# Myocardial iron load measured by cardiac magnetic resonance imaging to evaluate cardiac systolic function in thalassemia

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**Original Article**

## Abstract

**BACKGROUND:** The assessment of cardiac iron overload in thalassemia major has been considered as an important predictive factor of heart injury. The magnetic resonance imaging (MRI)-derived relaxation time parameter (T2*) varies inversely with iron level, and elevated myocardial iron levels by T2* are associated with depressed left ventricular (LV) ejection fraction (EF). We compared echocardiographic (ECHO) indices of systolic function to myocardial T2* in these patients.

**METHODS:** A cross-sectional database review identified 200 consecutive patients with thalassemia who underwent both ECHO and MRI T2* assessment.

**RESULTS:** There was a negative correlation between T2* measurement and ECHO EF ($r = -0.389$, $P < 0.001$). Using a cutoff value of 50% for differentiating LV normal and abnormal function by ECHO, T2* MRI had a sensitivity of 57.1%, a specificity of 89.9%, and an accuracy of 86.5% for predicting LV dysfunction. Receiver operating characteristic analysis showed that cardiac iron measurement had an acceptable value for discriminating normal and abnormal LV function (area under the curve = 0.769, 95% confidence interval: 0.653-0.885). With respect to the relationship between serum ferritin level and cardiac iron value, the level of serum ferritin was positively correlated with the level of cardiac iron load ($r = 0.257$, $P < 0.001$).

**CONCLUSION:** Myocardial iron load assessed by MRI T2* is associated with deterioration of the LV function assessed by ECHO with a high specificity and moderate sensitivity. It is important to identify the thalassemic patients with a risk of iron overloaded cardiomyopathy and heart failure.

**Keywords:** Thalassemia, Iron Overload, Magnetic Resonance Imaging, Ferritin, Accuracy

## Introduction

Anemia simultaneous with marrow expansion is main competing factor of cardiac injuries in thalassemia major. They can be an increase in cardiac outlet that lead to increasing of hearth function.[1,2]

Further, the cardiac iron sediment leads to decreasing hearth function in people with certain background.[3] Iron is too a risk factor for myocardium. Iron can be accumulate in cells as hemosiderin, ferritin. Free iron is the most toxic form that stimulates production of free radicals.[4,5] Furthermore, evaluation of cardiac iron overload as predictive factor of heart injury is important in thalassemia major. We have different way to evaluation of cardiac iron overload including measurement of plasma ferritin level, liver biopsy, cardiac echocardiographic (ECHO)-Doppler studies, and recently magnetic resonance imaging (MRI).[6]

MRI as a reliable, valid, and robust method can provide indirect assessment of cardiac iron overload.[7] Even, it has been advised to determination the degree of cardiac iron overload.[8] The reciprocals of T2 and T2*, known as R2 and R2*, are directly proportional to iron and demonstrate the most promising results.[9,10] In this

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method, the MRI-derived relaxation time parameter, T2*, changes inversely with iron level and thus elevated myocardial iron levels by T2* have been shown to be associated with depressed left ventricular ejection fraction (LVEF).[11,12]

Although this technique is progressively applied in different clinical settings and even prefers using ECHO, its diagnostic performance has been already unclear in thalassemia major patients. We therefore sought to directly compare echocardiographic indices of systolic function to myocardial T2* in these patients and determine the value of cardiac MRI for discriminating LV dysfunction measured basically by tissue Doppler ECHO.

## Materials and Methods

In this analytical cross-sectional study, 200 patients with major thalassemia aged between 10 and 20 were selected from Samen Alhojaj Center (Charity Foundation for Special Diseases) by census method from August 2013 to November 2014. A retrospective database review identified 200 consecutive patients with thalassemia who underwent both ECHO done at Shifa Hospital in Kerman University of Medical Sciences, Iran, and MRI T2* assessment in a private center in Tehran, Iran.

Medical Center in Samen Alhojaj permission for a database and medical record review was granted by the Kerman University of Medical Sciences Committee on Clinical Investigation. This database included baseline characteristics of the patients as well as medical history, medications, and laboratory data of consecutively enrolled patients. All patients were prescribed chelation therapy with deferoxamine typically beginning before the age of 7 years. The conventional chelation treatment was subcutaneous infusion of deferoxamine in a daily dose 30-50 mg/kg, 5-6 times/week. Chelation therapy was monitored by frequent estimation of ferritin.

MRI examinations were routinely performed within 10 days of transfusion. MRI was performed 2 weeks after ECHO. MRI measurements were performed using a 1.5-T clinical MRI scanner.

Myocardial T2* was assessed from a single midpapillary ventricular short-axis slice using a cardiac-gated, segmented, multi ECHO gradient ECHO sequence obtained in a single breath-hold, as previously described.[11]

Iron in the myocardium was quantified by measuring T2* (1/R2*), an MR relaxation parameter that has been shown to vary inversely with tissue iron concentration.[12-14,15] The T2* values were calculated using custom written

software developed in MATLAB (MathWorks Inc, Natick, MA).

Two-dimensional M-Mode and tissue Doppler imaging (TDI) (six segments of LV) was performed to assess LV function, conducted by Vivid 3 ECHO devices with 3 and 5 MHz probes. Systolic dysfunction was defined as mild if the EF was 41% to 50%, moderate if 31% to 40%, and severe if ≤ 30%.

Results were presented as mean ± standard deviation for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Correlation between the quantitative variables was examined using the Pearson's correlation coefficient test.

The diagnostic performance of MRI T2* according to the results of TDI was measured by the quantity of true positives, true negatives, false positives, and false negatives. In this regard, a cutoff point of 4 for 1/R2* (1-3 indicated normal value to moderate abnormal level and 4 or more indicated severe abnormal level) was measured by MRI T2*, and a cutoff 50% for differentiating LV normal and abnormal function by ECHO was considered. In the prediction system, the total prediction accuracy, sensitivity, and specificity were calculated.[16]

A receiver operating characteristic (ROC) curve was used to identify the best cutoff point, by which to maximize the sensitivity and specificity of discriminating LV normal and abnormal function. For the statistical analysis, the statistical software SPSS software for Windows (version 19.0, SPSS Inc., Chicago, IL, USA) was used. P values of 0.050 or less were considered statistically significant.

## Results

A total of 200 patients (93 males, mean age of 17.87 ± 6.27 years) were identified with thalassemia undergoing both ECHO and MRI T2* assessment. The mean duration of transfusion was 16.66 ± 7.26 months with a mean pre-transfusion hemoglobin level of 9.18 ± 1.39 g/dl, and the average serum ferritin level was 3023.55 ± 2258.41 ng/ml (Table 1).

The mean LVEF was 56.59 ± 5.78% (ranged 35-65%) that 10.0% of patients had EF < 50%. Systolic function as measured by ECHO EF was classified as normal in 96 cases (48.0%), mild dysfunction in 94 cases (47.0%), and moderate dysfunction in 10 cases (5.0%).

There was a significant negative correlation between 1/R2* measurement and ECHO EF (r = −0.389, P < 0.001). Furthermore, with respect to the relationship between serum ferritin level and cardiac iron value, the level of serum ferritin was

positively correlated with the level of cardiac iron load (r = 0.257, P < 0.001).

**Table 1.** Baseline characteristics and clinical data of the study subjects (n = 200)[*]

| Variables | N (%) |
|---|---|
| Gender (Male) | 93 (46.50) |
| Age (year) | 17.87 (6.27) |
| Family history of thalassemia | 59 (29.50) |
| Duration of transfusion (mo) | 16.66 (7.26) |
| Serum BUN | 26.60 (9.26) |
| Serum creatinine | 0.62 (0.16) |
| Serum hemoglobin | 9.18 (1.39) |
| Serum ferritin | 3023.55 (2258.41) |
| Serum platelet | 295.27 (153.33) |
| Serum ALT level | 61.72 (85.99) |
| Serum AST level | 48.09 (46.63) |
| Serum ALP level | 437.80 (225.75) |
| Serum T3 level | 141.27 (103.51) |
| Serum TSH level | 2.54 (1.39) |

[*] For qualitative variables, relative and absolute frequencies, and for quantitative variables, mean and standard deviation were used to present the statistics.
AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase, TSH: Thyroid-stimulating hormone, BUN: Blood urea nitrogen

Only 7.0% of the patients had normal level of cardiac iron, 41.5% had mild abnormal value, and 36.0% had moderate abnormal value of cardiac iron. In this parallel, severe abnormal value of iron was observed in only 15.5% of them. Using a cutoff point of 4 for 1/R2* (1-3 indicated normal value to moderate abnormal level and 4 or more indicated severe abnormal level) measured by MRI T2* and a cutoff 50% for differentiating LV normal and abnormal function by ECHO, T2* MRI had the sensitivity of 57.1%, specificity of 89.9%, positive predictive value of 40.0%, negative predictive value of 94.7%, and accuracy of 86.5% for predicting LV dysfunction. In this study to evaluate LV function in patients, tissue Doppler method was compared to MRI. It was shown tissue Doppler sensitivity of 57.1%, specificity 89.9%, and positive predictive value 94.7%.

ROC analysis was used to explore the sensitivity and specificity of threshold values of T2* for ventricular dysfunction, and the results of this analysis are presented in figure 1. Cardiac iron measurement had an acceptable value for discriminating normal and abnormal LV function (area under the curve = 0.769, 95% confidence interval: 0.653-0.885).
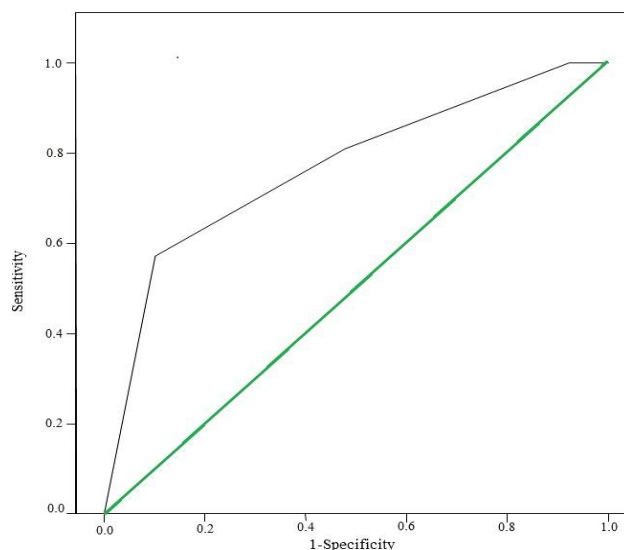


**Figure 1.** Receiver operator characteristic curves were constructed to investigate the diagnostic power of cardiac iron overload for predicting left ventricular dysfunction

## Discussion

The present study assesses diagnostic performance of myocardial T2* measured by cardiac MRI compared with ECHO to predict LV systolic function. We could show a mild to moderate adverse correlation between increased myocardial iron as measured by T2* and LVEF measured by ECHO. In this context, MRI T2* had a high specificity but a moderate sensitivity to predict LV dysfunction. In the literature, there are some available ECHO studies evaluating cardiac systolic function as well as volumetric parameters in thalassemic patients; however, detection of myocardial iron overload as an applicable indicator of systolic function has been recently described. In support of our study, some other studies demonstrated that MRI findings can be a good predictor of future cardiac dysfunction.[17-19]

In addition, in a study by Liguori et al.,[20] relationship between myocardial T2* values and cardiac volumetric and functional parameters in β-thalassemia patients was evaluated by cardiac magnetic resonance in association with serum ferritin levels. In our study, myocardial iron loading was found in 93.0% of our patients that was higher than that reported in Caucasian populations.[21]

The mean LVEF of our study population was 56.0% that only 10.0% of them had EF < 50%. In fact, thalassemic patients have greater LVEFs than normal subjects.[5] These patients have impaired LV function at higher values of EF than previously

thought.[5,19] This factor is important in the interpretation of the impaired EF. This fact is the main reason to consider higher cutoff point value (50.0%) for discriminating normal and abnormal LV systolic function in this study.

Serum ferritin levels are used as a main diagnostic indicator for identifying and monitoring of iron overload. In our study, the level of serum ferritin was positively correlated with the level of cardiac iron load. Contrarily, some studies in the literature have shown that the relationship between the cardiac T2* value and the serum ferritin level is either non-significant or weak.[22] It is suggested that myocardial iron levels can be also predicted using this parameter but weaker than the measurement of cardiac iron level.

The presented data were analyzed retrospectively, which is a limitation of our study. In addition, for assessing LV systolic function, we did not assess other variables such as strain and strain rate that should be considered in future studies. The main strength of this study was its large sample size. As far as the author is aware, no study has been done with the large sample size and it seems that this is the first study with a larger sample size which possibility of the establishment of random relations to minimize and suggests that the results are real.

## Conclusion

The current study demonstrates that myocardial iron load assessed by MRI T2* is mild to moderate associated with deterioration of the LV function assessed by ECHO with a moderate sensitivity and high specificity. It is important to identify the thalassemic patients with a risk of iron overloaded cardiomyopathy and heart failure.

## Acknowledgments

## Conflict of Interests

Authors have no conflict of interests.

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