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REVIEW

Early detection of cardiac involvement in thalassemia: From bench to bedside perspective

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Abstract

Myocardial siderosis is known as the major cause of death in thalassemia major (TM) patients since it can lead to iron overload cardiomyopathy. Although this condition can be prevented if timely effective intensive chelation is given to patients, the mortality rate of iron overload cardiomyopathy still remains high due to late detection of this condition. Various direct and indirect methods of iron assessment, including serum ferritin level, echocardiogram, non-transferrin-bound iron, cardiac magnetic resonance T2*, heart rate variability, and liver biopsy and myocardial biopsy, have been proposed for early detection of cardiac iron overload in TM patients. However, controversial evidence and limitations of their use in clinical practice exist. In this review article, all of these iron assessment methods that have been proposed or used to directly or indirectly determine the cardiac iron status in TM reported from both basic and clinical studies are comprehensively summarized and presented. Since there has been growing evidence in the past decades that cardiac magnetic resonance imaging as well as cardiac autonomic status known as the heart rate variability can provide early detection of cardiac involvement in TM patients, these two methods are also presented and discussed. The existing controversy regarding the assessment of cardiac involvement in thalassemia is also discussed.

Key words: Thalassemia; Iron overload; Cardiomyopathy; Serum ferritin; Heart rate variability; Magnetic resonance; Non-transferrin-bound iron

Core tip: The mortality of thalassemia major (TM) patients due to iron overload cardiomyopathy is still high even though it can be prevented with effective chelation. The role of reliable methods to determine cardiac iron status is very important in order to give a timely effective treatment. This review article provides a comprehensive summary and discussion of various iron assessment methods as well as their existing controversy for use from both basic and clinical reports that have been proposed or used to directly or indirectly determine the cardiac iron status in TM.

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INTRODUCTION

Thalassemia major (TM) is an inherited anemia caused by impaired synthesis of the beta goblin chain. The prevalence of thalassemia is high in the Mediterranean countries, the Middle East, Central Asia, India, Southern China and Thailand[1]. Approximately 60000 TM infants are reportedly born each year[2]. Due to severe hemolytic anemia, TM patients need to habitually receive blood transfusions beginning in infancy. Regular blood transfusions, increased intestinal iron absorption as well as the lack of active excretion of iron inevitably lead to an excess accumulation of iron in the body of TM patients including not only in the reticuloendothelial cells, but also in the parenchymal tissues as well[3]. Excess free iron participating in the Fenton-type reaction has been shown to contribute to the pathogenesis of hemochromatosis[4]. Among many complications due to iron overload, myocardial siderosis is the major cause of mortality in these TM patients[5].

At present, although bone marrow transplantation has been shown to effectively cure some selected patients, the cornerstone of treatment in TM is still with blood transfusion and iron chelation therapy. The effectiveness of iron chelation has markedly improved since the introduction of oral chelators, such as deferiprone[6] and deferasirox[7], resulting in prolonged life expectancy and increased quality of life in TM patients. Despite the effectiveness of iron chelators, iron overload cardiomyopathy can be reversible only if early intensive chelation has been initiated[8,9]. Once TM patients develop clinical symptom such as heart failure or arrhythmia, the prognosis usually becomes poor and death thereafter in spite of intensive chelation[10]. These findings indicate the importance of early detection of cardiac iron accumulation prior to the development of cardiac dysfunction, and that the intensive chelation can be given promptly to those patients who are at risk. Currently, various methods for the detection of cardiac involvement in iron overload condition have been reported both in animal models as well as in clinical studies. Nevertheless, there are still limitations of their use in TM patients due to controversial reports on their reliability or limited access to the machine used for the detection as well as their high cost. In this review article, various methods that have been proposed or used to directly or indirectly determine the cardiac iron status in TM reported from basic and clinical studies are comprehensively summarized and presented. The existing controversy regarding the assessment of cardiac involvement in thalassemia is also discussed.

ASSESSMENT OF CARDIAC INVOLVEMENT IN THALASSEMIA

Since clinical evaluation is unreliable to detect an early stage of iron overload cardiomyopathy in TM patients, several approaches have been used to determine cardiac iron status instead. These include the indirect cardiac iron assessment such as serum ferritin, echocardiogram, and electrocardiogram (ECG) as well as the direct but invasive assessment such as myocardial biopsy and liver biopsy. Since there has been growing evidence in the past decades that cardiac magnetic resonance imaging (MRI) as well as cardiac autonomic status known as the heart rate variability (HRV) can provide early detection of cardiac involvement in TM patients, these two methods will also be presented and discussed.

Serum ferritin

Serum ferritin has been used for decades as a predictor of iron overload status in clinical practice due to its strong correlation with hepatic iron[11], representing an indirect index for estimating the total body iron stores. It is inexpensive and accessible worldwide. Serum ferritin has been shown to have a positive relationship with the amount of blood transfusion in beta-thalassemia patients[12]. Furthermore, it has been shown that a serum ferritin level greater than 1800 μg/L was associated with the increased concentration of cardiac iron, and that serum ferritin greater than 2500 μg/L was associated with the increased prevalence of cardiac events[13].

The downturn of using serum ferritin as an assessment of iron overload is due to the fact that the increased level of serum ferritin is not specific to iron overload condition since its level can also be increased in other conditions such as inflammation, collagen diseases, hepatic diseases, and malignancy[14]. Evidence indicated that an increased serum ferritin levels might be a defense mechanism of the body against oxidative stress[15]. Moreover, a low serum ferritin level does not necessarily designate low risk of iron-induced cardiomyopathy[16]. Several studies in the last decade demonstrated that serum ferritin is not suitable for its use as a predictive indicator of myocardial iron deposition due to its lack of relationship with cardiac iron[17,18]. A recent study reported that many unexplained cardiac deaths in TM patients were found even though they had low serum ferritin levels[19], emphasizing the unreliable use of serum ferritin as a predictor for iron overload cardiomyopathy in TM patients.

Echocardiogram

Echocardiogram is a valuable tool for cardiac function monitoring in clinical practice. However, several studies demonstrated that it is not sensitive enough for early detection of the preclinical stage of cardiac involvement in TM patients due to the typical late onset of symptoms and signs[20]. Once cardiac dysfunction is detected by an echocardiogram, the survival rate of these patients is reduced[21,22], suggesting a late stage detection of the disease by this assessment. In addition, it has been shown that the absence of a reduced left ventricular ejection fraction (LVEF) does not exclude a significant risk of sudden potential cardiac decompensation from iron overload[23]. Since left ventricular function is often slightly higher than normal in thalassemia patients in the absence of

myocardial iron overload[24], the normal values of cardiac function by echocardiogram may not be able to rule out cardiac impairment by iron deposition in these patients. Therefore, routine monitoring of cardiac function by echocardiogram is not reliable in early detecting thalassemia patients with high risk of cardiac involvement in order to provide timely intensive treatment.

Electrocardiogram

Since most of TM patients with early cardiac involvement are asymptomatic, ECG has no value for screening of cardiac involvement in this group of patients[25]. Similar to echocardiogram, once the development of cardiac arrhythmias, such as premature atrial or ventricular contractions, first-degree atrioventricular block, atrial flutter, atrial fibrillation, ventricular tachycardia, and second-degree or complete heart block[26-28], is detected by ECG, it usually implies an advanced stage of disease[29,30]. Furthermore, a normal ECG does not exclude a risk of significant arrhythmia development in iron overload patients[25]. In a retrospective analysis, which included 27 transfusion-dependent thalassemia patients who underwent annual 24-h electrocardiographic monitoring, two patients developed significant clinical symptoms secondary to cardiac arrhythmias within one year of follow-up[31]. This result indicated that a 24-h electrocardiogram might be useful for arrhythmia detection, but is not totally predictive for life-threatening cardiac events. Therefore, both ECG and conventional 24-h ECG monitoring are not appropriate markers for early detection of cardiac involvement in thalassemia patients.

Liver and myocardial biopsy

Liver biopsy is a direct determination of liver iron concentration closely reflecting total body iron storage[32]. However, a previous study demonstrated that hepatic iron concentration correlates poorly with cardiac iron status and cardiac function[33]. These findings indicated that determination of iron level *via* liver biopsy does not reflect cardiac iron deposition. Moreover, this technique is an invasive procedure that is not suitable for regular monitoring of iron status in thalassemia patients.

A previous study has also shown that iron level determined by an invasive myocardial biopsy was not correlated with cardiac iron status and cardiac function[34]. This could be due to the fact that myocardial iron deposition was inhomogeneous in the heart[35]. As a result, myocardial biopsy is not recommended to be used as an indicator for cardiac iron overload assessment.

Superconducting quantum interference device

Superconducting quantum interference device (SQUID) biomagnetic liver susceptometry (BLS) has become a standard method in monitoring iron in the liver[36,37]. However, it has many limitations including its availability, cost, technical demands, and suboptimal reproducibility[38]. Together with the lack of heart data, SQUID has not been recommended for its use in the evaluation of cardiac iron status in patients with thalassemia.

Non-transferrin-bound iron

Non-transferrin-bound iron (NTBI), a free-form iron, can be detected in plasma when the iron binding capacity of transferrin is saturated[39]. This form of iron is able to generate free radical *via* the Fenton-type reactions, leading to peroxidative damage to membrane lipid and protein[40]. The rate of NTBI uptake into cells is approximately 300-fold greater than that of transferrin-bound iron[41] due to its independence on the presence of transferrin receptor[42] and none of feedback-regulated process[43]. Moreover, there is a positive correlation between the rate of NTBI uptake and cellular iron content[44]. Furthermore, a recent study demonstrated a direct correlation between NTBI and vital organ damage in thalassemia patients[45]. In a normal individual, there is no detectable NTBI[46]; on the other hand, hemochromatosis patients exhibit higher NTBI levels than controls[47]. The growing evidence on NTBI suggests that it could be a good index of iron overload in TM patients.

Despite these facts, currently there is neither a cut-point threshold to imply cardiac iron overload status nor even a universally accepted method for NTBI measurement at the present time[48]. Importantly, a poor correlation was found between the methods in a recent inter-laboratory survey[49]. As a consequence, these limitations minimize its use in clinical practice.

Cardiac magnetic resonance T2*

Cardiac magnetic resonance T2* (CMR T2*) has become a widely used tool for its accurate and non-invasive technique to measure iron deposition in heart[50]. Currently, this technique has been proven to be the most sensitive index and reproducible to assess cardiac iron available today[50,51]. Anderson *et al*[16] first reported a significant relationship between myocardial T2* below 20 ms and cardiac function parameters, such as LVEF ($r = 0.61$, $P < 0.0001$), left ventricular (LV) end-systolic volume index ($r = 0.50$, $P < 0.0001$), and LV mass index ($r = 0.40$, $P < 0.001$). A later study confirmed the correlation of myocardial T2* with not only systolic function but also diastolic function as well[52]. Moreover, an increase of myocardial T2* was also in accordance with improved cardiac function[17]. Previous studies in a fresh postmortem iron overloaded heart[53] and a gerbil model of iron overload[54] clearly demonstrated a negative correlation between CMR T2* values and myocardial iron deposition. It also confirmed the earlier studies that iron loading was deposited mostly in the epicardium and myocardium[35,55]. Until now, no clinical scenario other than cardiac iron overload is found to cause myocardial T2* below 20 ms[50]. Thus, these data implied that CMR T2* is more specific to cardiac iron status than other previously mentioned methods.

The prospective study by Kirk *et al*[56] indicated the significant strong association between cardiac T2* values and risk of heart failure development in TM patients. It

Table 1 Summary of the controversial correlation between cardiac magnetic resonance T2* and serum ferritin in thalassemia major

Population/size	Type of study	Findings	Correlation	Ref.
TM/652 patients	Prospective	Significant correlation between cardiac T2* and ferritin (r^2 = 0.003, P = 0.04)	/	Kirk *et al*[56]
TM/776 patients	Retrospective	Significant relationship between cardiac R2* and ferritin (r = -0.359, P < 0.0001)	/	Marsella *et al*[59]
TM/167 patients	Prospective	Myocardial T2* was correlated with serum ferritin (r = -0.34, P < 0.001)	/	Tanner *et al*[60]
TM/19 patients, SCD/17 patients	Cross sectional	Cardiac 1/T2* was correlated with ferritin level (r^2 = 0.33, P = 0.01)	/	Wood *et al*[61]
TM/106 patients	Prospective	No significant correlation between heart T2* and serum ferritin	×	Anderson *et al*[16]
TM/60 patients	Prospective	Serum ferritin did not correlate with cardiac iron values	×	Merchant *et al*[57]
TM/20 patients	Prospective	No correlation between serum ferritin and cardiac T2*	×	Kolnagou *et al*[58]
TM/47 patients	Retrospective	Cardiac T2* was not associated with the serum ferritin	×	Bayraktaroğlu *et al*[22]

TM: Thalassemia major; SCD: Sickle cell disease.

Table 2 Summary of the correlation between cardiac magnetic resonance T2* and cardiac function in thalassemia major

Population/size	Type of study	Findings	Correlation	Ref.
TM/776 patients	Retrospective	Significant correlation between LVEF and cardiac R2* (r = -0.327, P < 0.0001)	/	Marsella *et al*[59]
TM/106 patients	Prospective	Significant correlation of myocardial T2* below 20 ms with LVEF (r = 0.61, P < 0.0001), LVESVi (r = 0.50, P < 0.0001), and LV mass index (r = 0.40, P < 0.001)	/	Anderson *et al*[16]
TM/167 patients	Prospective	Significant relationship between myocardial iron and LVEF (r = 0.57, P < 0.001)	/	Tanner *et al*[60]
TM/67 patients	Cross sectional	Myocardial T2* related to LV diastolic function (EPFR, r = –0.20, P = 0.19; APFR, r = 0.49, P < 0.001; EPFR/APFR ratio, r = –0.62, P < 0.001)	/	Westwood *et al*[52]
TM/33 patients	Cross sectional	Good correlation of DT, Tei index and E/Em index with cardiac T2* values (P < 0.05, r = 0.70-0.81) and weak correlation of E/A with T2* (P < 0.05, r = -0.44)	/	Barzin *et al*[84]
TM/47 patients	Retrospective	Significant correlations of the myocardial T2* with LVESVi and LVEDVi (r = -0.32, P = 0.027; r = -0.29, P = 0.046, respectively)	/	Bayraktaroğlu *et al*[22]
TM/19 patients, SCD/17 patients	Cross sectional	Significant relationship between LVEF and myocardial T2*	/	Wood *et al*[61]

TM: Thalassemia major; SCD: Sickle cell disease; LVEF: Left ventricular ejection fraction; LVESVi: Left ventricular end systolic volume index; LVEDVi: Left ventricular end diastolic volume index; EPFR: Early peak filling rate; APFR: Atrial peak filling rate; DT: Deceleration time; E/Em: Early diastolic peak inflow velocity and early diastolic myocardial velocity ratio; E/A: Early and late transmittal peak flow velocity ratio.

demonstrated that 98% of patients who developed heart failure had the cardiac T2* less than 10 ms, with a relative risk (RR) of 160 (95%CI: 39-653). In the same study, the RR for cardiac T2* less than 6 ms was 270 (95%CI: 64-1129). Moreover, T2* threshold of 10 ms for predicted heart failure had a sensitivity of 97.5% (95%CI: 91.3-99.7) and a specificity of 85.3% (95%CI: 83.3-87.2). This study also demonstrated the significant relationship between cardiac T2* values and a risk of cardiac arrhythmia development in TM patients, but weaker than a risk of heart failure. A cardiac T2* less than 20 ms was figured in 83% of patients who develop arrhythmia, with a RR of 4.60 (95%CI: 2.66-7.95). The RR for a cardiac T2* less than 6 ms was 8.79 (95%CI: 4.03-19.2). The T2* threshold of 20 ms for predicted cardiac arrhythmia had a sensitivity of 82.7% (95%CI: 73.7-89.6) and a specificity of 53.5% (95%CI: 50.8-56.2). In addition, this prospective study clearly demonstrated the link between myocardial T2* and cardiac events. The one year risk of heart failure development was shown to be 14%, 30%, and 50% for T2* between 8-10, 6-8 and less than 6 ms, respectively. Therefore, myocardial T2* less than 10 ms strongly indicated clinically significant cardiac iron overload and an increase in risk of developing heart failure in TM patients.

When compared with conventional iron monitoring parameters, the correlation between CMR T2* and serum ferritin in TM patients has not been concluded (Table 1). Several studies indicated that serum ferritin was not correlated with cardiac T2*[16,22,57,58]. However, other studies with larger population size showed a weak relationship between serum ferritin and heart T2*[56,59-61]. Because serum ferritin is raised even in many common conditions such as inflammation or hepatic disease[14], the controversial correlation could be from subjects with a different underlying status included in each study. As a result, a guideline for intensive chelation therapy based on serum ferritin may be inappropriate for cardiological management in TM patients.

A prospective study of Tanner *et al*[62], which recruited 167 TM patients, showed the significant association between heart T2* values and LVEF. Patients with mild, moderate and severe cardiac iron overload (T2* 12-20, 8-12 and less than 8 ms, respectively) had impaired LVEF in

Table 3 Comparison of various methods to evaluate cardiac iron overload in thalassemia patients

Method	Advantages	Disadvantages
Serum ferritin	Easy and available Inexpensive	Poor predictor of iron overload[85,86] Nonspecific for cardiac iron Altered by many conditions[14]
Echocardiogram	Easy and available Inexpensive	Late indicator of cardiac involvement[21,23]
Liver biopsy	Total body iron estimation[32]	Invasive No correlation with myocardial iron deposition[33]
Myocardial biopsy		Invasive No correlation with cardiac iron status and function[34]
ECG	Easy and available Inexpensive	Ineffective screening parameter for cardiac iron overload[25,31]
SQUID	Standardized noninvasive index for liver iron[36]	Lack of availability, technical demands, and reproducibility Costly
NTBI	Direct parameter of freeform iron resulting in peroxidative damage[87]	Application for the study of heart iron pending Limited availability No generally accepted method[48], and poor correlation between methods[49]
CMR T2*	Method of choice for the assessment of tissue iron deposition in last decade[51] Noninvasive measurement of cardiac iron deposition[50] Available High sensitivity and reproducible[50] Correlation with clinical outcome[16,17,56,62,63]	Costly

ECG: Electrocardiogram; SQUID: Superconducting quantum interference device; NTBI: Non-transferrin-bound iron; CMR T2*: Cardiac magnetic resonance T2*.

5%, 20% and 62%, respectively ($P < 0.001$). Table 2 summarized studies that showed the significant correlation between CMR T2* and cardiac function in TM patients. These studies suggest that myocardial T2* could be a useful application to determine cardiac iron overload tending to deteriorate cardiac function. As a result, CMR T2* may be suitable for use as an assessment of cardiac iron deposit in thalassemia patients for early detection of the cardiac iron status before the detection of clinical signs and symptoms of iron overload cardiomyopathy.

Since several studies showed a remarkably strong correlation of heart T2* value with clinical cardiac complications, including heart failure and arrhythmia, CMR T2* had been applied to monitor cardiac iron deposition in TM patients in UK[63,64]. Interestingly, the mortality rate was significantly reduced. Nowadays, CMR T2* is recognized as the method of choice for evaluation of cardiac iron deposition in TM patients[51]. However, the limitation of this technique is its rather expensive cost and only limited medical centers around the world are equipped with this technique.

The pros and cons of different approaches that monitor cardiac iron overload condition in thalassemia patients are summarized in Table 3.

HRV IN THALASSEMIA MAJOR

HRV is used to indicate the variation over time of the period between successive heartbeats and determine cardiac autonomic function and overall cardiac health[65]. HRV analysis has been used to determine the cardiac autonomic function in patients with post-myocardial infarction[66,67]. Reduced HRV parameters were associated with a significant increased mortality in these patients[68,69]. A prospective study indicated that HRV analysis on 1-year post-myocardial infarction follow-up patients also had prognostic significance[70]. Furthermore, HRV parameters have been shown to a strong predictor of mortality in patients with heart failure[71,72], cardiac transplantation[73], and diabetic neuropathy[74].

Due to its non-invasiveness and easy derivation, HRV has been investigated as one of the promising parameters to initially detect cardiac involvement and has been widely studied in thalassemia in the last decades. A number of studies on HRV in TM patients have been reported since Franzoni *et al*[75] first proposed that HRV was depressed in TM patients. A summary of previous studies that exhibited the significantly reduced HRV parameters in TM patients and thalassemic mice is described in Table 4. All of previous studies reported that HRV parameters were reduced both in TM patients and thalassemic mice, indicating that thalassemic condition exerted some degrees of cardiac autonomic dysfunction. A recent study which investigated autonomic function by six quantitative autonomic function tests demonstrated that the prevalence of subclinical autonomic function impairment was higher in thalassemia patients compared to controls[76]. This result confirmed that thalassemia patients have autonomic dysfunction in some degree. In prospective studies by Kardelen *et al*[77] and De Chiara *et al*[78], no evidence of abnormal echocardiographic finding was shown in TM patients with reduced HRV. Therefore, a significantly reduced HRV could be an early indicator of preclinical stage of heart disease in TM group. Nevertheless, the evidence of HRV in TM patients has not been extensively

Table 4 Summary of heart rate variability findings from both clinical and basic studies in thalassemia

Population/size	Type of study	Findings	Ref.
34 TM patients and 20 healthy subjects	Prospective	Significantly depressed both time and frequency domain HRV parameters in TM patients	Rutjanaprom *et al*[20]
32 TM patients and 46 control subjects	Prospective	Significantly reduced all HRV parameters in TM patients	Kardelen *et al*[77]
19 TM patients and 19 healthy volunteers	Cross sectional	Significantly lower both time and frequency domain HRV parameters in the TM group	Franzoni *et al*[75]
100 TM patients and 60 healthy controls	Cross sectional	Lower SDNN in TM with ectopia while markedly increased LF/HF ratio in this group.	Oztarhan *et al*[88]
48 Thalassemia patients and 45 healthy subjects	Cross sectional	Significantly reduced time domain parameters in the thalssemia group	Gurses *et al*[89]
9 TM patients and 9 healthy subjects	Cross sectional	Significantly lower LF/HF ratio during tilt in TM patients than in control subjects	Veglio *et al*[90]
21 TM patients and 15 healthy subjects	Cross sectional	Significantly lower in all HRV parameters in TM group than in control group	Ma *et al*[91]
13 wildtype, 13 HbE/β thalassemia and 13 *mu*β+/− mice	Cross sectional	Depressed all HRV parameters in the heterozygous βglobin knockout mice (*mu*β+/−)	Incharoen *et al*[92]
810 wildtype and 810 heterozygous betaknockout mice	Prospective	Higher LF/HF ratio in thalassemic mice than those in the wild type	Kumfu *et al*[82]
12 wildtype and 12 heterozygous betaknockout mice	Prospective	Depressed HRV in betathalassemic mice compared to wild type	Thephinlap *et al*[93]

TM: Thalassemia major; HRV: Heart rate variability; SDNN: Standard deviation of all NN intervals; LF: Low frequency power; HF: High frequency power.

Table 5 Summary of the correlation between HRV and serum ferritin in thalassemia major

Population/size	Type of study	Findings	Correlation	Ref.
34 TM patients and 20 healthy subjects	Prospective	No correlations between HRV parameters and serum ferritin	×	Rutjanaprom *et al*[20]
19 TM patients and 19 healthy volunteers	Cross sectional	No correlation between HRV parameters and serum ferritin	×	Franzoni *et al*[75]
21 TM patients and 15 healthy subjects	Cross sectional	No relationship of HRV parameters with serum ferritin	×	Ma *et al*[91]

TM: Thalassemia major; HRV: Heart rate variability.

Table 6 Summary of the relationship between heart rate variability and cardiac function in thalassemia major

Population/size	Type of study	Findings	Correlation	Ref.
34 TM patients and 20 healthy subjects	Prospective	None of the echocardiographic parameters was correlated with HRV	×	Rutjanaprom *et al*[20]
32 TM patients and 46 control subjects	Prospective	Reduced HRV were described in TM despite no echocardiographic abnormality	×	Kardelen *et al*[77]
19 TM patients and 19 healthy volunteers	Cross sectional	No correlation between HRV parameters and echocardiographic parameters	×	Franzoni *et al*[75]
20 TM patients	Prospective	Abnormal HRV in TM with no evidence of ventricular dysfunction	×	De Chiara *et al*[78]

TM: Thalassemia major; HRV: Heart rate variability.

investigated when compared to that in post-myocardial infarction patients. Until now, none of studies has focused on the association between HRV and mortality in TM patients.

After the first report of HRV in TM patients by Franzoni *et al*[75], several studies have examined HRV in TM patients in order to seek the correlation between HRV and currently used iron overload parameters. No correlation between HRV parameters and serum ferritin in TM patients has been demonstrated (Table 5). Moreover, no correlation between HRV parameters and cardiac function in TM patients has been shown (Table 6). It is possible that HRV is not correlated with iron overload condition because several anemic diseases other than thalassemia, including sickle cell anemia[79], iron deficiency anemia[80], vitamin B12 deficiency anemia[81], could also impair cardiac autonomic function. Nevertheless, some evidence demonstrated that autonomic status determined by HRV is correlated with iron overload condition. In a study with thalassemic mice[82], it has been shown that

those thalassemic mice had a higher Lfnu, lower Hfnu, and higher Lf/Hf ratio than those in the wild-type mice. More interestingly, iron administration in both types of mice resulted in significantly higher NTBI levels concomitant with increased Lfnu and Lf/Hf ratio and decreased Hfnu. Moreover, iron chelator significantly decreased the Lfnu, Lf/Hf ratio, and increased the Hfnu in those iron overload thalassemic mice. This prospective study suggested that iron overload condition could contribute to progressive deterioration of the impaired cardiac autonomic function.

In conclusion, although CMR T2* is now recognized as the method of choice in evaluation of iron deposition in the heart[51], evidence suggested that TM patients must be prevented rather than treated even before cardiac iron loading becomes detectable on CMR T2* because of leading causes of cardiac tissue damage by other iron mediated mechanisms, such as those induced by labile plasma iron[83]. HRV might be used as an alternative approach to assess cardiac involvement in TM patients. Due to its easy access and much lower cost compared to CMR T2*, 24-h Holter monitoring for HRV analysis can be performed in most health providing centers. However, more evidence is needed to validate its use before it can be applied in clinical practice. Further studies are also needed to demonstrate the correlation between HRV and CMR T2* as well as the clinical application of HRV as a predictive marker in TM patients.

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