

# T2-weighted cardiovascular magnetic resonance and echocardiographic arterial elasticity criteria for monitoring cardiac siderosis in patients with beta-thalassemia major

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**Background:** Despite the availability of iron chelators, toxicity due to increased iron load is the leading cause of death in thalassemia major patients, especially in Iran. This study was performed to determine the association between cardiovascular magnetic resonance using T2-weighted sequences (CMR T2\*) and diagnostic value of echocardiographic arterial elasticity in major beta-thalassemia patients without cardiac symptoms in Isfahan, Iran, in 2019 and 2021. **Materials and Methods:** This cross-sectional study assessed the association between CMR T2\*, advanced echocardiographic arterial elasticity criteria, and serum ferritin in 67 patients with major beta-thalassemia patients without cardiac symptoms at Chamran Cardiovascular, Medical, and Research Center in Isfahan, Iran, in 2019–2021. Data analysis was performed among the 67 patients using SPSS, version 24.0 (Statistical Procedures for Social Sciences, Chicago, Illinois, USA). Spearman's rank test was used to assess the correlation between T2\*CMR, echocardiographic arterial elasticity criteria, and ferritin. All parameters are presented as mean  $\pm$  standard deviation. The results were considered statistically significant at  $P < 0.05$ . **Results:** There was a positive correlation between CMR T2\* and arterial elastance index ( $P = 0.035$ ,  $r = 0.258$ ), according to the Spearman test. In addition, CMR T2\* was not correlated with the serum ferritin ( $P = 0.158$ ,  $r = 0.201$ ). **Conclusion:** Totally, according to the obtained results, it may be concluded that the arterial elastance index from echocardiography and the CMR T2\* may be indicators of myocardial iron overload in patients with major beta-thalassemia patients without cardiac symptoms.

**Key words:** Arterial elasticity, echocardiography, ferritin, major thalassemia, T2\*CMR

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## INTRODUCTION

Beta-thalassemia is the most common genetic hemoglobinopathy disorder worldwide, especially in Iran. For patients with beta-thalassemia major, heart failure due to iron-overload cardiomyopathy is the leading reason of mortality.<sup>[1,2]</sup> In developed countries, about 70% of thalassemia deaths are due to iron overload in the heart. This is despite the fact that many of these patients die before the age of 35 due to treatments based on iron chelators.<sup>[3]</sup> This disease has a high prevalence in our country, so that

the incidence of beta-thalassemia gene in the south and southeast of Iran has been reported 8%–10%.<sup>[4]</sup> The use of blood transfusions as a hypertransfusion regimen allowed patients with thalassemia major to grow and develop relatively normally. However, frequent blood transfusions increase the amount of iron in the body and thus iron deposition in vital organs such as liver, heart, and endocrine glands causes many problems for patients. It should be noted that the body's iron is not excreted by the liver and kidneys, so it is necessary to use drugs that help to excrete iron by chelating.<sup>[5,6]</sup> The use of iron chelators and their dosage requires an accurate assessment of the body's iron stores, and for this

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purpose, various methods are used, including measuring serum ferritin level or assessing liver iron levels using liver biopsy. This recent method, in addition to being an invasive method, does not provide an accurate assessment of the amount of iron in the heart.<sup>[7,8]</sup> For this reason, noninvasive methods are used to measure the level of iron in the heart and liver. One of these methods is T2\*CMR, which has been performed in Iran recently. T2\*CMR is performed using paramagnetic properties and evaluation of parameters including T2 relaxation enhancement induced by high-molecular-weight iron complexes such as ferritin and hemosiderin, which accumulate in siderotic tissues, allowing rapid measurement of cardiac hepatic iron load, and ultimately helps to diagnose tissue hemosiderin and myocardial hemosiderosis before clinical manifestations.<sup>[9,10]</sup> In patients with a reduced ventricular function, a T2\* value <20 ms is correlated with iron overload. Furthermore, patients with T2\* values <10 ms are at higher risk for heart failure in the upcoming year. These findings have been confirmed in observational, prospective, and randomized controlled studies of iron chelation in thalassemia patients.<sup>[11-13]</sup> Tissue echocardiography is another noninvasive method also used to evaluate the effects of iron deposition on the heart and to evaluate the results of treatment with chelators.<sup>[14]</sup> One of the parameters that can be calculated indirectly from echocardiography is the degree of arterial stiffness or flexibility of the arteries. This method of assessing the amount of iron in the heart tissue is cheaper and more accessible than T2\*CMR.<sup>[15]</sup> There are a few studies in the existing literature on the relationship between T2\*CMR and advanced echocardiographic arterial elasticity criteria. If such relationship is found, it may be used as a prognostic tool for myocardial iron overload. Therefore, the aim of this study was to evaluate the relationship between myocardial T2\* and echocardiographic arterial elasticity criteria in patients with thalassemia major.

## MATERIALS AND METHODS

This cross-sectional study was performed among 67 patients with major thalassemia at Chamran Cardiovascular, Medical, and Research Center in Isfahan, Iran, in 2019 and 2021 with history of at least 15-year transfusion. Inclusion criteria of patients in this study are that they first received a pack cell a week ago and also performed T2\*CMR in the past year, aged ≥10 years with myocardial T2\* >6 mseconds without clinical symptoms of cardiac dysfunction (orthopnea, exercise intolerance, and arrhythmias). The majority of the patients were receiving chelation therapy with subcutaneous desferrioxamine (20–30 mg/kg/d 3 days/week). Duration between doing CMR and echocardiography was maximum 90 days. The exclusion criteria were comprised of valvular heart disease, pulmonary artery hypertension, systemic hypertension, structural heart disease, heart failure,

diabetes mellitus, thyroid and parathyroid disorders, congenital heart diseases, and contraindication for CMR. The association between T2\*CMR and echocardiographic arterial elasticity criteria was assessed in the study population. The data collection and analysis associated with this study were approved by Isfahan Medical University Ethics Committee (IR.MUI.MED.REC.1398.164), and written consent was obtained from all participants.

Magnetic resonance imaging (MRI) was performed for all patients at Al Zahra Hospital, Isfahan, Iran, with a 1.5 Tesla scanner (Achieva 1.5T A-series, Siemens Medical Systems).<sup>[16]</sup> Scan duration was 14–21 min. For the measurement of myocardial T2\*, we used the Royal Brompton protocol which is based on a single short-axis mid-ventricular slice halfway between the base and the apex of the left ventricle was attained by means of a single breath-hold electrocardiography-gated multi-echo method and it was acquired at 8 separate echo times (TE 3–22.6 ms). The repetition time between RF pulses was between 125 and 223 ms, depending on the echo time used.<sup>[17]</sup>

Two-dimensional and Doppler echocardiography was performed using the Philips Epiq 7C with a S5-1 (2.5MHz) probe via transthoracic approach. We used standard parasternal short-axis view just below the tips of mitral valve leaflets for measurements of LV systolic and end-diastolic dimensions.<sup>[18]</sup> Echocardiographic signal was recorded simultaneously on videotape and then analyzed off-line by two independent and experienced investigators blinded to the condition of the trial subjects.

Arterial elastance index will be calculated through the following formula. Elastic properties of aorta are useful not only in representing basic mechanical behavior of the arterial system but also in predicting outcome.

$$\text{Arterial elastance index} = \text{SBP} \times 0.9/\text{LVSV}$$

In this formula, SBP stands for systolic blood pressure determined with a cuff sphygmomanometer of the left brachial artery under standardized conditions.<sup>[19]</sup> LVSV stands for left ventricular stroke volume (ml) and will be calculated through the following formula.

$$\text{LVSV (ml)} = \pi \times \left( \frac{\text{LVOT}}{2} \right)^2 \times \text{LVOT VTI}$$

In this formula, LVOT diameter stands for left ventricular outflow tract diameter (mm) and is measured in the parasternal long-axis view in systole. The LVOT velocity time integral provides information regarding blood velocity across the time period of systole and is in the units of cm. Typical values are close to 2 cm.<sup>[20]</sup>

For each measurement, three consecutive cardiac cycles were analyzed and an average was obtained. These parameters provide information about the structure of the aorta. Disruption of these parameters means a structural change in the arterial wall.

Data analysis was performed among the 67 patients using SPSS, version 24.0 (Statistical Procedures for Social Sciences, Chicago, Illinois, USA). All parameters are presented as mean  $\pm$  standard deviation. Spearman's rank test was used to assess the correlation between T2\*CMR, echocardiographic arterial elasticity criteria, and ferritin. Ferritin was measured using the enzyme-linked immunoassay device (Anthos 2020 model, Austria). Furthermore, to fit the proper line of variable, we used the Loess method. The results were considered statistically significant at  $P < 0.05$ .

## RESULTS

From September 2019 to June 2020, 67 patients (34 females and 33 males) were included in this study. The mean age was  $27.93 \pm 8.53$ , with a range of 13–61 years. The mean value of Hb and serum ferritin was  $9.80 \pm 1.12$  (g/dL) and  $1772.28 \pm 1801$  (ng/ml), respectively. The demographic data, biochemistry, and hematologic profile of patients are summarized in Table 1. The mean relaxation time of heart was  $25.45 \pm 11.28$  mseconds (msec). In the present study, the relaxation time of cardiac MRI was respectively  $>20$  msec in 42 (71.2%) patients, 25 patients (37.3%) had myocardial iron overload. T2\*CMR ranges are summarized in Table 2.

As depicted in Figures 1 and 2, in the present study, there was no significant correlation between serum ferritin, Hb, and the reported iron level in T2\*CMR ( $P = 0.158$ ,  $r = 0.201$ , and  $P = 0.739$ ,  $r = 0.042$ ), respectively. Furthermore, from the data in Figure 3, it is apparent that there was a positive

correlation between T2\*CMR and arterial elastance index ( $P = 0.035$ ,  $r = 0.258$ ), according to the Spearman test.

## DISCUSSION

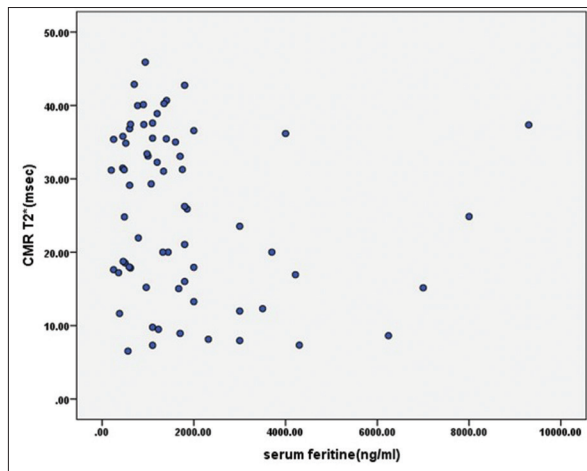
The aim of the present study was to determine the relationship between T2\*CMR and echocardiographic arterial elasticity criteria in patients with major thalassemia. We found that T2\*CMR was not correlated with the serum ferritin and Hb. In addition, the most striking result to emerge from the data is that T2\*CMR was correlated with arterial elastance index from echocardiography. The main limitations of the current study were disappointment to conduct echocardiography for all the patients owing to imprecise measurement of the arterial elastance index, and two patients were not able to measure the arterial elastance index due to poor echo windows; in addition, echocardiograms were not performed at the time of the CMR studies, but this passed time enough to statistically not affect the results of the measurements.

Numerous studies have described that cardiac hemosiderosis takes place in 70%–100% of thalassemia major cases.<sup>[2,3]</sup> Our results showed that 71.2% of all patients had cardiac iron

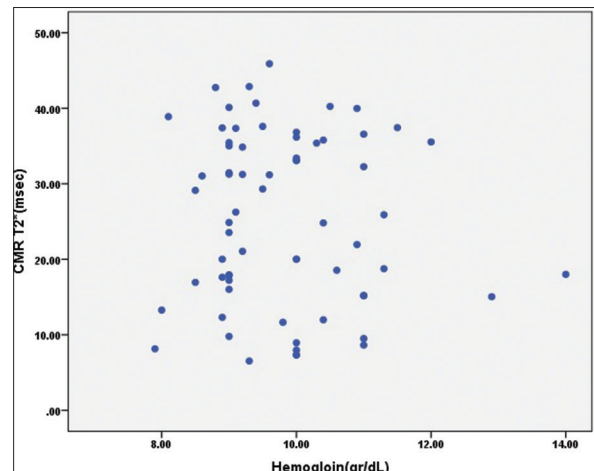
**Table 1: Demographic data, biochemistry, and hematologic profile**

Patient characteristics	Median or cases
Age (years)	27.93 $\pm$ 8.53
Sex (male/female)	33/34
Weight (kg)	57.02 $\pm$ 10.32
Height (cm)	161.37 $\pm$ 9.49
Systolic BP (mmHg)	106.67 $\pm$ 12.30
Diastolic BP (mmHg)	66.71 $\pm$ 10.35
Hemoglobin (g/dL)	9.80 $\pm$ 1.12
Serum ferritin (pmol/l)	1772.28 $\pm$ 1801.6

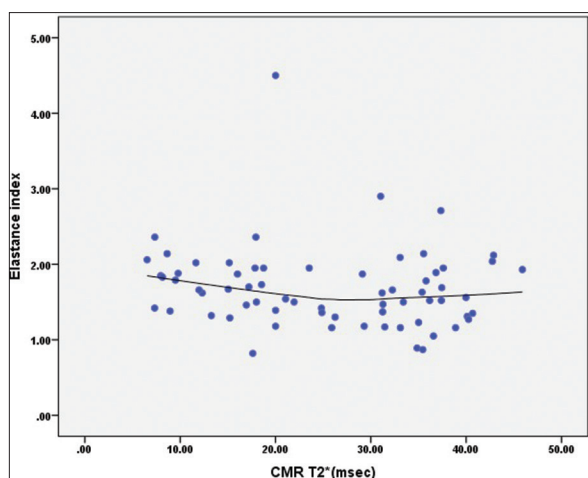
\*Data are expressed as absolute values or mean $\pm$ SD. SD=Standard deviation; BP=Blood pressure



**Figure 1:** Correlation between serum ferritin level and T2\*CMR ( $P = 0.158$ ,  $r = 0.201$ ). T2\*CMR = T2\* cardiovascular magnetic resonance



**Figure 2:** Correlation between hemoglobin level and T2\*CMR ( $P = 0.739$ ,  $r = 0.042$ ). T2\*CMR = T2\* cardiovascular magnetic resonance



**Figure 3:** Correlation between T2\*CMR and arterial elastance index ( $P = 0.035$ ,  $r = 0.258$ ), according to the Loess method to fit the proper line of variable. T2\*CMR = T2\* cardiovascular magnetic resonance

**Table 2: Geometric mean baseline myocardial T2\*±standard deviation, ms**

T2*CMR range	Number of patients	Percent	Mean±SD
>20 ms	42	62.7	32.8±6.78
14-20 ms	12	12	17.02±1.34
10-13.99 ms	4	4	12.30±0.69
<9.99 ms	9	13.4	8.23±1.07
Total	67	100	

\*Data are expressed as absolute values and percentages, or mean±SD. SD=Standard deviation; CMR=Cardiovascular magnetic resonance

overload which is in agreement with similar studies, such as the study by Azarkeivan *et al.*<sup>[17]</sup>

In the current study, there was no significant correlation between serum ferritin and the reported iron level in heart MRI T2\*. Although, like the current study, T2\*CMR has not been associated with ferritin level in several occasions. On the other hand, some authors have characterized a negative correlation between ferritin and T2\* values.<sup>[21-23]</sup> However, there is no denying that an increase in serum ferritin of patients with thalassemia major with a T2\*CMR <20 ms can be considered as a predictor of increased tissue iron overload.

Furthermore, another important aspect of our study was a positive correlation between T2\*CMR and arterial elastance index from echocardiography ( $P = 0.035$ ,  $r = 0.258$ ). Similar to our finding, many studies have suggested changes in vascular endothelial function and arterial elastance in patients with beta-thalassemia detects early myocardial dysfunction related to myocardial iron overload.<sup>[2,24,25]</sup> On the other hand, one of the causes of arterial stiffness in these patients is iron overload. The existence of a relationship between T2\*CMR and arterial elastance in this study in line with other studies confirms this issue. Vogel *et al.* showed that the incidence of wall

motion abnormalities was significantly higher ( $P < 0.04$ ) in patients with myocardial iron overload.<sup>[26]</sup> In accordance with our study aims, Aypar *et al.* also found the efficacy of correlation between T2\* cardiovascular magnetic resonance and tissue Doppler imaging parameter in predicting myocardial iron load in patients with beta-thalassemia major.<sup>[27]</sup>

According to the findings of the current study, in a retrospective analysis of 319 patients with beta-thalassemia major, Alpendurada *et al.* reported that when myocardial T2\* was <20 ms, there was a significant decline in echocardiogram factors related to elastance, such as RV function with worsening cardiac iron loading.<sup>[28]</sup>

Totally, according to the obtained results, it may be concluded that although ferritin may be still a useful parameter for assessment of iron loading of the heart, could not accurately predict cardiac iron overload, as measured by T2\*CMR in major beta-thalassemia patients without cardiac symptoms. The results will illustrate the diagnostic value of T2\*CMR in the diagnosis of cardiac iron overload in thalassemia patients.

It can also be concluded from the results of the present study that arterial elastance index from echocardiography and the T2\*CMR by affirming each other for positive correlation may be the most valuable indicator of myocardial iron overload in patients with major thalassemia. Further studies with larger sample sizes and more power are required to attain more definite results.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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