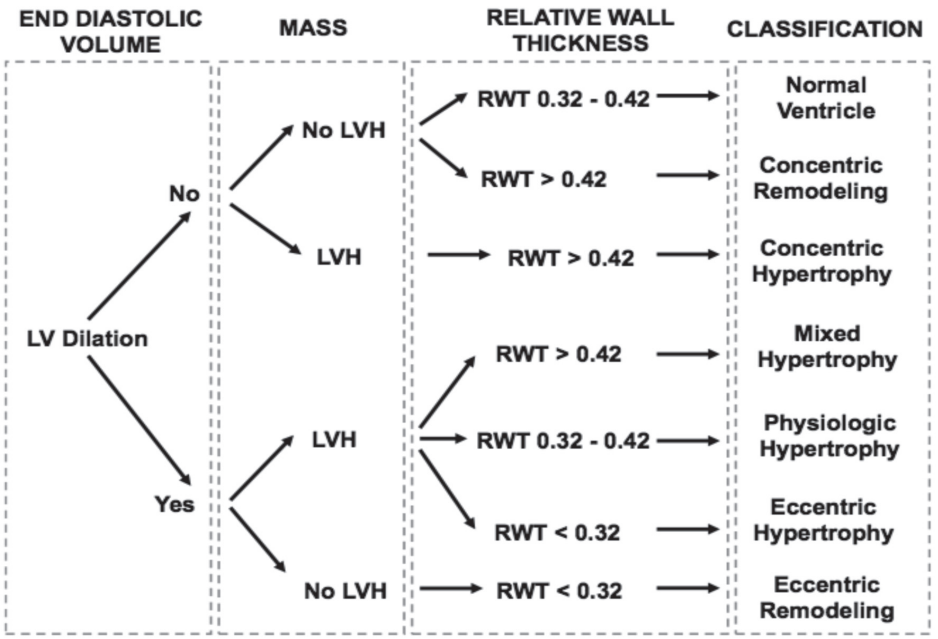

Figure 1. Development of hypertrofic and consantric hypertrophy [5].

(Table 1). According to echocardiographic findings, we showed left ventricular hypertrophy and increased cardiac output in patients with thalassemia. We also revealed increased left ventricular end-diastolic parameter, increased left ventricular septum and left ventricular posterior wall measurements (Figure 1). In patients with thalassemia alterations in left ventricular configuration were detected in indicated percentages of patients as follows: normal geometry, 70%; eccentric hypertrophy 20%; concentric hypertropy, 4% concentric remodelling pattern 6% respectively (Table 2).

Table 2. Evaluating of cardiac geometry with echocardiography in children with thalassemia major.

	n	Percantage		Control Group
Normal	60	70,60%	85	100,00%
Egsantric Hypertrophy	17	20,00%	0	0,00%
Consantric Remodeling	5	5,90%	0	0,00%
Consantric Hypertrophy	3	3,50%	0	0,00%

Table 3. Evaluating of diastolic heart function according to cardiac geometry of patients in children with thalassemia major.

	Normal n:147	Eksentrik Hipertrofi n:17	Konsentrik Remodeling n:5	Konsentrik Hipertrofik n:3	p
mpilv	0,38±0,07	0,48±0,08	0,51±0,04	0,52±0,05	0,0001
Dtlve	5,7±1,32	6,04±1,91	7,44±1,47	6,95±0,87	0,018
Dtlva	0,1±0,11	0,68±2,4	0,1±0,02	0,1±0,01	0,032
Dtlve/a	2,32±0,43	2,24±0,6	1,88±0,56	2,29±0,19	0,179
Dtlvsys	0,11±0,02	0,11±0,02	0,11±0,01	0,11±0,01	0,658
Dtlvivrt	54,88±11,67	64,82±12,03	65,2±10,71	64±7,94	0,002
Dtlvivct	29,64±6,92	35,41±8,91	41±7,78	39,67±9,07	0,0001
Dtlvat	384,95±34,1	391,06±40,89	423,6±35,27	394,33±56,62	0,104
Dtlvet	278,7±22,69	265,24±28,62	281±20,16	260±34,12	0,084
Dme	1,11±0,24	1,26±0,18	1,28±0,23	1,5±0,13	0,002
Dma	0,95±4,02	0,76±0,23	0,77±0,23	0,83±0,16	0,997
Dmea	1,81±0,28	1,74±0,33	1,73±0,33	1,84±0,19	0,731
Dmdect	145,57±19,95	133,59±16,12	130±6,71	126±22	0,094
Tme	0,2±0,02	1,42±5,05	0,17±0,03	0,22±0,01	0,028
Mapse	1,38±0,14	1,34±0,15	1,28±0,22	1,4±0	0,319

Dlve: Doppler tissue imaging left ventricular E wave velocity, Dlva: Doppler tissue imaging left vetricular A wave velocity, Dlve/a: Doppler tissue imaging left ventricular E/A wave velocity range, Dtlvsys: Doppler tissue left ventricular systolic velocity, Dtlvivrt: Doppler tissue left ventricular isovolumetric relaxation time, Dtlvivct: Doppler tissue imaging left ventricular isovolumetric contraction time, Dtlvat: Doppler tissue imaging left ventricular a time duration, Dtlvet: Doppler tissue imaging left ventricular e time duration,

The study group classified into two subgroups according to ferritin levels (ferritin <2500 Group 1, Ferritin >2500 Group 2), and there were no significant differences between these subgroups in terms of cardiac functions. We found that ferritin levels are not suitable for evaluating early cardiac dysfunction (Table 3).

According to echocardiographic findings, left ventricular measurments, systolic and diastolic functions, left ventricular mass index and cardiac output levels evaluations were comparable between subgroups without any significant differences among them. In our study we also revealed marked increase in ferritin levels and QTc levels (Table 4).

When we classified the study group into two subgroups according to their MR T2* index as Group 1 MR T2* index<20 (9 patients) and Group 2 MR T2* index>20 (76 patients), we found marked increase in ferritin levels and marked increase in QTc levels on ECGs (Table 5).

Table 4. Comparison of study subgroups according to ferrtin levels.

	<2500 Ferritin n:65	>2500 Ferritin n:20	P
Age	13,15±7,18	13,45±6,86	0,871
Bsa	1,2±0,42	1,21±0,37	0,919
Hr	92,28±15,54	94,45±18,51	0,603
QTc	390,94±16,76	396,3±25,32	0,275
Ivmas	114,64±58,14	118,91±46,27	0,765
Ivsd	8,63±1,85	8,75±1,59	0,795
Lvdd	43,15±7,31	44,5±5,45	0,450
Lvds	27,06±4,74	27,4±3,07	0,765
Lvpwd	7,34±1,95	7,5±1,67	0,739
Lvedv	87,17±34,04	92,2±27,1	0,548
Ejection fraction	67,29±4,68	69,2±4,18	0,106
Dlve	1,37±0,2	1,37±0,22	0,56
Dlva	0,68±0,16	0,69±0,21	0,17
Dlv e/a	1,93±0,32	1,81±0,37	0,161
Cardiac output	5,26±2,04	6,01±2,12	0,157

İVSd: interventricular septum diastolic diameter, LVDd: left ventricular diastolic diameter, LVDs: left ventricular systolic diameter, Lvpwd: left ventricular posterior wall diastolic diameter, Dlve: Doppler tissue imaging left ventricular E wave velocity, Dlva: Doppler tissue imaging left vetricular A wave velocity, Dlve/a: Doppler tissue imaging left ventricular E/A wave velocity range

DISCUSSION

Long-term blood transfusion therapy in patients with thalassemia major causes extravascular hemolysis and excessive storage of iron due to increased intestinal absorption. Therefore hemosiderosis may develop in several organs. Excessive iron storage in myocardium causes ventricular dysfunction. Congestive heart failure and arrhytmias are major causes of death [8].

In terms of ventricular function, 2 different phenotypes are present): (i) a dilated cardiomyopathy phenotype, characterized by left ventricular dilatation and reduced contractility, leading to congestive heart failure; (ii) a restrictive cardiomyopathy phenotype,

Table 5. Comparison of cardiac MR findings betwen subgroups (according to MR T2* index).

	<20 MR n:11	>20 MR n:74	P
Age	17,67±6,38	17,55±5,23	0,954
Bsa	1,36±0,31	1,47±0,26	0,282
Hr	82,56±12,26	88,45±13,45	0,234
QTc	406,78±20,54	391,08±18,28	0,027
Lvmas	131,96±47,63	146,13±42,99	0,385
Ivsd	8,89±1,54	8,6±1,34	0,167
Lvdd	46,78±4,47	46,2±5,34	0,827
Lvds	29,11±2,71	29,33±3,69	0,871
Lvpwd	8,58±1,92	8,38±1,48	0,306
Lvedv	102,44±24,15	105,53±28,04	0,762
Ejection fraction	67,78±4,18	67,83±5,31	0,980
Dlve	1,38±0,13	1,32±0,2	0,397
Dlve	0,76±0,15	0,72±0,18	0,599
Dlve/a	1,9±0,35	1,89±0,37	0,950
Cardiac output	5,76±1,92	6,28±2,04	0,494

İVSd: interventricular septum diastolic diameter, LVDd: left ventricular diastolic diameter, LVDs: left ventricular systolic diameter, Lvpwd: left ventricular posterior wall diastolic diameter, Dlve: Doppler tissue imaging left ventricular E wave velocity, Dlva: Doppler tissue imaging left vetricular A wave velocity, Dlve/a: Doppler tissue imaging left ventricular E/A wave velocity range

characterized by restrictive left ventricular filling with subsequent pulmonary hypertension, right ventricular dilation, and heart failure [9].

This study shows that in young adults with β thalassaemia but no clinical signs of cardiac involvement, there are abnormalities of left ventricular morphology and systolic and diastolic functions. All these findings are in agreement with those reported by others and they are related to the increased cardiac output caused by the chronic anemia. Our study also shows a decrease in left ventricular systolic and diastolic functions owing to an increase in the afterload and a reduced contractile state, which is probably secondary to iron toxicity [10].

Although cardiac hemochromatosis generally causes dilated cardiomyopathy characterized by increase in left ventricular diastolic diameter and systolic dysfunction, in some patients it may cause restrictive cardiyomyopathy which is characterized by decreased left ventricular capacity. Systolic cardiac dysfunction is seen frequently but there are also many recent studies about diastolic dysfunction in hemachromatosis. Current studies about iron- related myocardial toxicity suggest that iron toxicity firstly damages electrical activity before myocardial injury. Atrial and ventricular dilatation, thickening of ventricular wall, marked increase in cardiac mass and fibrosis of cardiac conduction system may develop [11-13].

According to some resources cardiac MRI assessment of T2* and ejection fraction measurements on an annual or biannual basis considered as the gold standard assessments of cardiac iron storage. However, according to some resources ejection fraction estimated by MRI is much more efficient than ECHO, allowing recognition of preclinical cardiac dysfunction. Cardiac T2* values less than 10 ms indicate high risk for subsequent cardiac decompensation and warning of aggressive iron chelation therapy [14,15].

When we compared thalassemia major patients with the control group according to cardiac measurements (LV mass, LVDd, LVDs, LVPwd) and cardiac output, a significant increase in these parameters, and a significant decrease in left ventricular diastolic function (decreased DLV e/a) have been found in the study group.

Significant correlation between left ventricular ejection fraction and serum ferritin concentration was found, and patients with higher (>2500 ng/dl) serum ferritin concentrations had a lower ejection fraction than patients with lower ferritin concentrations (<1000 ng/dl) [16,17].

As we classified our subgroups according to ferritin level and cardiac MRI T2 * there was no difference revealed in ventricular systolic and diastolic functions and cardiac output between the subgroups. According to the results of many studies, serum ferritin concentration is not a reliable indicator of body iron storage since it increases even in any simple inflammation [18].

Recent studies suggest that ferritin level is not a reliable marker for evaluating serum iron levels because it also increases in several chronic diseases, in infections and inflammatory diseases as an acute phase reactant.

In 30% of our patients we revealed ventricular deformation. Patients with left ventricular deformity were

found with normal systolic but decreased diastolic functions.

CONCLUSION

In this study we aimed to find most usable techniques for evaluating early cardiac dysfunctions in patients with thalassemia major who were followed in pediatric hematology polyclinic. In patients with thalassemia major who have defective left ventricular geometry and mass, a significant decrease in the right and left ventricular diastolic functions has been detected. Even in young asymptomatic children with beta-thalassemia major, serial echocardiography seems warranted in order to adjust cardioprotective therapy. As a result, patients with thalassemia major ventricular systolic and diastolic functions should be evaluated, and geometrical assessments by echocardiographic measurements during routine cardiac controls.

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