

## Cardiac Evaluation, Holter Monitoring and Evaluation of Heart Rate Variability in Patients with Thalassemia Major

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### Abstract

**Introduction:** Cardiac complications due to iron accumulation are the main cause of death in patients with thalassemia major. Our study aimed to investigate the value of heart rate variability in showing the risk of early cardiac exposure and arrhythmia due to iron accumulation and the availability of heart rate variability (HRV) as a noninvasive method in children with major thalassemia.

**Material and Methods:** This study was carried out at the 24-hour Holter electrocardiography examination by comparing 30 patients with beta-thalassemia major diagnosis and 30 healthy control groups in Dicle University Faculty of Medicine, Department of Pediatric Hematology and Oncology and Pediatric Cardiology.

The heart rate variability, time, and frequency indexes of the two groups were compared. The relationship between serum ferritin levels and HRV parameters was evaluated.

**Results:** Sixteen of the patients with major thalassemia were girls (53%), 14 were boys (47%) and the mean age was  $10.1 \pm 3.8$  years. The 24-hour Holter ECG parameters, maximum heart rate, SDNN, RMSSD, pNN50, TP, LF, and VLF parameters were significantly lower in the patient group than the control group. According to ferritin values, patients were divided into Group I with ferritin values between 1500 - 2500 ng/ml, Group II between 2501 - 5000 ng/ml, and Group III with those over 5000 ng/ml. Heart rate change parameters and groups separated according to ferritin values were compared. The maximum heart rate was significantly higher in Group I compared to Group II and Group III ( $p = 0.03$ ). There was no significant difference between groups between other parameters. The ectopic hit was detected in eight of the patients. The atrial or ventricular ectopic hit was detected in Holter ECG in four of the 24 patients whose echocardiography findings were normal.

**Conclusion:** In our study, we found that the value of ferritin alone was not sufficient to indicate cardiac influence. Even if echocardiographic examinations are normal, autonomous dysfunction, atrial and/or ventricular early hit can be detected, so patients with TM should be given 24-hour Holter ECG monitoring as well as echocardiographic examination.

**Keywords:** Thalassemia Major; Heart Rate Variability; Ferritin

### Introduction

Thalassemia is the most common single gene-disease [1]. It is an autosomal recessive disease that occurs as a result of disruption in the synthesis of one or more hemoglobin polypeptides. Cardiac complications are the most important cause of mortality and morbidity in patients with thalassemia major (TM). The causes of cardiac dysfunction are the increase in ventricular contractility due to chronic hemolytic anemia, expansion of ventricular and iron accumulation. In the late stages of cardiomyopathy associated with iron accumulation, left ventricular diastolic dysfunction, pulmonary and peripheral edema, arrhythmias and congestive heart failure are observed [2,3].

Autonomic nervous system activity is typically measured by serial cardiovascular autonomic function tests, but these tests are not useful because they are invasive and complex in pediatric patients. Heart rate variability is an easy-to-apply, noninvasive and reliable index that measures the neuronal modulation of heart rate in children with beta-thalassemia major. Decreases in heart rate variability provide the detection of accompanying autonomic dysfunction.

In this study, our aim is to early recognition of cardiac autonomic neuropathy developing in children with beta-thalassemia major and to prevent mortality and morbidity due to autonomic neuropathy. For this purpose, the availability of heart rate variability as a noninvasive method in children with thalassemia major diagnoses was investigated.

### Materials and Methods

This study was carried out at the 24-hour Holter electrocardiography examination by comparing 30 patients with beta-thalassemia major diagnosis and 30 healthy control groups in Dicle University Faculty of Medicine, Department of Pediatric Hematology and Oncology and Pediatric Cardiology.

A form was created for patients with gender, age of diagnosis, follow-up time, history of drug use, monthly and annual transfusion amount. Physical examination of the patient group and the findings (scale, height, body surface area, blood pressure, number of heartbeats) were recorded in the study form. Serum ferritin levels were studied with a full blood count.

All of the patients were receiving iron chelation treatment. 80% of the patients used deferasirox, 3.3% desferoksamin, 3.3% deferiprone, and 13.3% desferoksamin+deferiprone combination therapy. Fourteen (93.3%) of patients in Group I (ferritin 1500 - 2500 ng/ml) used deferasirox and one (6.7%) used desferoksamin. In Group II (ferritin 2501 - 5000 ng/ml), 7 (88%) of patients used exjade, one (12%) used deferiprone, four (57%) of patients in Group III (ferritin > 5000 ng/ml) used desferal+ferriprox, and three (43%) used exjade. Four patients using desferal+ferriprox combination therapy were in Group III (ferritin > 5000 ng/ml).

Time and frequency variability analyzes of heart rate variability (HRV) in correlation with patients' hemodynamics and ferritin levels were performed with Holter monitoring. Patients were selected for children with major thalassemia between the ages of 4 and 18 who received erythrocyte transfusion and were treated with iron chelation. In the last six months, those with secondary diseases that cause cardiac dysfunction and who use drugs that can perform cardiac arrhythmia have been excluded from the study.

The control group was formed from healthy children who did not have any cardiovascular disease as a result of anamnesis, physical examination, and laboratory examinations, similar in age and gender distribution. Children with diseases such as diabetes mellitus, hypertension, dysrhythmia, hyperthyroidism, chronic kidney failure, migraines, epilepsy, drug use that may affect OSS were not included in the study.

Echocardiography and 24-hour Holter electrocardiography were performed on all TM patients (Group I, Group II, Group III) and control group. The families of all the children who were recruited were given detailed information about the study and an informed consent

form was obtained. For this study, permission was obtained from the Ethics Committee of Dicle University Faculty of Medicine.

Holter records were obtained with der Mar Reynolds Pathfinder Holter ECG device. After Holter records were manually decontaminated, the time and frequency-dependent HRV parameters that the device calculated automatically were used. The results were evaluated by the same pediatric cardiologist according to guidelines published by the European Society of Cardiology and the Pacing and Electrophysiology Society of North America.

**Statistical analysis**

SpSS 21.0 statistical package program was used for statistical analysis. Values were given as an average standard deviation. The normality of the distribution was evaluated by the Shapiro-will test. In comparing the two group averages of continuous variables with normal distribution; student’s t-test was used. One-Way Variance Analysis (ANOVA) was used in continuous measurement variables. Kruskal-Wallis ANOVA test was used between groups to compare variables that did not conform to normal distribution. Ki-Square Test was used in categorical variables. In the group of categorical variables; Fisher’s Exact Ki-Square Test was used in tables with fewer than five subject numbers. The fact that the P-value was less than 0.05 was considered statistically significant.

**Results**

In our study, 16 of the patients were girls (53%), 14 were boys (47%) and their ages were between 4 years and 3 months, and 16 years and 10 months (mean 10.1 ± 3.8 years). The control group was 17 girls (57%), 13 boys (43%) and aged between 4 years and 17 years, and 2 months (mean 10 ± 3.8 years). When the patient and the control group were evaluated by age and gender, the groups were similar (p = 0.92).

Patients with thalassemia major (TM) were divided into three groups: Group I with ferritin values between 1500 - 2500 ng/ml, Group II with a value of 2501 - 5000 ng/ml, and Group III with a value of more than 5000 ng/ml. The mean value of ferritin in group I was 1917. 2 ± 259; The mean value of ferritin in group II was 3783. 7 ± 925. 3; The mean ferritin value of the patients in Group III was 7461. 1 ± 1714. 7. The mean ferritin value of the TM-diagnosed patients was 3708. 5 ± 2430. 6 (Table 1).

Groups	Number of Patients (N)	Ferritin (Mean ± SD)	Minimum Ferritin	Maximum Ferritin
Group-I	15	1917.2 ± 259	1507	2369
Group-II	8	3783.7 ± 925.3	2753	4922
Group -III	7	7461.1 ± 1714.7	5204	9322
Total	30	3708.5 ± 243.6	1507	9322

**Table 1:** Distribution of the average ferritin value of groups.  
SD: Standard Deviation.

All of the patients were receiving iron chelation treatment. 80% of the patients used deferasirox, 3.3% desferrioxamine, 3.3% deferiprone and 13.3% desferoxamine+deferipron combination therapy. In Group III (ferritin > 5000 ng/ml), four (57%), desferoxamine+deferipron, and three (43%) deferasirox were used. In Group I (ferritin 1500 - 2500 ng/ml), 14 (93.3%) of patients used deferasirox and 1 (6.7%) used deferoxamine. In Group II (ferritin 2501 - 5000 ng/ml), 7 (88%) of patients used deferasirox and one (12%) used deferiprone.

Two patients with thalassemia had mild mitral insufficiency, one patient had mild tricuspid insufficiency, one patient had mild mitral insufficiency, one patient had mild tricuspid insufficiency, and one patient had mild mitral insufficiency and moderate tricuspid insuffi-

ciency. Echocardiography findings of twenty-four patients were evaluated as normal. An echocardiographic examination of a patient could not be performed after the patient did not want to have the examination done. Echocardiography findings of two patients in Group I, one patient in group II, and two patients in group III were evaluated as pathological, there was no statistical difference between groups ( $p = 0.64$ ) (Table 2).

	EKO		Total
	Normal	Pathological	
Group I	13 (%44.8)	2 (%6.9)	15 (%51.7)
Group II	6 (%20.7)	1 (%3.4)	7 (%24.1)
Group III	5 (%17.2)	2 (%6.9)	7 (%24.1)
Total	24 (%82.8)	5 (%17.2)	29 (%100)

**Table 2:** Comparison of intergroup EKO findings.

Maximum heart rate, Standard deviation of all NN ranges throughout recording (SDNN), SDNN Index, Square root of the sum of the differences of consecutive NN intervals in the 24-hour recording (RMSSD), Ratio of NN 50 to the total number of NNs (pNN50), Total power Table (TP), low frequency (LF), and Very low frequency (VLF) parameters were found to be significantly lower in the patient group compared to the control group. In our study, there was no statistical difference between patient and control groups between 24-hour average heart rate, minimum heart rate, SDANN Index, High frequency (HF), and LF/HF parameters ( $p > 0.05$ ) (Table 3).

Measurements	Patient Group (Mean ± SD)	Control Group (Mean ± SD)	P
Average Heart Rate	93.53 ± 12.3	91 ± 10.7	0.39
Minimum HR	55.07 ± 7.5	53.1 ± 8.4	0.95
Maximum HR	153.3 ± 16.8	166.8 ± 19.5	0.005
SDNN	101.2 ± 31.3	121.4 ± 29.9	0.01
SDNN İndeks	46.6 ± 17.4	63.27 ± 13.5	< 0.001
SDANN İndeks	90.7 ± 28.3	104.9 ± 30.3	0.06
RMSSD	32.6 ± 16.4	42.7 ± 13.6	0.01
pNN50	11.2 ± 10.8	19.9 ± 11.9	0.004
TP	2307.18 ± 1575.8	3934.38 ± 1588.4	< 0.001
VLF	1378.1 ± 978.3	2496.56 ± 1088.5	< 0.001
LF	508.94 ± 310.5	885.68 ± 383.9	< 0.001
HF	417.7 ± 363.8	492.9 ± 288.6	0.34
LF/HF	1.93 ± 1.4	2.08 ± 1.2	0.65

**Table 3:** Evaluation of Holter ECG parameters of the patient and control group 24 hours a day.

Max HR: Maksimum Heart Rate; Min HR: Minimum Heart Rate.

The 24-hour Holter ECG parameters were compared among the groups separated according to the values of the ferritin. The maximum heart rate was significantly higher in Group I compared to Group II and Group III ( $p = 0.03$ ). There was no significant statistical difference between groups among the other Holter ECG parameters compared ( $p > 0.05$ ) (Table 4).

Measurements	Group I (Mean ± SD)	Group II (Mean ± SD)	Group III (Mean ± SD)	P
AHR	95.33 ± 14.9	89.63 ± 7.9	94.14 ± 10.8	0.58
Min. HR	55.87 ± 8.7	53.88 ± 7.5	54.71 ± 5.3	0.93
Max HR	161.13 ± 17.3	144.13 ± 7.9	147 ± 16.6	0.03
SDNN	105.07 ± 33.9	96.63 ± 31.8	98.14 ± 28.2	0.08
SDNN İndeks	50.47 ± 16.9	44.13 ± 1.4	41.14 ± 17.6	0.46
SDANN İnd.	94.8 ± 30.5	83.5 ± 27.9	90.14 ± 26.1	0.67
RMSSD	35.07 ± 15.6	31 ± 16.5	29.14 ± 19.7	0.71
pNN50	12.4 ± 10	11.13 ± 11.5	8.7 ± 12.7	0.76
TP	2640.46 ± 1687.2	2082.33 ± 1522.9	1849.95 ± 1449.3	0.50
VLF	1589 ± 1133.9	1267.39 ± 877.9	1052.64 ± 689.2	0.47
LF	588.94 ± 303.8	491.52 ± 306.3	421.7 ± 354.3	0.63
HF	504.46 ± 384.6	322.27 ± 322.5	340.84 ± 368.2	0.43
LF/HF	1.68 ± 1.14	2.2 ± 1.37	2.14 ± 1.96	0.63

**Table 4:** Comparison of Holter ECG parameters between groups 24 hours a day.

Holter ECG of the patients was evaluated. Holter ECG of twenty-two patients was normal. The ectopic beat was detected in eight patients. Rare unifocal ventricular extrasystole in two patients, rare supraventricular extrasystole (SVE) and very rare ventricular extrasystole in one patient, rare unifocal supraventricular extrasystole and 18 SVE couplets in one patient, rare unifocal SVE and two SVE beat were detected in one patient, rare SVE in one patient, rare SVE and 16 beats of ectopic atrial rhythm once, moderate SVE and SVE couplets in one patient, and numerous ectopic atrial beats. Compared to the echocardiography findings of the patients and the presence of ectopy beats, the ectopic beat was detected in Holter ECG in four (80%) of the five patients whose echocardiography findings were pathological. Ectopia was detected in four (16.6%) of the 24 patients whose echocardiography findings were normal, and the difference was statistically significant ( $p = 0.039$ ).

The ectopic beat was detected in 3 (20%) of 15 patients in Group I, 2 (25%) of 8 patients in Group II, and 3 (42.9%) of 7 patients in Group III in comparison of ectopic beat presence and groups separated by ferritin value. With the increase in the value of ferritin, the incidence of ectopic beat increased, but the difference was not statistically significant ( $p = 0.52$ ).

The patient group and the control group were compared in terms of ectopic beat presence. The ectopic hit was detected in eight patients in the patient group. No ectopic hits were detected in the control group and the difference was statistically significant ( $p = 0.002$ ).

### Discussion and Conclusion

71% of the causes of death in patients with beta-thalassemia are of cardiac origin. When heart failure occurs, the prognosis is quite bad. Risk of cardiomyopathy may decline with intensive early administration of chelation therapy. However, due to the late appearance of both symptoms and echocardiographic abnormalities, early recognition of cardiomyopathy is difficult [4]. The increase in survival time in thalassemia is explained by the improvements in chelation treatment, as well as better control of anemia and the introduction of angiotensin-converting enzyme (ACE) inhibitors in heart failure [5,6].

In patients with thalassemia major, rhythm disorders often begin with atrial extrasystoles in the second decade, after which ventricular extrasystoles appear and the frequency increases. Cardiac exposure in thalassemia begins with arrhythmia and progresses towards heart

failure. If there is a decrease in the ejection fraction with resistant arrhythmia, this indicates that heart failure may develop within a year [7].

In animal experiments, iron-related cardiac toxicity was first found to disrupt electrical transmission. Postmortem examinations showed atrial and ventricular dilatation due to iron storage in myocardial cells, thickening of the ventricular walls, increased heart weight, fibrosis in the myocardium and message system [8,9].

In many studies, it was stated that decreased heart rate variability was associated with ventricular arrhythmia and sudden cardiac death regardless of other risk factors [10,11]. In our study, patients with TM were grouped according to ferritin values, follow-up times, the ectopic hit presence in the 24-hour Holter, and echocardiographic evaluation. The mean age of the patients was  $10 \pm 3.8$  years. In our study, there was no significant difference between gender and age, according to the value of ferritin. Although the mean value of ferritin in female patients ( $4173 \pm 2797$ ) was higher than in male patients ( $3177 \pm 1892.4$ ), there was no statistical difference between ferritin values associated with gender. The mean value of ferritin in patients with thalassemia major diagnosis was  $3708.5 \pm 2430.6$ .

In the study conducted by Borgna, *et al.* in which the value of ferritin is considered to be a limit of 1000 ng/ml, it was found that cardiac complications and hypogonadism were less common in patients below this value. It has also been reported that the life expectancy of female patients is longer than that of male patients and the incidence of heart failure is lower, even if there is no significant difference between ferritin levels. In our study, no gender difference was determined according to the value of ferritin [12,13].

All of the patients were receiving iron chelation treatment. Combination treatments with DFP (75 - 100 mg/kg/day, 3 doses) and DFO (40 - 60 mg/kg/day) 7 days a week by the international committee of oral chelators; it is fast, effective, and reliable in the excretion of iron from the heart and other organs. It is especially recommended in patients (those with pre-stem cell transplantation or severe cardiac load) who are incompatible with DFO, where DFP alone is inactive, and whose iron load should be reduced rapidly [14]. In our study, combination therapy was applied to four patients with compliance problems with subcutaneous DFO treatment with a ferritin value of over 5000 ng/ml. In two of these four patients, mild tricuspid and mitral insufficiency were detected in EKO and rare unifocal ventricular extrasystole was detected in one patient in Holter ECG, sparse unifocal supraventricular extrasystole and 18 SVE couplets were detected in one patient. Three of the four patients were in the follow-up group for more than ten years, and one was in the group with a follow-up period of five to ten years. No symptomatic congestive heart failure was detected in any of the patients.

In our study, echocardiographic evaluation of patients with TM was performed. No correlation was observed between the increase in serum ferritin value and the change in echocardiography findings. Ferritin is affected by the presence of inflammation, infection, and many chronic diseases as an acute phase reactant. Data are available that ferritin levels are not a reliable test for showing iron accumulation [15].

In the 2009 study of Delibas, *et al.* [16] there was no significant difference between left ventricular diastolic functions and cardiac measurements among the groups separated by the value of ferritin. No association between myocardial hypertrophy and ferritin was observed.

Heart rate variability indicates autonomic neuronal dysfunction of the heart and decreased HRV is an indicator of poor prognosis. There was a close association between increased sympathetic activity or decreased parasympathetic activity and a tendency to fatal arrhythmias [17].

In our study, the value of HRV in showing the risk of early cardiac exposure and arrhythmia due to iron accumulation and the availability of heart rate variability as a noninvasive method in children with thalassemia major diagnosis were investigated. 24-hour Holter ECG parameters of patients and control group were compared.

Maximum Heart Rate, SDNN, SDNN Index, RMSSD, pNN50, TP, LF, and VLF parameters were found to be significantly lower in the patient group compared to the control group ( $p < 0,005$ ). In our study, there was no significant difference between patient and control groups between 24-hour average heart rate, minimum heart rate, SDANN Index, HF, and LF/HF parameters ( $p > 0.05$ ). The results were found to be consistent with the former studies [18-21].

In a 2004 study by Franzoni F, *et al.* [19] they showed that heart rate variability in patients with thalassemia major decreased significantly compared to the control group, and they concluded that the decrease in heart rate variability occurred without cardiac clinical findings in thalassemia patients. In their 2005 study, Gurses., *et al.* showed that heart rate variability indicating autonomous control of the heart was significantly lower in patients with thalassemia than in control groups, and as a result of their studies, they concluded that the tendency to arrhythmia in patients with thalassemia increased compared to normal population. Rutjanaprom., *et al.* [20] in 2009, Kardelen., *et al.* [22] in 2008, all HRV parameters in the TM patient group were shown to be significantly lower than the control group and interpreted the results of these studies as evidence of early cardiac autonomic neuropathy in thalassemia patients.

Chiara., *et al.* [21] in patients with 20 TM patients with regional wall movement disorder in radionuclide angiography; Doppler found that decreased left ventricular ejection fraction in echocardiography and abnormal diastolic measurements were in line with the decrease in heart rate variability. At the end of the study, they concluded that a decrease in heart rate variability could be detected in patients with thalassemia without cardiac clinical findings.

In our study, heart rate variability parameters were compared among groups separated according to ferritin values. The maximum heart rate was significantly higher in Group I compared to Group II and Group III ( $p = 0.03$ ). There was no significant difference between groups between 24-hour average heart rate, minimum heart rate, SDANN Index, HF, and LF/HF, SDNN, SDNN Index, RMSSD, pNN50, TP, LF, and VLF parameters ( $p > 0.05$ ).

Although there was a significant difference in the 24-hour Holter review compared to the control group in the groups divided into ferritin values, no significant difference was found between the groups. Similar results were found in the study conducted by Delibas., *et al* [16]. Changes in ferritin values did not make a significant difference in patients' heart rate variability. Ferritin values do not help us in monitoring both cardiac functions and electrical changes of patients with thalassemia. Although the SDNN index is significantly lower than the control group in both studies, the fact that there is no significant difference between the groups according to the values of ferritin suggests that the value of ferritin does not help in the early detection of the risk of developing arrhythmia.

In our study, 24-hour Holter examination of 22 patients was interpreted as normal. Atrial and/or ventricular extra systol was detected in eight patients. Arrhythmia often begins with atrial extrasystoles in the second decade. Ventricular extrasystoles appear in the middle of the second decades and their frequency is increasing [23]. In our study, the ectopic beat was not detected in patients with follow-up for less than 5 years. The ectopic beat was detected in 2 (15.3%) of patients with follow-up between 5-10 years and 6 (46%) of patients with follow-up for more than 10 years. In our study, it was found that the incidence of ectopic hit increased as the follow-up time of the patients increased.

In our study, the ectopic beat was detected in 16.6% of patients whose echocardiography findings were normal. Since iron-related cardiac toxicity disrupts electrical transmission first, the risk of dysrhythmia can be determined by 24-hour Holter ECG and HRV parameters without echocardiographic and clinical findings.

Early change in HRV parameters can be seen before systolic and diastolic functions give echocardiographic findings. SDNN is thought to be related to an increase in cardiac sympathetic neuronal activity caused by chronic diastolic and systolic insufficiency, which is likely

to be low in the group with TM [24]. When the SDNN index is determined below 30 milliseconds from age-appropriate LF height and time parameters in the LF/HF ratio from frequency parameters, dysrhythmia treatments of these patients should be evaluated on the spectrum of medical treatment and automated external defibrillator implantation [25-27].

In our study, it was determined that the time parameters were statistically significantly lower in the thalassemia group, especially when SDNN compared to the thalassemia patient group and the control group ( $p = 0.01$ ). No significant changes were detected in this index in grouping according to ferritin values ( $p = 0.08$ ). SDNN value was not detected below 30 milliseconds considered critical in any of our patients.

As a result; before the echocardiographic deterioration in systolic and diastolic functions is detected in patients with thalassemia major; changes in heart rate variability parameters and ectopic beat are observed in the early period. We believe that ferritin levels alone are not sufficient to indicate the cardiac status of patients. In patients with thalassemia major without cardiac complaints, it is important to evaluate heart rate variables with 24-hour Holter ECG monitoring to predict the risk of arrhythmia and heart failure due to iron accumulation.

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