Original Article

EP & Arrythmia

Heart Rate Recovery as a Novel Test for Predicting Cardiac Involvement in Beta-Thalassemia Major

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Background: Abnormal heart rate recovery (HRR) is predictive of cardiac mortality. Autonomic abnormalities in beta-thalassemia major (TM) patients have been reported in previous studies. However, the importance of low HRR in exercise stress test in TM patients has not yet been ascertained. Therefore, this study will be the first of its kind in the literature.

Methods: Exercise stress test was performed on 56 TM patients who were being treated at the Thalassemia Center of our hospital, along with 46 non-TM iron deficiency anemia (IDA) patients as a control group. Values for HHR were recorded at 1, 2, 3, 4 and 5 min, and HRR was calculated by the difference of heart rate at peak exercise and at a specific time interval following the onset of recovery.

Results: All HRR values were found to be lower in TM patients compared to those in the IDA group. Exercise capacity [metabolic equivalents (METs)] was also found to be low in these patients (p < 0.001) as well. Total exercise time was significantly lower in the TM group compared to the IDA group (8.40 ± 1.7 min vs. 11.17 ± 1.51 min, p < 0.001). Exercise capacity (METs) was also lower in the TM group compared to the IDA group. Mean T2* value was 28.3 ± 13.7 ms in TM patients on magnetic resonance imaging (MRI). In addition, there are 18 TM patients with T2* value was < 20 ms.

Conclusions: This study found that TM was independently associated with low HRR. Such a condition is an indicator of autonomic dysfunction in TM patients, since abnormal HRR is related to impaired autonomic response. In addition, impaired HRR may be a marker of early cardiac involvement in patients, whose T2* value is high on MRI. Modifying HRR with a cardiac rehabilitation program in TM patients with impaired HRR is a field open for further investigation.

Key Words: Beta thalassemia major • Exercise stress test • Heart rate recovery • Magnetic resonance imaging

INTRODUCTION

Iron cardiomyopathy is a leading cause of death in

transfusion-dependent thalassemia major (TM) patients, and magnetic resonance imaging T2* (MRI T2*) can recognize preclinical cardiac iron overload. However, the technology is unavailable to many medical centers. In thalassemic patients, cardiac T2* has been recently used to evaluate myocardial iron content and has been correlated to left ventricular ejection fraction reduction. Cardiac involvement in thalassemia affects mainly the myocardium: iron overload of the myocytes reduces left ventricular distensibility.[1,2] Also, heart failure is the most frequent manifestation of cardiac involvement. However, early diagnosis and iron depletion improve survival by reducing organ iron overload, especially in the myo-

cardium. Elevated iron could affect autonomic nervous system activity, possibly by impairing neuronal function or interfering with other elements of the baroreceptor reflex pathways external to the heart. Alternatively, intrinsic electrical activity of the specialized pacemaker myocytes located in the sinoatrial node could also be disrupted by iron as a result of modulation of a number of membrane currents, Ca2+ handling or intracellular signalling.[3]

Heart rate recovery (HRR) is an expression of decreased heart rate in a specified time, in the recovery period at the end of an exercise test. In healthy individuals, the heart rate rapidly decreases through increased parasympathetic tone and decreased catecholamine levels at the sino-atrial node at the end of exercise. Abnormal HRR is defined as ablunted heart rate decrease after exercise, which is independently associated with increased mortality and morbidity.[4-8] HRR is a strong indicator of fitness and partial mediator of the autonomic nervous system.[4,5,8,9] In addition, HRR has been shown to be similar to traditional risk factors and related to clinical outcomes, even in individuals with no evident cardiovascular disease.[6,10] HRR is related to increased mortality, independent from the systolic function, the angiographic severity of disease or exercise capacity. Therefore, assessment of HRR is recommended as a non-invasive method for assessment of cardiovascular risk in children and adults.[11-13] However, the mechanism and clinical correlation of abnormal HRR has not yet been fully understood.

Presence of autonomic dysfunction in TM patients has been demonstrated in an earlier study.[14] The influence of autonomic dysfunction on HRR and clinical events was not known for these patients. In the present study, we aimed to investigate the exercise properties of TM patients, and the relationship between HRR and cardiac involvement by comparing T2 scores.

METHODS

Patients population

Our study enrolled 56 TM patients who were being treated at the Thalassemia Center of our hospital between January and December 2014, along with 46 iron deficiency anemia (IDA) patients as a control group

without TM. A two-unit blood transfusion was given as necessary to TM patients in terms of hemodynamics (physical activity, occupation) every three to four weeks. The average of the last three measurements was used to determine Hb values. On the other hand, there were no differences in hemoglobin values among the study groups.

The following were exclusion criteria for patients in our study: left ventricular ejection fraction (LVEF) of less than 50% in echocardiography, any active inflammatory process, below 18 years of age, diabetes mellitus, hypertension, and previous ischemic heart disease. Informed consent was obtained from all the patients, and our study was approved by the Ethics Committee of the Antalya Education and Research Hospital.

Echocardiographic measurements and data

Echocardiographic imaging of patients and IDA group were obtained at the Antalya Education and Research Hospital Cardiology Clinic using a PhilipsEPIQ 7 echocardiography device (Philips Healthcare, 3000 Minuteman Road Andover, MA, USA), and a 2.5 MHz probe. All images were recorded to include 3 consecutive heart beats for later evaluation. Echocardiographic evaluation was done with patients in the left lateral decubitus position accompanied by ECG monitoring consistent with recommendations of the American Echocardiography Society.[15] LVEF was calculated using modified Simpson's method, with end-diastole and systole volumes measured with echocardiography.

Exercise stress test

Patients waited for 10 minutes in a supine position to stabilize the heart rate before starting the exercise test. They were asked not to use substances that affecting heart rate like cigarettes or caffeine in the 48 hours prior to testing. The symptom-limited treadmill exercise test was performed on patients to evaluate exercise time, exercise capacity [metabolic equivalents (Mets)], and heart rare recovery using the standard multistage Bruce protocol.[16] The exercise testing began with subjects walking slowly for 3 min at 1.7 m/h at a 10% grade; thereafter, speed and grade increased every 3 min until patient exhaustion. Patient electrocardiogram, heart rate and blood pressure were recorded during the last minute of each stage of exercise. This exercise data included duration on treadmill, age-predicted heart rate

achieved and capability measurements in terms of METs. Starting heart rate, peak heart rate, heart rate at 1-5 min in recovery, and blood pressure measurements were taken during established protocol exercise stage intervals to calculate pressure rate product (PRP). Exercise was terminated when the participants reached their target HR (85% of their age- and sex-predicted maximal HR), and the participants immediately got off the treadmill and rested in a supine position. Exercise testing was terminated prematurely for the following reasons: limiting chest discomfort, dyspnea, fatigue, or leg discomfort. All exercise testing was performed according to American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines[1,7] and hospital ethics committee approval was obtained for this prospective study.

Heart rate recovery

Heart rate data during the exercise were obtained from the continuously recording electrocardiographic monitor. Recovery data at the end of the exercise were obtained when the patient was resting in a supine position for 10 min. HR data were recorded at the end of every min during recovery period, and defined as HRR 1, HRR 2, HRR 3, HRR 4 and HRR 5. HRR was calculated by subtracting the heart rate value at that moment from the peak heart rate during exercise (e.g., HRR 1 = peak HR during exercise − HR at recovery min 1). Chronotropic response was evaluated in both groups and obtained using the following formula employing HR reserve:

Chronotropic index = (HR peak − HR baseline) / (220-age-HR baseline) × 100[18,19]

Chronotropic incompetence was defined as < 0.8 of chronotropic index.[19,20]

MRI T2*

MRI was performed by Magneto Symphony Graniand 32, 1.5 Tesla (Siemens, Germany, 2009) in Antalya Education and Research Hospital (Antalya, Turkey). Each scan lasted about 20 minutes and included measurement of cardiac T2*. Cut-off points using this MRI instrument were as follows: cardiac: normal > 20 ms, mild: 14-20 ms, moderate: 10-14 ms, severe < 10 ms.[21]

Statistical analysis

In this study, data were expressed as mean ± standard deviation for continuous variables, with counts and percentages for categorical variables. Data were tested for normal distribution using the Kolmogorov-Smirnov test, and frequencies, means and standard deviations were calculated by descriptive statistics. Independent Samplest Test (parametric) and Mann Whitney U-test (non-parametric) were used to assess the differences between the variables in patients with beta-thalassemia and IDA individuals. Correlations of variables were evaluated using the Pearson or Spearman's correlation analysis; a correlatiaon coefficient between 0-0.3 indicated a weak correlation, and 0.7-1.0 indicated significant correlation. A p value < 0.05 was considered statistically significant. Statistical analyses were conducted with a commercially available software package (SPSS version 16.0, SPSS, Chicago, IL, USA).

RESULTS

The symptom-limited exercise test was done on a total of 102 patients (56 TM patients, 46 IDA patients). There was no significant difference between the two groups regarding physiological variables such as body mass index (BMI), hemoglobin level, basal heart rate, age, and gender. However, there was a significant difference in serum iron (SI), ferritin and transferrin saturation (TS) ($p < 0.001$). Baseline clinical properties and exercise characteristics of the TM and the IDA patients are shown in Table 1 and 2. The mean patient age was 24.5 ± 6 years in TM group, and 24.1 ± 6 years in the IDA group (p = 0.70).

Due to exercise exhaustion, 13 patients with TM (23.2%) and 5 IDA patients (10.8%) left the exercise test before reaching the target heart rate. Overall, total exercise time was significantly lower in the TM group compared to the IDA group (8.40 ± 1.7 min vs. 11.17 ± 1.51 min, p < 0.001). Exercise capacity (METs) was also lower in the TM group compared to the IDA group (10.13 ± 1.81 METs vs. 13.10 ± 1.88 METs, p < 0.001). The mean peak HR was 170.43 ± 13.49 bpm during exercise in the TM group and 181.65 ± 15.85 bpm in the IDA group, and the difference was statistically significant (p < 0.001). HR reserve (220-age-baseline HR) was 107 ± 11 in the

Table 1. Baseline clinical and exercise characteristics according to thalassemia major and iron deficiency group

Characteristics	Iron deficiency group (n = 46)	Thalassemia group (n = 56)	p value
Age, mean (±SD) year	24.1 (±6)	24.5 (±6)	0.78
Male, n (%)	25 (54.3)	31 (55.4)	0.91
Tobacco use, n (%)	3 (6.5)	3 (5.3)	0.80
BMI, mean (±SD), kg/m²	21.56 (±2.3)	21.08 (±2.6)	0.33
Baseline HR, (±SD), bpm	84.8 (±16)	87.6 (±12)	0.34
Baseline SBP, mean (±SD), mmHg	115 (±8)	115 (±6)	0.83
Baseline DBP, mean (±SD), mmHg	70 (±5)	69 (±5)	0.69
RPP baseline, mean (±SD), mmHg*bpm	108 (±26)	102 (±21)	0.23
Hemoglobin level (g/dL)	9.06 ± 0.52	8.84 ± 1.01	0.48
SI (μg/dL)	21.09 ± 8.42	88.01 ± 33.6	< 0.001
Ferritin (ng/ml)	4.57 ± 1.99	37.05 ± 7.34	< 0.001
TS (%)	4.42 ± 2.28	26.84 ± 1.23	< 0.001

Values are expressed as mean and standard deviation. p < 0.05 value indicates significance. In all cases, differences were not statistically significant. BMI, body mass index; HR, heart rate; RPP, rate pressure product; SBP, systolic blood pressure; SI, serum iron; TS, transferrin saturation. (RPP = HR * SBP). One way analysis of variance, Independent samples t-test, Mann-Whitney U-test.

Table 2. Exercise characteristics after exercise according to thalassemia major and iron deficiency anemia group

Characteristics (mean ± SD or median 25th-75th %)	Iron deficiency group (n = 46)	Thalassemia group (n = 56)	p
HR Stage 1, bpm	107 (±11)	121 (±14)	< 0.001
HR Stage 2, bpm	121 (±14)	138 (±16)	< 0.001
HR Stage 3, bpm	142 (±16)	159 (±16)	< 0.001
HR Stage 4, bpm	173 (±16)	171 (±10)	0.48
RPP Stage 1	146 (±31)	156 (±31)	0.10
RPP Stage 2	178 (±40)	187 (±39)	0.25
RPP Stage 3	204 (±28)	217 (±46)	0.17
RPP Recovery	154 (±32)	141 (±25)	0.03
Peak HR, bpm	181 (±15)	170 (±13)	< 0.001
HR reserve	111 (±17)	107 (±11)	0.29
Chronotropic index	84 (±11)	76 (±11)	0.001
Exercise capacity (METs)	13.1 (±1.8)	10.1 (±1.8)	< 0.001
Exercise time, minute	11.1 (±1.5)	8.4 (±1.7)	< 0.001
1-min HRR	34 (28-51)	31 (24-36)	0.004
2-min HRR	59 (52-70)	50 (40.3-61)	0.002
3-min HRR	64 (59-71)	55 (47.3-68)	0.003
4-min HRR	68 (63-77)	59 (50.5-70.8)	0.001
5-min HRR	68 (60-79)	60 (51-72)	0.002

Values are expressed as mean ± standard deviation or median 25th-75th%. p < 0.05 value is significant. HR, heart rate; METs, metabolic equivalents; RPP, rate pressure product; SD, standard deviation. (Rate Pressure Product = Heart Rate * Systolic Blood Pressure), One way analysis of variance, Independent samples t-test, Mann-Whitney U-test.

thalassemia group and 111 ± 17 in the IDA group, and the difference was not statistically significant (p = 0.30). The mean chronotropic index was 0.76 ± 0.11 in the TM group, and 0.84 ± 0.11 in the IDA group, with a statistically significant difference (p = 0.001).

HRR 1, HRR 2, HRR 3, HRR 4, and HRR 5 values were statistically significantly lower in the TM group compared to the IDA group, independent from exercise time (p = 0.004, p = 0.002, p = 0.003, p = 0.001, p = 0.002, respectively) (Figure 1, Table 2). There was a consistent and significant decline in HRR and T2* values. Figure 2A, Figure 2B, Figure 2C, Figure 2D and Figure 2E showed a
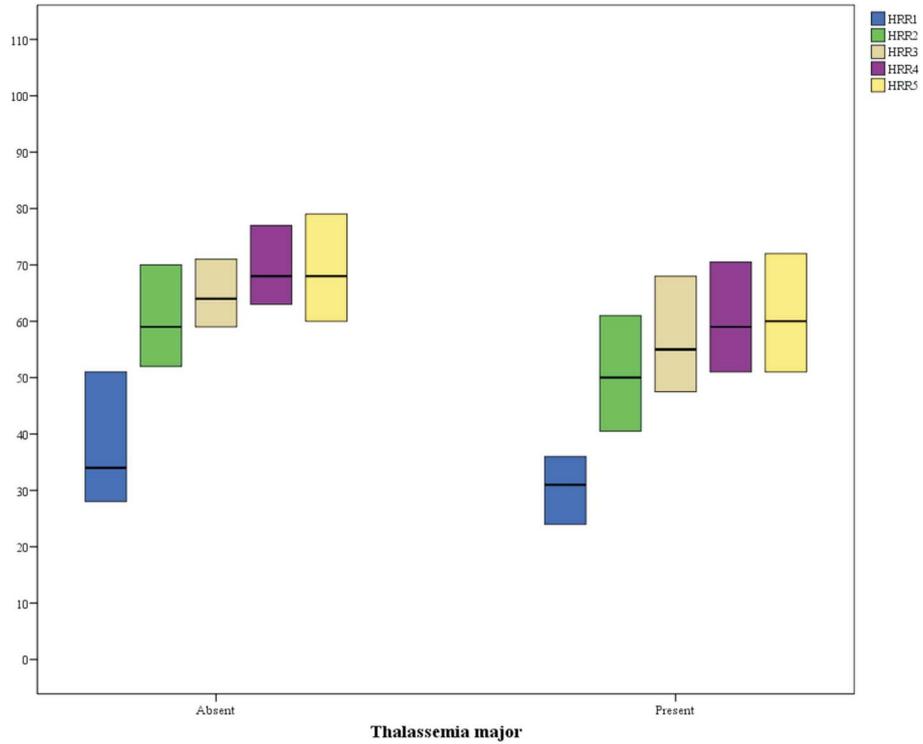
Figure 1. *The association between presence of thalassemia major and heart rate recovery. HRR, heart rate recovery.*
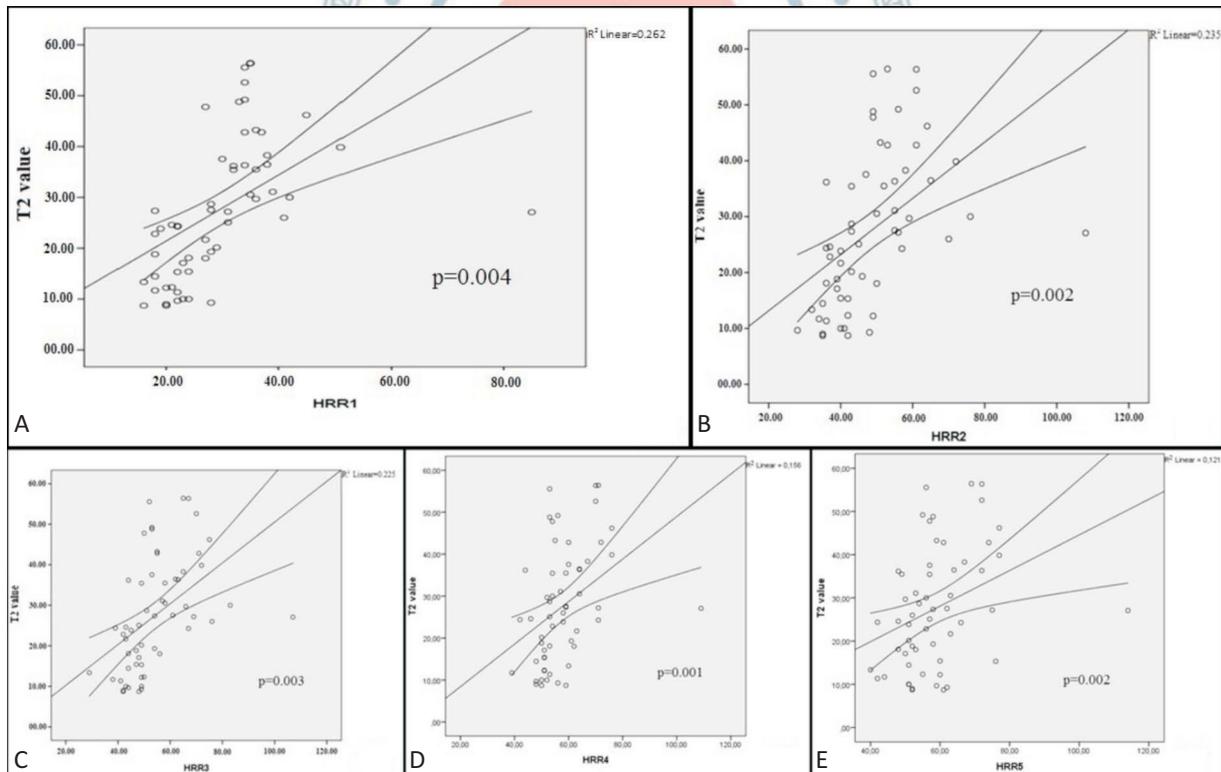

Figure 2. *(A) Relationship between HRR 1 and cardiac T2*. (B) Relationship between HRR 2 and cardiac T2*. (C) Relationship between HRR 3 and cardiac T2*. (D) Relationship between HRR 4 and cardiac T2*. (E) Relationship between HRR 5 and cardiac T2*. As shown in the figure, analysis is statically significant according to regression and average lines.*

relationship between HRR and cardiac T2*.

Correlation analysis between HRR and exercise time was performed on the whole group, with no correlation found between HRR 1 min and exercise time (Spearman's correlation coefficient was 0.162 and p = 0.10); however, there was a weak positive correlation between HRR 2, HRR 3, HRR 4, HRR 5 and exercise time. Spearman's correlation coefficient was 0.222 (p = 0.03) for HRR 2, and exercise time 0.216 (p = 0.03) for HRR 3, 0.250 (p = 0.01) for HRR 4, 0.249 (p = 0.01) for HRR 5.

When the groups were analyzed separately, in the TM group, there was a positive correlation between HRR 2 min and exercise time (r = 0.282, p = 0.04). A correlation was not detected between other HRR values and exercise time in TM patients. However, in the IDA group, there was no correlation found between HRR values (include all HRR values) and exercise time.

Correlation analysis between exercise capacity (METs) and HRR values was done in the whole group. A correlation was not detected between HRR 1 value and exercise capacity (Spearman's correlation coefficient 0.149 and p = 0.14); however, a weak positive correlation was detected between HRR 2, HRR 3, HRR 4, HRR 5 values and exercise capacity (p = 0.02, 0.03, 0.01 and 0.01, respectively; r = 0.229 and 0.217, 0.244, 0.253, respectively). In addition, when the groups were analyzed separately, in the TM group, there was a positive correlation between HRR 2 min and exercise capacity (r = 0.274, p = 0.04). However, in the IDA group, there was no correlation between HRR values (include all HRR values) and exercise capacity.

Mean T2* value was 28.3 ± 13.7 ms in the TM patients; T2* value was < 20 ms in 18 patients (33%). In TM patients with T2* values < 20 ms and > 20 ms, HRR values were compared and the results are illustrated in Table 3.

Correlation analysis between HRR and T2 scores was done in TM patients, with no correlation detected between HRR values and T2 scores. Moreover, a correlation was not detected between exercise time, exercise capacity and T2* value. Pearson's correlation coefficient for HRR 1 and T2 score was -0.024 (p = 0.86), for HRR 2 and T2 score was 0.053 (p = 0.70), for HRR 3 and T2 score was 0.079 (p = 0.57), for HRR 4 and T2 score was 0.096 (p = 0.49), and for HRR 5 and T2 the score was 0.099 (p = 0.48).

There were no statistical significance in the rate pressure product (RPP) stages and recovery, RPP is a measure of the stress put on the cardiac muscle based on the number of times it needs to beat per minute and the arterial blood pressure it is pumping against (SBP). It will be a direct indication of the energy demand of the heart and thus a good measure of the energy consumption of the heart. Rate pressure product allows you to calculate the internal workload or hemodynamic response.[22]

No correlation was detected between the T2* value and exercise time (p = 0.65), and similarly no correlation was found between T2* value and exercise capacity (p = 0.62).

DISCUSSION

HR response after exercise test has been shown to be predictive and prognostic in many studies.[11,23,24] HRR is a strong indicator of fitness and partial mediator of autonomic nervous system. Autonomic dysfunction at a certain level has been shown in TM patients;[14] however, the influence of this on HRR values is not yet known.

Iron is an essential element which forms a necessarily component of biological systems. However, when this element is present in extremes, it can produce tissue damage due to oxidative stress.[25] Excess body iron can be collected in the heart, liver, spleen, bone marrow, pituitary, pancreas, and the central nervous system, causing damage to these organs. Iron overload cardiomyopathy results from the accumulation of iron in the myocardium, and it is the leading cause of morbidity and

Table 3. HRR in patients with T2* < 20 ms vs. those with > 20 ms

Characteristics	T2* < 20 ms (n = 18)	T2* > 20 ms (n = 38)	p
HRR 1	30.5 ± 6.0	31.5 ± 12.4	0.70
HRR 2	49.6 ± 12.6	52.7 ± 14.9	0.42
HRR 3	54.7 ± 12.1	58.5 ± 14.6	0.80
HRR 4	57.6 ± 11.7	61.0 ± 13.2	0.33
HRR 5	57.8 ± 12.0	62.2 ± 14.3	0.23

Values are expressed as mean ± standard deviation. p < 0.05 value is significant. In all cases, differences were not statistically significant. HRR, heart rate recovery. One way analysis of variance, Mann-Whitney U-test, Independent samples t-test.

mortality in patients receiving recurrent blood transfusion therapy.[26] The incidence of cardiomyopathy due to iron overload is increasing and usually managed by cardiologists.

In this study, we calculated HRR values at the first, second, third, fourth, and fifth minutes during the recovery period after a submaximal exercise test in patients with TM and healthy individuals. We found that all HRR values were impaired in the patients with TM, compared to the IDA group that was matched for age, smoking, BMI, and sex.

Autonomic function is impaired in patients with heart failure, and abnormal HRR is related to decreased exercise capacity.[27,28] Cardiac failure remains as the major cause of death in beta-thalassemia major. In our study, decreased HRR response was observed, and decreased exercise capacity was detected in TM patients compared to the IDA group. These findings may be an indicator of autonomic dysfunction. We also found in our investigation that the peak heart rate during exercise test was lower in TM patients compared to the IDA group. This observation might be associated with decreased sympathetic stimulus and autonomic dysfunction in TM patients.

There are a small number of studies investigating the association between HRR value, aerobic fitness, and mortality. Kokkinos et al.[29] evaluated HRR (recovery at min 1 and 2), aerobic fitness and all causes of mortality on the basis of a follow-up of 6.2 years, and found that low aerobic fitness and low HRR increased mortality risk by 7-fold compared to those who had a good aerobic fitness and high HRR. In our study, exercise capacity, exercise time and HRR values were found lower in TM patients compared to the IDA group. Further studies are required to investigate the influence of these findings on mortality in TM patients.

In our study, all HRR values (HRR 1, HRR 2, HRR 3, HRR 4, HRR 5) were found to be lower in TM patients compared to the IDA group. Low HRR was detected to be associated with poor aerobic fitness in an earlier study.[30] Besides, baseline abnormal HRR is associated with increased mortality and can predict mortality.[31] Jolly et al. achieved 41% recovery and improved survival in patients with abnormal baseline HRR through cardiac rehabilitation program.[31] However, sufficient data are not available regarding the influence of cardiac rehabilitation program on exercise parameters in TM patients and its clinical significance. Some other studies have shown that exercise training could modify HRR; however, the clinical benefit of this modification on HRR and whether it reflects to endpoints is not still known.[32,33] Studies are required investigating the influence of cardiac exercise rehabilitation program on HRR in TM patients with abnormal HRR.

In this study, we also detected that exercise capacity (METs) and exercise time was lower in patients with TM than in the IDA group. Hao et al.[34] provided a significant improvement in METs values through cardiac rehabilitation program. However, the influence of this exercise training on exercise capacity and its association with clinical outcomes is not yet known.

In a study of Hai et al.,[35] the some patients underwent and other patients bypassed a cardiac rehabilitation program after acute myocardial infarction, which were later compared. While both METs and HRR values were observed to improve in patients who underwent a cardiac rehabilitation program, only METs values improved but HRR did not change in the IDA group, which did not undergo a cardiac rehabilitation program. Given these studies, it seem that improved HRR is related with only exercise training.

Abnormal HRR reflects abnormal vagal tone[8,9] and prognostic value of abnormal HRR has been shown in many patient populations in many studies.[10,11,36] Exercise training was also shown to improve autonomic tone,[37,38] endothelial dysfunction[39] and positively affect all cause mortality in patients with coronary heart disease.[40] Useful autonomic effects of exercise training are realized through increased vagal reactivation, and the influence on HRR is explained with this mechanism. However, the influence of exercise training on HRR and whether it is useful on clinical endpoints is not known.

There are many methods that define iron load in TM patients. Cardiac MRI is the most important among them and is only presently available noninvasively with the potential to assess quantitatively myocardial iron load.[12,41] MRI constructs images from transmitted microwave signals induced by exciting protons in the body in a high magnetic field. In noniron-overloaded hearts, these signals are homogenous, and relaxation time (time to fade excited signals) lasts for a longer duration

(brighter over time). In iron-overloaded hearts, however, the iron paramagnetic effect produces changes in MR signal intensity and susceptibility, and shortens the relaxation time and darkens the image more quickly.[42] MRI scanning can refocus the signals returning from the tissues, using a special radiofrequency pulse [spin echo (SE)] or by using special small magnetic fields called gradients [gradient echo (GE)] at specific time intervals [echo time (TE)].[43] MRI measures a parameter called "T2*", which is defined as the rate of loss of signal in tissues that are iron-loaded.[44] Increased myocardial iron accumulation on MRI leads to decreased T2*. While T2* value < 20 ms shows iron load in cardiac tissues and an absence of cardiac dysfunction, T2* < 6 ms indicates severe cardiac siderosis and predicts development of 50% cardiac dysfunction within one year.[45,46] In addition, according to November 2009 American Heart Association report, cardiac T2* < 10 ms predicts cardiac event development within one year with 98% sensitivity and 86% specificity.[12,45] In our study, a correlation was not detected between T2* values and HRR values, which could be an outcome of small number of subjects. The association between HRR and T2* can be revealed more explicitly in a larger cohort. In addition, considering that mean T2* value of our patients is 28.3 ms and only 18 patients had a T2* value of < 20 ms, impaired HRR may be an early marker of cardiac dysfunction in TM patients. In TM patients, there was no correlation between HRR and T2*, here may also be influenced by factors that small number of patients, also HRR could be affected in the early stages before showing involvement with MRI T2*. Because in our study, HRR values were found significantly lower in TM patients than IDA group. These early findings may reflect autonomic dysfunction in TM patients. This case is an open spectrum to be searched, with further studies to be performed in the future.

Impaired HRR may be an early marker of cardiac dysfunction. Impaired HRR is an indicator of autonomic dysfunction. We consider that impaired HRR in patients with TM shows autonomic dysfunction, on this basis autonomic dysfunction may be an early sign of cardiac involvement.

The value of HRR as a marker to show early cardiac involvement may be increased through more comprehensive studies, showing that T2* values decrease during follow up of TM patients with impaired HRR.

Limitations

This study had several limitations. First, the study was a single center study. It was not large enough to detect HRR in patients whom T2 score was high and low, or in other words, the number of patients was limited. Other parameters such as heart rate variability (HRV) and gas analysis were not evaluated during exercise test. With all these limitations, our country is not enough wealthy to perform MRI for T2 score in patients with iron deficiency anemia. Thus, we were unable to provide the data about the T2 in both groups. In our study, exercise capacity was measured as METs and exercise time as min, while symptom-limited exercise time was taken rather than maximum exercise time.

CONCLUSIONS

Low HRR in an exercise test reflects cardiovascular fitness and/or abnormal autonomic status in TM patients. Abnormal HRR is an indicator of autonomic dysfunction and may be a predictor of early cardiac involvement in this group of patients. Future studies may investigate the other parameters affecting HRR and the influence of impaired HRR on clinical endpoints in TM patients.

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DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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