ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Multisegmental Tissue Doppler Imaging and Biochemical Indicators in Thalassemia Major

Talasemi Majorda Çok Segmentli Doku Doppler ve Biyokimyasal Göstergeler

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Abstract

Introduction: Since heart failure is among the most important mortality reasons among Thalassemia Major patients, these patients must be regularly checked for heart problems.

Our study was planned to compare pulse wave doppler images and segmental tissue doppler images from 8 different areas and their copeptin, NT-pro ANP, NT-proBNP, CK-MB, and ultra-sensitive troponin I value with those of healthy individuals.

Materials and Methods: Fifty-nine Thalassemia Major patients over the age of 10, who were asymptomatic concerning cardiac symptoms, were divided into two groups (Group 1T2*<20 msn and Group 2: >20 msn). Echocardiography data and biochemical parameters of patient groups were compared with the control group.

Results: In both patient groups, NT-proBNP values were found to be significantly higher compared to the control group (p<0.001), and no correlation was found between NT-proBNP and cardiac MRI. In tissue doppler imaging of lateral and medial sections of the mitral annulus, it was seen that IVCT and IVRT measurements of both patient groups were extended and Myocardial Performance Index (MPI) measurements were increased. E´, A´, and S measurements of Group 1 were found to be lower compared to the control group. There were no significant differences between the groups in terms of copeptin, NT-proANP, CK-MB, and US-Troponin I values.

Conclusion: Investigated biochemical indicators could not be strongly correlated with iron accumulation. By calculating MPI values with tissue doppler echocardiography, global cardiac dysfunction may be identified earlier and chelation therapy may be revised.

Öz

Giriş: Talasemi Majör hastalarında kalp yetmezliği en önemli ölüm nedenlerinden biri olduğundan, bu hastaların düzenli olarak kalp sorunları açısından kontrol edilmesi gerekmektedir.

Çalışmamızda, Talasemi Majör hastalarında 8 farklı bölgeden alınan nabız dalga doppler görüntüleri ve segmental doku doppler görüntülerinin yanı sıra copeptin, NT-pro ANP, NT-proBNP, CK-MB ve ultra-duyarlı troponin I değerlerinin sağlıklı bireylerle karşılaştırılması planlandı.

Gereç ve Yöntem: Kalp ile ilgili semptomları bulunmayan, 10 yaş üzeri 59 Talasemi Majör hastası iki gruba ayrıldı (Grup 1: T2*<20 msn ve Grup 2: T2*>20 msn). Hasta gruplarının ekokardiyografi verileri ve biyokimyasal parametreleri kontrol grubu ile karşılaştırıldı.

Keywords
Thalassemia, tissue Doppler imaging, T2* MRI

Anahtar kelimeler
Talasemi, doku doppler görüntüleme, T2* MRI

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Bulgular: Her iki hasta grubunda NT-proBNP değerleri kontrol grubuna göre anlamlı derecede yüksek bulundu (p<0,001) ve NT-proBNP ile kardiyak MRG arasında ilişki bulunmadı. Mitral anülüsün lateral ve medial kesimlerine ait doku doppler görüntülerinde her iki hasta grubunda da IVCT ve IVRT ölçümlerinin uzadığı ve Miyokardiyal performans indeksi (MPI) ölçümlerinin arttığı görüldü. Grup 1'in E´, A´ ve S ölçümleri kontrol grubuna göre daha düşük bulundu. Copeptin, NT-proANP, CK-MB ve ultra-duyarlı Troponin I değerleri açısından gruplar arasında anlamlı bir fark saptanmadı.

Sonuç: İncelenen biyokimyasal göstergeler demir birikimi ile güçlü bir şekilde ilişkilendirilemedi. Ancak doku doppler ekokardiyografi ile MPI değerleri hesaplanarak, bütünsel kardiyak fonksiyon bozukluğu daha erken tespit edilebilir ve şelasyon tedavisi yeniden düzenlenebilir.

Introduction

Beta-thalassemia major is a hereditary blood disorder, resulting in severe anemia as a result of anomalies in the beta chain of hemoglobin. In β-thalassemia patients, severe anemia develops progressively, starting from the first few months of extrauterine life. These patients require regular blood transfusions to treat severe anemia, which develops as a result of ineffective erythropoiesis, and to improve survival (1-4). Regular blood transfusions impose a significant iron burden on the organism, in particular on the heart and endocrine organs (5-9). Although iron chelators are used today to prevent iron burden, and to shape the treatment, regular monitoring of the body iron burden is necessary. Body iron burden alone is not sufficient in the determination of treatment, and monitorization of cardiac iron burden, which is directly related to long-term survival (10,11). The technique, considered the gold standard for monitoring cardiac iron burden, is cardiac T_2* Magnetic Resonance Imaging (T_2* MRI) (2). However, the unavailability of the T_2* MRI application in all healthcare institutions and its restricted use when available, the requirement of an appointment for MRI scans, potential problems, caused by the software program, and the patients' fear of MRI scans, suggest that it would be appropriate to use novel and reliable methods, which are easy to implement in clinical monitorization of patients.

Ferritin has been used for long years as a marker for monitoring iron accumulation in thalassemia patients and adjustment of iron chelation treatment doses. However, ferritin levels may be elevated in many conditions, such as inflammation, liver, and kidney disorders (12,13). In addition, there are studies, showing that ferritin levels are not associated with cardiac iron accumulation (14). Many studies have been conducted to determine whether various cardiac biomarkers were correlated with ferritin and whether they could be considered as an indicator in the demonstration of cardiac iron accumulation (15,16). Cardiac biomarkers include troponin, Creatinine Kinase MB (CK-MB), natriuretic peptides (N-terminal atrial natriuretic peptide (NT-ANP) and N-terminal brain natriuretic peptide (NT-BNP) and recently, copeptin. Copeptin molecule, a precursor peptide to arginine vasopressin (AVP), whose excretion is thought to be triggered by endogenous stress mechanisms, has been studied in non-thalassemia populations for various indications, in particular acute myocardial infarct and heart failure (17-19).

The objective of this study is to compare pulse wave (PW) Doppler images and segmental tissue Doppler (TD) images from 8 different areas and their NT-proANP, NT-proBNP, CK-MB, ultra-sensitive troponin I, and copeptin value of beta-thalassemia (ß-Thal) patients, who were grouped according to cardiac iron accumulation, with those of healthy individuals.

Materials and Methods

Before the study, approval was obtained from Akdeniz University Faculty of Medicine, Clinical Studies Ethics Committee. Informed consent was obtained from the persons in patient and control groups, who were over the age of 18, and from parents of persons, who were under the age of 18.

Patient and Control Group

63 ß-Thal patients, over the age of 10, who had been regularly monitored by Akdeniz University, Faculty of Medicine, Department of Pediatric Hematology, and as the control group, 29 healthy individuals with matching ages and genders, were included in the study. 4 patients in the ß-Thal group were excluded due to the absence of recent (within the last 6 months) T_2* MRI results. 5 persons in the control group were excluded from the study due to anemia, discovered during the study (hemoglobin <12 g/dL).

Cardiac MRI results of patients within the last six months were accessed via hospital electronic system records and MRI scans of all patients were made using a 1.5-Tesla (Siemens Magnetom Avanto) device. Patients were divided into two groups based on their T_2* MRI results:

Group 1: T_2* MRI < 20 msn n=26

Group 2: T_2* MRI ≥ 20 msn n=33

Age, gender, height, weight measurements, and last exercise dates of 59 ß-Thal patients and 24 control group individuals were recorded. After at least 10 minutes of rest and after confirmation that they had not consumed tobacco, alcohol, tea, and coffee within the last 2 hours and they had not made intensive exercise for the last 6 hours, blood pressure measurements were taken. Then, the blood samples of participants were taken to three separate tubes (with EDTA, heparin, and plain serum tube). After the acquisition of blood samples, while complete blood counts were studied on the same day, serum (for CK-MB, us-TrI, and NT-proBNP) and plasma (for NT-proANP, copeptin) were separated and stored at -80°C.

Measurement of Biochemical Parameters

Hemograms were studied using Advia 120 device and US-Troponin I, CK-MB, and NT-proBNP were measured using Siemens Centaur XP and Immulite 2000 devices. Copeptin and NT-proANP concentrations were determined via Sandwich enzyme-linked immunosorbent assay (20) method, using commercial kits (Copeptin: Cat. No: MBS2600645 and NT-proANP: Cat. No: MBS2023123) in line with kit protocols.

Echocardiographic Evaluation

Conventional and Tissue Doppler ECHO images of participants were obtained using 3 MHz probes of Vivid 7 Pro, Horten, Norway, device, with the patient lying on the left side. In conventional ECHO, regional contractile anomalies, systolic and diastolic diameters, volumes, ejection fraction, fractional shortening, and diameters of cardiac cavities were evaluated. Left ventricle (LV) diastolic functions were measured via transmitral pulse wave (PW) Doppler velocity records at the apical four-chamber position. Systolic and diastolic functions were recorded three consecutive times and the mean values for the same were recorded.

In TD ECHO, measurements of periods, required for MPI of both ventricles, were made using Pulse Wave Tissue Doppler (PWTD) mode. For this, recordings were obtained from a total of eight regions, with prompt on lateral and medial segments at the mitral valve level, lateral and medial at the tricuspid valve level, medial and basal at the intraventricular septum level, and LV and right ventricle (RV) lateral wall segment. In the records, measurements for wave and time intervals were taken separately. MPIs were calculated according to guidelines (20).

Statistical Analysis

Analyses were made using SPSS 22.0 package program. Descriptive statistics were presented using frequency, percentage, mean, standard deviation, and median, minimum, and maximum values. p values, less than 0.05 were deemed as statistically significant. In the analysis of relationships between categorical variables, Fisher's Exact Test or Pearson chi-Square test was used. In the normality test, when the number of samples in the group was less than 50, the Shapiro-Wilks test and when the number of samples was greater than 50, the Kolmogorov-Smirnov test was used. In the analysis of the difference between the measured values of the two groups, the Mann-Whitney U test was used when the normal distribution assumption could not be satisfied. In non-parametric comparison of the three groups Kruskal-Wallis test and for significant cases, Bonferroni-Dunn test was used as a post-hoc test. When the normal distribution assumption is satisfied, the ANOVA test was used in the comparison of three groups and the Tukey test was used in dual comparisons. The relationships between continuous variables, which are inconsistent with ordinal or normal distribution, were studied with the Spearman correlation test, and the Pearson correlation test was applied for those, which are consistent with normal distribution.

Results

In this study, while no significant difference was seen between the mean age of the control group and the patient group, it was determined that the mean age of Group 1 was higher compared to Group 2. No difference was seen between the groups in terms of gender, body mass index (BMI), height, and weight. Hemoglobin values were found to be higher in the control group, compared to the patient group ($p<0.001$). NT-proBNP values were found to be higher in both patient groups, compared to the control group ($p<0.001$). No significant differences were seen between the groups concerning CK-MB, NT-proANP, and copeptin values (Table 1). Concerning US-Troponin, I value, only two patients had above-normal values. T_2* MRI result of one of these patients was 41.47 and the other patient's value was 10.23 and they had no active cardiac complaints. US-Troponin I values of the control group were measured in the normal range. Therefore, they were not included in the comparison.

No significant differences were found between the groups in terms of mean values for all conventional ECHO parameters (Table 2). As a result of the evaluation of TD measurements from the medial and lateral sides of the mitral valve, it was

Table 1. Clinical and biochemical parameters of the cases

Variables	Group 1 n=26	Group 2 n=33	Control n=24	P1	P2	P3
Gender	17F/9M	15F/18M	9F/15M	NS	NS	NS
Age median (min-max) year	24.6 (13.5-41.9)	18 (10.5-36.9)	22.2 (15.6-33)	0.009	NS	NS
Height (cm) mean ± SD	156.9±8.8	160.1±12.8	-	NS	-	-
Body Weight (kg) mean ± SD	49.6±8.8	54.8±14.2	-	NS	-	-
BMI (kg/m²) mean ± SD	20.1±2.5	21±3.3	-	NS	-	-
Hemoglobin g/dL mean ± SD	10.2±1.5	9.6±0.6	14.1±1.2	NS	<0.001	<0.001
Nt-ProBNP pg/mL mean ± SD	136.6±140.3	163.5±213.2	36.1±33.5	NS	<0.001	<0.001
CK-MB ng/mL mean ± SD	1.7±3.8	0.9±0.5	0.9±1.7	NS	NS	NS
Nt-ProANP pg/mL mean ± SD	211.3±162.9	167.8±122.9	110.1±48.4	NS	NS	NS
Copeptin pg/mL mean ± SD	23.9±17.3	30.9±25.9	33.3±14.7	NS	NS	NS

P1.Group 1 versus Group 2; P2. Grup 1 versus Control; P3. Grup 2 versus Control; NS. Non-significiant

Table 2. Conventional echocardiographic parameters

Variables mean ± SD	Group 1 n=26	Group 2 n=33	Control n=24	P1,P2, P3
AO (mm)	23.8±4.3	21.5±4.8	26.9±2	NS
LA (mm)	33.6±5.2	31±6.5	33.1±3.3	NS
AO/LA	0.7±0.1	0.7±0.2	0.8±0.1	NS
IVSD (mm)	9.4±2.2	9.8±2.3	8.8±1.4	NS
LVEDD (mm)	46.1±8.7	48.1±5.4	46.4±4.2	NS
LVPWD (mm)	9.1±1.5	8.2±2.2	8.8±1.6	NS
IVSS (mm)	13.4±3.0	13.1±2.2	12.1±2.0	NS
LVS (mm)	30.1±5.4	29.0±4.4	29.8±4.2	NS
LVPWS (mm)	12.9±2.8	11.8±2.6	12.3±2.2	NS
EF (%)	64.9±10.3	70±6.2	66.3±6.0	NS
FS (%)	36.4±8.1	39.9±5.3	36.6±4.7	NS
PVMAX (m/s)	1.1±0.1	1.1±0.2	1.1±0.1	NS
ME (m/s)	1±0.2	1±0.2	0.9±0.1	NS
MA (m/s)	0.5±0.2	0.6±0.1	0.6±0.1	NS
ME/MA	1.9±0.5	1.7±0.5	1.6±0.5	NS
TE (m/s)	0.6±0.2	0.7±0.1	0.6±0.1	NS
TA (m/s)	0.5±0.1	0.5±0.1	0.4±0.1	NS
TE/TA	1.2±0.4	1.3±0.5	1.2±0.4	NS

found that E, A, and S wave values in Group 1 were lower compared to those in the control group for both medial and lateral measurements of the mitral valve ($p<0.05$). In both patient groups, prolongations were seen in Interventricular Contraction Time (IVCT) and Interventricular Relaxation Time (IVRT) values in both medial and lateral measurements and an increase in MPI ($p<0.05$). E/E´ value, calculated with a measurement of the lateral annulus, was found to be higher in Group 1, compared to both Group 2 and the control group ($p=0.001$ and $p<0.001$); there were no significant differences in medial mitral annulus measurements (Table 3).

In Table 4, TD samples, obtained from the medial and lateral sides of the tricuspid valve, are evaluated. IVCT values, measured in both areas, were found to be prolonged in patient groups, compared to the control group ($p=0.001$ and $p<0.001$). Similarly, an increase was seen in MPI ($p<0.01$).

In TD ECHO scans, the E value, included in interventricular septum median (IVSM) parameters, was found to be lower in Group 1 compared to the other two groups ($p=0.001$). IVSM A value was found to be lower in both patient groups compared to the control group ($p<0.001$ with Group 1; $p=0.001$ with Group 2). IVSM S value of Group 1 was found to be lower compared to those of the other two groups ($p=0.001$ with Group 2; $p<0.001$ with Group 1). IVSM E/A rates of the patient groups were found to be higher compared to those of the control group ($p<0.05$). IVSM IVCT values of the patient groups were found to be higher compared to those of the control group ($p<0.05$). Concerning IVSM IVRT values, a prolongation was observed only in Group 1 compared to the control group ($p=0.001$). IVSM MPI values of patient groups were found to be significantly higher compared to those of the control group ($p<0.05$). Interventricular septum basal (IVSB) A value was found to be lower in patient groups compared to the control group ($p<0.05$). IVSB IVCT times of patient groups were found to be longer compared to those of the control group ($p<0.001$). IVSB IVRT times of patient groups were found to be longer compared to those of the control group ($p<0.05$). IVSB MPI values of patient groups

Table 3. Tissue Doppler measurements taken from the medial and lateral area of the mitral valve

MM mean± SD	Group 1 n=26	Group 2 n=33	Control n=24	P1	P2	P3
E	9.9±2.3	13.8±4	12.2±2.1	<0.001	0.004	NS
A	6.8±2.7	8.9±2.1	9.3±1.6	0.009	0.001	NS
S	7.1±1.7	8.7±1.4	8.9±1.0	0.001	<0.001	NS
E/A	1.6±0.6	1.7±0.7	1.4±0.3	NS	NS	NS
IVCT	66.8±13.0	70.9±15.1	53.9±8.2	NS	0.002	<0.001
IVRT	72.7±14.3	74.6±10.8	61.2±6.2	NS	0.005	<0.001
ET	270.1±23.4	274.3±26.1	279.0±29.1	NS	NS	NS
MPI	0.5±0.5	0.6±0.5	0.4±0.2	NS	0.004	<0.001
E/E’	1.1±0.2	1±0.4	1±0.2	NS	NS	NS
ML mean ± SD	Group 1 n=26	Group 2 n=33	Control n=24	P1	P2	P3
E	12.6±4.7	17.9±4.4	16.6±3.0	<0.001	0.003	NS
A	7.1±3.8	7.7±2.3	10±1.7	NS	<0.001	0.007
S	8.8±2.9	10.6±2.2	10.7±1.9	0.044	0.046	NS
E/A	2.3±1.0	2.5±0.9	1.7±0.4	NS	NS	<0.001
IVCT	67.0±12.7	65.5±14.7	54.5±7.5	NS	0.001	0.007
IVRT	68.7±11.1	69.2±12.6	60.9±9.8	NS	0.047	0.028
ET	271.8±27.5	276.5±26.3	282.1±30.7	NS	NS	NS
MPI	0.5±0.1	0.5±0.1	0.4±0.1	NS	<0.001	0.001
E/E’	0.9±0.3	0.6±0.3	0.6±0.1	0.001	<0.001	NS

P1: Group 1 vs. Group 2; P2: Grup 1 vs. Control; P3: Grup 2 vs. Control; NS: Non-significant. Units of time-related parameters (IVCT, IVRT, ET) were measured in milliseconds; waves (E, A, S) were measured in meters/second

were found to be significantly higher compared to those of the control group ($p<0.001$). In ET values, no significant differences were seen between the groups both in IVSM and IVSB measurements (Table 5).

In the measurement, conducted on the left ventricle lateral (LVL) wall, A and S wave averages in Group 1 were found to be lower compared to those in the control group ($p<0.05$). No significant difference was found between the groups concerning LVL ET mean values. Right ventricular lateral (RVL) IVCT mean values were found to be prolonged in the patient group, compared to in the control group ($p<0.05$). In records, obtained from RVL, Group 1 IVRT value was found to be prolonged compared to the control group ($p<0.05$). No differences were found between groups concerning mean RVL E, RVL A, RVL S, RVL E/A, and RVL ET values (Table 6).

No significant correlation was found between cardiac T_2* MRI results of the patient group and TD echo results with biochemical indicators. A correlation, albeit weak, was determined only between NT-proBNP, among biochemical indicators of patients in Group 1, with MRI results ($p=0.027$, $r=-0.442$).

Discussion

The toxic effects of iron accumulation in the heart are one of the most significant causes of mortality and morbidity in thalassemia. Therefore, direct and indirect monitoring of the effects of cardiac iron is required at regular intervals. While cardiac iron may be directly imaged using MRI, whether this iron has caused a loss of function in the heart may only be understood (indirectly) using ECHO, electrocardiogram, etc., methods (21). However, no biochemical markers, showing the cardiac-specific iron burden have been discovered until today.

Evaluation of Biochemical Parameters

When NT-proANP, NT-proBNP, CK-MB, and copeptin are considered in patient and control groups, only NT-proBNP was found to be higher in the patient group, compared to the control. In line with the literature, in recent studies, it has been shown that NT-proBNP was elevated compared to controls, in ß-Thal patients, who had no clinical symptoms of heart failure (22-26). Among these studies, in the study by Kremastinos et al. (22,23) latent cardiac diastolic dysfunction

Table 4. Tissue Doppler measurements taken from the medial and lateral area of the tricuspid valve

TM mean± SD	Group 1 n=26	Group 2 n=33	Control n=24	P1	P2	P3
E	12.2±2.8	13.6±3.2	12.3±2.1	NS	NS	NS
A	7.6±3.1	9.8±4.0	9.4±1.6	NS	NS	NS
S	9.3±1.8	10.2±1.9	9±1.1	NS	NS	NS
E/A	1.8±0.6	1.6±0.7	1.3±0.3	NS	NS	NS
IVCT	74.4±11.8	69.8±12.6	54.2±8.6	NS	<0.001	0.001
IVRT	69.8±13.7	73.3±13.2	61.2±6.2	NS	NS	0.003
ET	268.3±28.6	277.4±28.6	280.5±28.2	NS	NS	NS
MPI	0.5±0.1	0.5±0.1	0.4±0.1	NS	0.002	0.001
E/E’	0.5±0.1	0.6±0.3	0.5±0.1	NS	NS	0.031
TL mean ± SD	**Group 1 n=26**	**Group 2 n=33**	**Control n=24**	**P1**	**P2**	**P3**
E	13±3.7	15.6±3.1	14±2.0	0.001	NS	NS
A	13.3±4.3	14.3±4.6	12.0±2.7	NS	NS	NS
S	13.5±3.3	15.0±2.5	13.3±1.9	NS	NS	0.022
E/A	1±0.3	1.2±0.4	1.2±0.3	NS	NS	NS
IVCT	68.2±13.3	68.1±11.3	54.7±10.2	NS	<0.001	<0.001
IVRT	73.2±11.0	69.3±14.8	63.4±7.5	NS	0.002	NS
ET	282.7±31.2	269.1±27.5	277.3±23.4	NS	NS	NS
MPI	0.5±0.1	0.5±0.1	0.4±0.1	NS	<0.001	0.001
E/E’	0.5±0.1	0.5±0.2	0.4±0.1	NS	NS	NS

P1: Group 1 vs. Group 2; P2: Grup 1 vs. Control; P3: Grup 2 vs. Control; NS: Non-significant. Units of time-related parameters (IVCT, IVRT, ET) were measured in milliseconds, waves (E, A, S) were measured in meters/second.

Table 5. Tissue doppler measurements, taken from basal and median interventricular septum

IVSb mean± SD	Group 1 n=26	Group 2 n=33	Control n=24	P1	P2	P3
E	10.3±2.8	13.2±2.8	12.2±2.1	0.003	NS	NS
A	6.8±2.2	8±2.4	9.3±1.6	NS	0.003	0.037
S	7.7±1.3	9.6±1.4	8.9±1.0	0.001	0.053	NS
E/A	1.7±0.6	1.8±0.6	1.4±0.3	NS	NS	0.017
IVCT	72.7±12.9	67.3±10.0	53.9±8.2	NS	<0.001	<0.001
IVRT	74±10.4	71.9±11.5	61.2±6.2	NS	0.002	0.002
ET	263.9±26.8	272.1±24.1	279.0±29.1	NS	NS	NS
MPI	0.6±0.1	0.5±0.1	0.4±0.1	NS	NS	NS
IVSm mean ± SD	**Group 1 n=26**	**Group 2 n=33**	**Control n=24**	**P1**	**P2**	**P3**
E	9.5±1.9	11.9±2.6	12.2±2.4	0.001	0.001	NS
A	5.2±1.8	6.5±1.6	8.2±1.2	NS	<0.001	0.001
S	5.8±1.1	7.3±1.1	7.9±0.9	0.001	<0.001	NS
E/A	2±0.7	2±0.8	1.5±0.4	NS	0.009	0.014
IVCT	67.9±11.2	70±11.5	57.0±9.9	NS	0.002	<0.001
IVRT	79±11.2	73.5±13.5	66.7±10.2	NS	0.001	NS
ET	272.2±27.3	274.5±27.1	274.2±26.1	NS	NS	NS
MPI	0.55±0.10	0.53±0.09	0.45±0.07	NS	0.001	0.011

P1: Group 1 vs. Group 2; P2: Grup 1 vs. Control; P3: Grup 2 vs. Control; NS: Non-significant. Units of time-related parameters (IVCT, IVRT, ET) were measured in milliseconds; waves (E, A, S) were measured in meters/second.

Table 6. Tissue Doppler measurements taken from the right and left lateral ventricle wall

LVL Mean ± SD	Group 1 n=26	Group 2 n=33	Control n=24	P1	P2	P3
E	11.6±4.0	16.8±4.8	14±3.2	<0.001	NS	0.044
A	6.5±3.1	7.6±2.3	8.3±1.7	NS	0.015	NS
S	7.4±2.7	9.5±2.9	9.3±2.3	0.022	0.038	NS
E/A	2.3±1.3	2.5±1.1	1.8±0.5	NS	NS	0.015
IVCT	60.1±14	65.2±10.1	52.7±8.4	NS	NS	<0.001
IVRT	70.8±12.6	72.4±9.2	64.3±11.1	NS	NS	0.020
ET	274.1±33.6	277.2±23.7	276.4±29.9	NS	NS	NS
MPI	0.5±0.1	0.5±0.1	0.4±0.1	NS	NS	0.001
RVL mean ± SD	**Group 1 n=26**	**Group 2 n=33**	**Control n=24**	P1	P2	P3
E	13±3.0	14.4±3.7	14.6±2.5	NS	NS	NS
A	12.3±4.5	13.1±3.8	13.3±3.1	NS	NS	NS
S	12.0±2.5	13.2±2.7	12.9±2.1	NS	NS	NS
E/A	1.2±0.7	1.2±0.4	1.2±0.4	NS	NS	NS
IVCT	69.1±11.9	69.8±11.7	60.7±12.3	NS	0.042	0.022
IVRT	73.3±12.7	68.9±13.5	65.0±9.3	NS	0.022	NS
ET	282.8±31.3	267.0±25.1	279.4±27.4	NS	NS	NS
MPI	0.5±0.1	0.5±0.1	0.5±0.1	NS	NS	0.032

P1: Group 1 vs. Group 2; P2: Grup 1 vs. Control; P3: Grup 2 vs. Control; NS: Non-significant. Units of time-related parameters (IVCT, IVRT, ET) were measured in milliseconds; waves (E, A, S) were measured in meters/second

parameters and NT-proBNP are in correlation, and in the study by Tschöpe et al. (24), and Akpınar et al. (25), diastolic parameters were not correlated with NT-proBNP, yet an elevation in NT-proBNP without correlation, has been detected.

Delaporta et al. (27), divided 187 asymptomatic ß-Thal patients into MRI groups as in our study and calculated dry iron weights and consequently found a significant difference between groups in terms of NT-proBNP values. In our study, although this value was higher in patients compared to in the control group, no inter-group differences were seen in patient groups. Kostopoulou et al. (28), in a study, conducted on 90 asymptomatic ß-Thal patients, have divided the groups based on E/E´ values (diastolic dysfunction classification) and have evaluated proANP and NT-proBNP levels and shown that these parameters were early indicators of cardiac effects and it has been stated that the levels increased in case of presence of cardiac dysfunction. In our study, no significant inter-group difference was seen concerning NT-proANP. It was contemplated that the reason for the high measurement of natriuretic peptide NT-proBNP in the patient group and failure of NT-proANP to obtain a significant increase in patient groups, was the possibility of an influence on secretion by secondary reasons (such as volume burden, chronic anemia, asymptomatic patient distribution), rather than effects of cardiac iron accumulation on NT-proANP.

The lack of an inter-group significant difference concerning copeptin, suggests that this molecular structure could be elevated more in acute cases, rather than chronic cardiac failure (17). The reason for asymptomatic patient distribution suggests that copeptin release was not sufficient because asymptomatic patients constituted the majority of the study population.

Evaluation of Tissue Doppler ECHO Parameters

PWTD, among ECHO techniques, is a novel technique compared to ECHO and in particular in early detection of diastolic function, may provide more meaningful results compared to PW Doppler, regardless of preliminary burden. It may also provide information concerning regional cardiac dysfunction (10). Although sometimes the results of PWTD studies on thalassemia patients conflict, in publications, it has been stated that this technique was promising (10, 26, 29, 30).

Tissue doppler E´, A´, and S measurements, taken from medial (2) and lateral (ML) segments of the mitral valve, were decreasing in Group 1 compared to Group 2 and the control group and this suggested that increasing iron accumulation caused a decrease in the relaxation ability of these regions of the myocardium. These results were interpreted to suggest that diastolic effects, which could not be detected on PW Doppler, could be detected with PWTD and these support the thesis that left ventricle dysfunction was between normal and prolonged relaxation patterns in Group 1.

When these results are evaluated without considering their significance, it was seen that Group 1 had the lowest LVL E´, A´, and S values and this was interpreted as diastolic involvement of the LVL segment. As a result of literature research, a study, conducted by Vogel et al. (10), was found concluding, in line with our study, that a decrease had been observed in E´ and S values in basal and lateral segments of 52 ß-Thal patients compared to the control group and no significant differences had been observed in A´ values. Similarly, in a study, conducted by Balkan et al. (31), on asymptomatic ß-Thal patients, it has been found that the patient group had decreased S and E´ values in PWTD images, obtained from the septal annulus and no significant difference has been found between the groups in terms of A´. In another study, conducted by Yavuz et al. (32), in contrast to our study, while an increase has been detected in the patient group for left ventricle basal E´, no difference has been observed for A´. As for interventricular septum basal results of the same study, while no significant difference has been detected neither for A´ nor E´, an increase has been detected in E´ in the interventricular septum median and LVL in the patient group. It has been concluded that the results could be explained with restrictive type diastolic dysfunction, yet an influence of preliminary burden was also possible. In a study, conducted by Agha et al. (33), no significant intergroup differences have been found in E´, A´, and S waves. In another study, conducted by Ragab et al. (34), 25 ß-Thal patients with a mean age of 12±5.7 have been included in the study, and images have been obtained from anterior, inferior, septal and lateral areas of the mitral annulus. In the study, it has been found that while S and A´ waves in patients were similar to those in the control group, E´ value was decreased in the patient group in lateral, anterior, and inferior measurements. Such discrepancies in the values, found in various studies, may be explained by the lack of a standard protocol in the studies, variations in measurements due to the dynamic structure of the heart, varying age distribution, racial characteristics of patients, and the location and extent of segmental iron retention.

In waves, measured at RVL, no significant inter-group differences were detected. While there are limited studies on this issue, in the study, conducted by Vogel et al. (10), RVL E´ values of 52 ß-Thal patients, are lower compared to the control group, and no significant inter-group differences have been seen concerning RVL S and RVL A´. In the same study, in the records, obtained from the right ventricular basal segment, it has been observed that S and E´ had increased and A´ had decreased in the patient group. In a study, conducted by Yavuz et al. (32), on younger 61 ß-Thal patients have been evaluated and RVL and E´ and A´ values in the right ventricular basal segment are higher in the patient group. These inter-study differences were caused by the segmental effects of iron on the heart and the variability of the age range of the selected patient profile between groups.

In a study, Pepe et al. (35), have shown that the quantity of iron retention in the interventricular septum in cardiac T_2^* MRI, reflected total cardiac iron burden. Therefore, records were taken and evaluated from the septums of patients using the TD method. In our study, IVSB E´ and S waves were lower in Group 1, compared to Group 2 and A´ value was lower in Groups 1 and 2, compared to the control group. IVSM E´ and S waves were lower in Group 1 and Group 2 compared to in control group and A´ value was lower in Groups 1 and 2 compared to in control group. In our patient group, it was seen that iron accumulation caused a deterioration of relaxation ability in the ventricular septum. In a study on a young patient group, conducted by Yavuz et al. (32), no differences have been observed compared to controls in terms of measurements in IVSB and E´ value in IVSM has been determined to be higher in the patient group and therefore, the results in the study have not been interpreted as significant and this has been attributed to the young age of selected patient profile and low level of iron accumulation, which had not yet caused any cardiac effects in septum (32).

When the E/E´ rates of the patient and control group are compared, it was seen that only the E/E´ rate, measured in the mitral lateral segment, was increased in Group 1, compared to Group 2 and the control group. This is consistent with the literature and in studies on asymptomatic ß-Thal patients, conducted by Kremastinos et al. (22), it is increased in the patient group compared to controls and increased more significantly with age (23). Similarly, in a study on 90 asymptomatic ß-Thal patients, conducted by Kostopoulou et al. (28), E/E´ rates have been found to have increased in the patient group (28). In our study, it was contemplated that the reason for the lack of an inter-group difference in terms of TM and TL E/E´ values, was the preservation of RV diastolic functions

In our study, IVRT, IVCT, and ET measurements were taken from eight different tissue doppler windows and MPI was calculated. It was seen that in Mitral Medial (2), ML, and IVSB windows, IVRT, IVCT, and MPI values were prolonged in Group 1 and Group 2, compared to the control group. Similarly, in the IVSM window, while IVCT and MPI were found to have been prolonged in Group 1 and Group 2 compared to the control group, IVRT was found to have been prolonged only in Group 1 compared to the control group. When the parameters in MPI calculation are considered, it was seen that the reason for the increase in MPI was related to the prolongation of IVRT and IVCT, rather than the change in ET (no inter-group differences). We concluded that the presence of chronic anemia or the presence of additional aggravating factor, played a role at least in our patient group, in the increase of MPI in MM, ML, IVSB, and IVSM, along with iron accumulation.

Tissue doppler and correlation statistics, were analyzed for all patients, regardless of iron accumulation status, and in addition, for the group with iron accumulation (Group 1). Consequently, a strong correlation value could not be obtained in both group. Tissue doppler correlation values, which posed statistical significance, were detected weakly in E´, A´, and S waves, measured in the left side of the heart and interventricular septum. This situation could be explained with the conduction of a study on the asymptomatic patient group, the presence of segmental iron retention, and individual-specific hemodynamic entities at the moment of measurement.

Study Limitations

Two-dimensional speckle-tracking echocardiography is a new method, which has some limitations of the assessment of LV torsion. There is the crucial dependence on correct acquisition of a LV apical short-axis view (36). Monte et al. (37) showed no significant differences in longitudinal strain value between thalassemia and healthy individuals using the strain imaging by speckle tracking echocardiography. Tantawy et al. (38) and Parsaee et al. (39) the global LV longitudinal strain was significantly impaired in the patients compared with the controls, although radial and circumferential strain values were similar between the two groups. There were no significant correlations between cardiac T_2* MRI and speckle echocardiographic parameters in these studies. We perform TD echocardiography because of more usefull, quick and standart method in determine of diastolic dysfunction.

The difficulty of real-time iron burden imaging , deposition of iron in the heart in the form of a patch and inadequacy of MRI alone in the long-term monitoring, and instantaneous nature of functional evaluation (40), its insufficient contribution by itself in case of use of chelators, make only the use of the combination of these two monitorization techniques, meaningful (35).

Conclusion

In our study, investigated biochemical indicators could not be strongly correlated with iron accumulation. Detection of early cardiac dysfunction is very important since appropriate chelation therapy could allow recovery of heart function. We believe that in addition to T_2^* MRI, conventional ECHO, TD ECHO, ECG, and intermittent monitoring of ferritin and NT-pro BNP level have to use at least once a year. In particular, by calculating MPI values with TD echocardiography, global cardiac dysfunction may be identified earlier and chelation therapy may be revised.

We believe that future comparisons, made with MRI results of patients, by making standardized regional evaluations in the future (both for MRI and ECHO), would be more valuable for the demonstration of the relationship between iron accumulation and cardiac dysfunction.

Ethics

Ethical Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of Akdeniz University Faculty of Medicine with the (approval number: 70904504/181, date: 24.04.2015).

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Footnotes

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