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Cardiac T2* magnetic resonance analysis of membranous interventricular septum in assessment of cardiac iron overload in pediatric thalassemia patients: A pilot study

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Abstract

Background: Cardiac iron deposition in transfusion-dependent thalassemia patients is patchy in distribution. **Purpose:** The purpose of this study is to assess the correlation between T2* matrices of membranous interventricular septum (MIVS) and T2* values of muscular interventricular septum (IVS) on magnetic resonance imaging (MRI) and to evaluate the relationship of myocardial T2* at these two locations with MRI-estimated liver iron concentrations (LIC) and electrocardiographic (ECG) parameters. **Material and Methods:** MRI of heart and liver was performed in 16 consecutive pediatric patients of transfusion-dependent thalassemia major to calculate liver iron concentration and T2* time of membranous and muscular IVS. ECG parameters of these patients were charted and correlated with MRI parameters. **Results:** No significant correlation between T2* values of muscular IVS and MIVS was observed. Mean T2* of MIVS (9.8 ms) was significantly lower than that of muscular IVS (26.9 ms). T2* of MIVS correlated strongly with LIC where as a weak correlation was observed between T2* of IVS and LIC. Significantly higher mean QTc (corrected QT interval) value (439.86 ms) was seen in patients with T2* IVS <20 ms. **Conclusion:** Addition of T2* analysis of MIVS to the existing MRI protocol, consisting of muscular IVS analysis, may offer a more sensitive estimation of cardiac iron overload.

Key words: Cardiac; heart; magnetic resonance imaging; pediatrics; thalassemia

Introduction

Thalassemia is one of the most common genetic diseases in the world with highest observed burden in Asia, especially in India and Middle Eastern countries.[1,2] Severity of this disease can range from mild to fatal. Majority of the disease-related mortalities are due to cardiomyopathy (71%) resulting from iron deposition in the organ because of frequent blood transfusion.[3,4] The incidence of

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iron-overload cardiac disease in patients with thalassemia is estimated to be approximately 11.4–15.1%.[5] Management of this complication begins by assessment of cardiac iron overload and administration of iron chelating agents in requisite amounts.

Magnetic resonance imaging (MRI) offers an opportunity for noninvasive assessment of systemic iron overload by estimating end-organ iron deposition utilizing a gradient recalled echo T2-weighted sequence with incremental echo times (TEs), referred to as T2* relaxometry or T2* mapping. The region of interest (ROI) measurement on a T2* map gives an estimate of the "relaxation time" (T2*). Alteration in T2* measurement has been considered as a sensitive marker in detection of cardiac iron overload (and thus subclinical cardiomyopathy) even with acceptable serum ferritin and MRI-estimated liver iron concentrations (LIC).[6-8] Recent studies have revealed promising early evidence of improved survival on initiation of ferrochelation, following isolated cardiac iron overload detected by T2* measurements.[5]

Most of the previous studies have used a single location (mid anterior septum) to draw ROI and subsequently generate a T2* value. However, measurement of iron overload of a single myocardial segment, assessed on a single imaging plane, cannot truly represent the complete "global" myocardial burden as the myocardial iron deposition has been shown to be patchy in distribution. Authors of this study visually noticed that, on generating a T2* relaxation map of the myocardium, interventricular septum (IVS) at the membranous portion produced lesser T2* values than rest of the cardiac segments in few patients prior to this study. The aim of this study was to assess whether the T2* matrices of membranous interventricular septum (MIVS) show any correlation with the traditionally obtained muscular interventricular septum (IVS). We also evaluated relationship of the myocardial T2 relaxation time at these two locations with electrocardiographic (ECG) and MRI-estimated LIC parameters.

Material and Methods

Patients

This was a prospective observational study and was carried out at a tertiary level, university-based teaching hospital over a period of 1 year after approval from institutional review board. A total of 24 patients with diagnosis of β-TM were referred from pediatric hemato-oncology division of the institute for MRI assessment of cardiac and liver iron overload. Out of 24, only 16 patients underwent MRI, predominantly due to financial reasons. All the patients had been regularly transfused and were on iron chelation therapy. All the 16 consecutive cases done within a year were included in this analysis and none was excluded. Informed consent was obtained from parents of all the patients.

Data were collected from clinical files such as duration and frequency of blood transfusion as well as chelation therapy, type of chelation therapy, laboratory parameters such as serum ferritin, and liver function test. Echocardiography and ECG were performed in all the patients on the day of MRI scan. Moreover, MRI and ECG were performed a day before the next transfusion date and at least 3 weeks after the previous blood transfusion.

Protocol for MRI and image analysis

MRI was done on a 1.5-T (Siemens Avanto, Erlangen, Germany) system with an actively shielded whole body superconducting magnet. Imaging was done using an 8 channel Torso phased-array body coil.

Liver iron concentration (LIC) was measured by the most widely recognized method developed by Gandon *et al.*[9] A set of five breath-hold Gradient Echo sequence with fixed TR and different TE and flip angles prescribed for 1.5-T scanner was used and a free, online worksheet provided by University of Rennes was employed to obtain LIC.[10]

Cardiac imaging was performed using body matrix coil and prospective ECG triggering. A short breath-hold coaching session was performed for each patient prior to the scan. Quantitative T2* relaxation maps (MapIt, Siemens Healthcare, Erlangen, Germany) were obtained in a single 10-mm mid-ventricular short-axis view and four-chambered view using a single breath-hold gradient echo sequence with eight TEs (2.4-16 ms). The field of view varied between 300 and 320 mm. The TR between each radiofrequency was 20 ms. The matrix was 128 × 192. Acquisition time per slice was 8–12 s. The addition of a four-chambered sequence added less than 1 min to the overall scan time. Adequate breath-hold was achieved in all the patients in our study.

MRI of all the patients was analyzed by two radiologists in tandem (IK, AV) with 6 and 14 years of experience, respectively. T2* value of muscular IVS was obtained using a full thickness ROI in short-axis view [Figure 1]. T2* value of MIVS was obtained in four-chmbered view, drawing ROI near atrioventricular junction on the IVS [Figure 2].

ECG analysis

A surface, 12-lead ECG of each patient was recorded with 25 mm/s paper speed at 10 mm/mV amplitude. ECGs were first evaluated by a pediatrician (PA) who was blinded to MRI findings, were scanned at high resolution, and were sent to a cardiologist (SK) who was blinded to both MRI and clinical diagnosis. Final consensus was made by both these investigators along with a senior pediatrician (VG) in tandem, and ECG findings were charted in terms of presence/absence of arrhythmia, heart rate, PR interval, QRS duration, QT, QTc, QTp (predicted QT interval), Tp Te (T peak T end), and T axis.

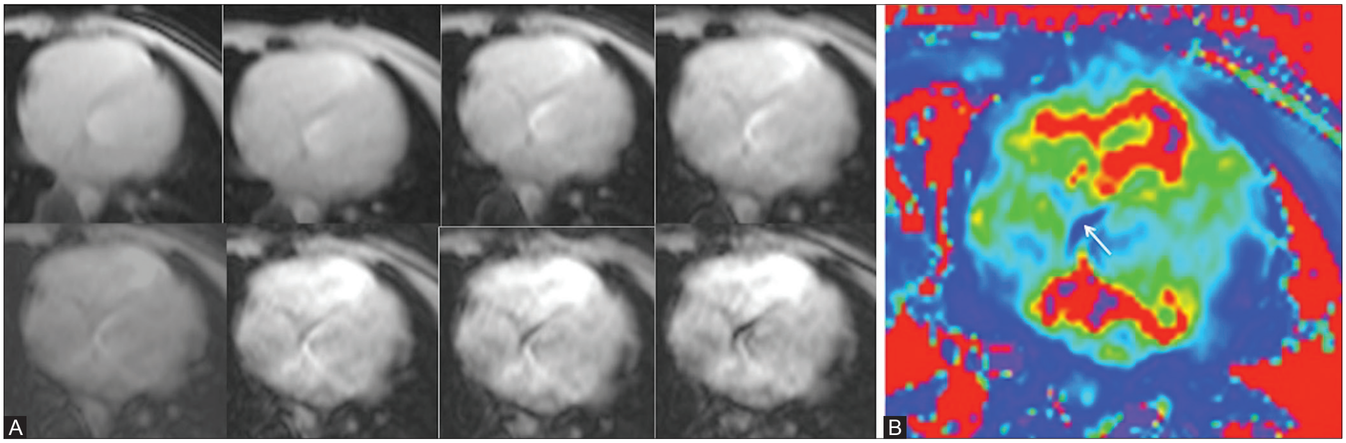

Figure 1 (A and B): Four-chambered view using gradient echo sequence with eight echo times (2.4.6–16 ms) (A) and quantitative T2* relaxation map (B) at membranous interventricular septum

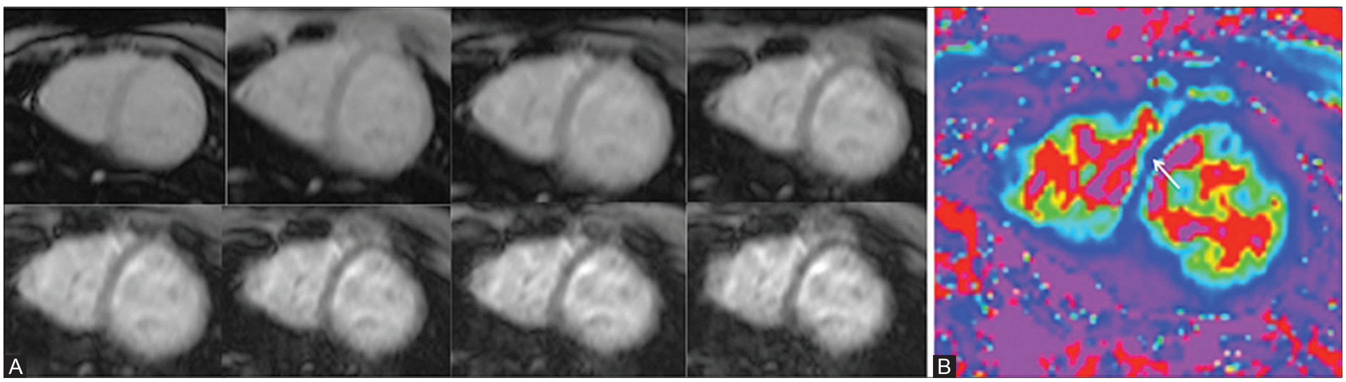

Figure 2 (A and B): Mid-ventricular short-axis view using gradient echo sequence with eight echo times (2.4.6–16 ms) (A) and quantitative T2* relaxation map at muscular interventricular septum (B)

Statistical methods

Statistical analysis was performed using SPSS software (IBM Corp 2013. Version 22.0, Armonk, NY). Student's *t*-test was applied to determine difference of two groups for the parametric variables. A Pearson correlation test was used to assess correlation between two parameters. *P* value of 0.05 or less was considered significant.

Results

A total of 16 children were included in this study with mean age of 10.9 years (range 7–14 years). Of these patients, 14 cases were male and 2 were female. All these 16 cases were on deferasirox therapy. A summary of patients' clinical, laboratory, ECG, echocardiographic, and MRI data is charted in Table 1.

Table 1: Summary of patients clinical, laboratory, ECG, echocardiographic, and MRI data

	Mean	Range
Age (years)	10.9	7-14
S. Ferritin (ng/ml)	3763	650-8915
Left ventricular ejection fraction	70.2	65-77
Total bilirubin (mg/dl)	2.28	0.9-5.1
Indir bilirubin (mg/dl)	1.83	0.6-4.4
AST (U/l)	36.33	19-73
ALT (U/l)	45.33	26-65
HR (bpm)	97.6	69-124
PR interval (ms)	130	107-170
QRS duration (ms)	76.2	65-89
QT (ms)	336.9375	297-408
QTc (ms)	432.9375	397-480
QTp (ms)	248	200-308
T2* (IVS)	26.9875	4.6-51
T2* (MIVS)	9.8125	4.6-22.4
LIC (MRI) (μmol/g)	297.5	190-350

There was no significant correlation between T2* values of muscular IVS and MIVS [Figure 3]. Mean values of T2* of MIVS (9.8 ms) were significantly ($P = 0.001$) lower than that for muscular IVS (26.9 ms).

There was no significant correlation between MRI estimated LIC, T2* values of muscular IVS, T2* value of MIVS, and serum ferritin with any of the ECG parameters. Moreover, no significant correlation was observed between serum ferritin and LIC, and T2* IVS and T2* MIVS. There was a weak linear inverse correlation between LIC and T2* IVS ($r = -0.513$; $P = 0.042$) [Figure 4]. Better, inverse linear correlation was observed between LIC and T2* MIVS ($r = -0.615$; $P = 0.015$), which further improved on addition of quadratic effect [Figure 5]. The quadratic effect (one bend in the regression line) was tested using a hierarchical multiple regression model which showed that addition of a nonlinear quadratic component resulted in significant incremental predictive capability of this model ($P = 0.042$).

Only one of the patients in the present study had arrhythmia (premature atrial contraction) who had T2* IVS and T2* MIVS values of 6.5 and 4.6 ms, respectively. The cases were divided into those with cardiac iron overload and those without, based on T2* values at muscular IVS. Mean values of various ECG parameters were compared between the two groups using independent Student's *t*-test and the results are summarized in Table 2. Mean QTc interval (439.86 ms) was significantly higher in the group with T2* IVS <20 ms. Rest of the ECG parameters were not significantly different amongst the two groups.

Since none of the previous studies have analyzed T2* value of MIVS, we could not ascertain the value of cutoff for this region to predict cardiac iron overload, and median value of 8.5 ms was chosen to compare the ECG parameters between two groups [Table 2]. Mean QTc was higher (437.25 ms) in the group with T2* MIVS <8.5 ms, although the difference with group T2* MIVS ≥8.5 ms was not statistically significant.

Discussion

The need to quantify cardiac iron burden carries significant therapeutic and prognostic significance in thalassemia patients. Tissue diagnosis was previously considered as gold standard in this regard; however, myocardial biopsy is a risky procedure and due to patchy distribution of iron deposition, endomyocardial biopsies can miss the area of iron deposition and can lead to false-negative results.[11-13] In the modern-day noninvasive cardiology, cardiac MRI is considered gold-standard technique for quantification of cardiac iron overload. Studies have shown that inclusion

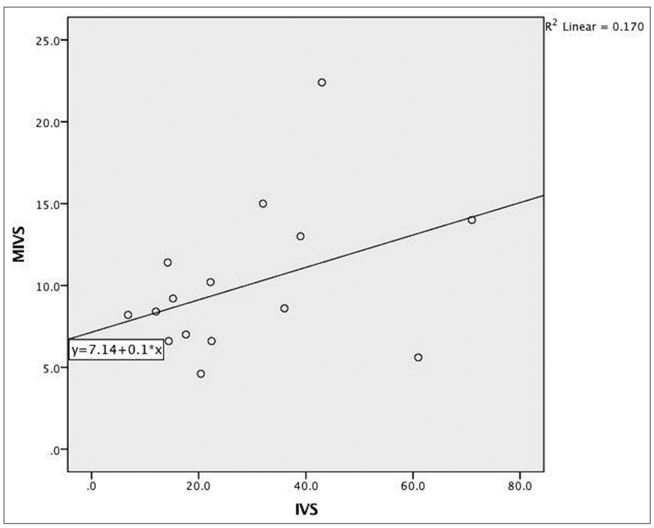

Figure 3: Scatter plot showing relation between T2* values of membranous (MIVS) and muscular (IVS) portions of interventricular septum. No significant correlation was seen between the two

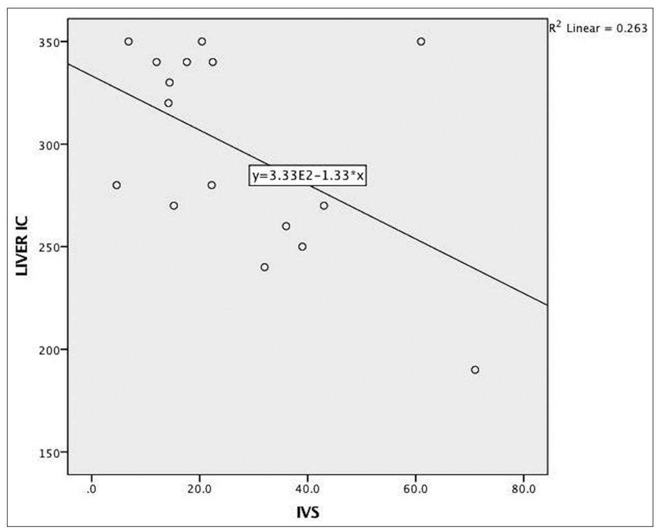

Figure 4: Scatter plot showing relation between MRI-derived liver iron concentration (LIC) and T2* time obtained at muscular portion of interventricular septum (T2* IVS). A weak inverse linear correlation is observed

Table 2: Electrocardiographic findings of patients with β-TM according to cardiac T2* values of muscular and membranous interventricular septum

	Muscular interventricular septum			Membranous interventricular septum		
	T2* MRI ≥20 n=9	T2* MRI <20 n=7	P	T2* MRI ≥8.5 n=8	T2* MRI <8.5 n=8	P
HR	96.75±15.6	97.17±14.4	0.36	93.5±10.7	100.3±17.7	0.38
PR (ms)	129.25±16.8	131.2±23.8	0.46	132.3±16.5	127.3±22.5	0.65
QRS (ms)	76.5±5.8	75.8±9.8	0.15	74.3±6.6	78.5±7.8	0.83
QT (ms)	336.11±20.5	338±28.7	0.16	340.63±13.0	333.25±30.5	0.036
QTc (ms)	427.56±14.5	439.86±28.1	0.05	428.63±17.6	437.25±25.1	0.21
QTp (ms)	253.33±28.1	241.14±26.9	0.698	252.5±27.9	243.5±28.2	0.55
T axis (degrees)	39.57±10.1	51.4±4.8	0.33	43.3±12.1	45.6±8.5	0.57

**P* value is test of significance

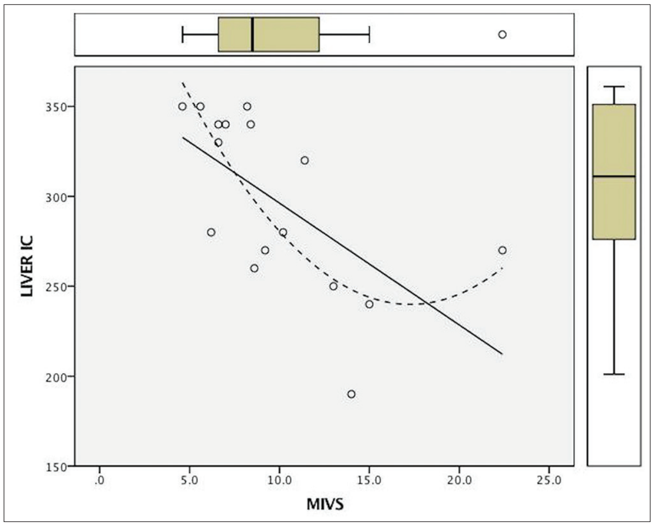

Figure 5: Scatter plot showing relation between MRI-derived liver iron concentration (LIC) and T2* time obtained at membranous portion of interventricular septum (T2* MIVS)

of cardiac MRI in management of thalassemia patients improves patient survival.[14] The advantages of cardiac MRI include its noninvasive nature, ability to detect preclinical iron deposition, and ensure complete iron removal with aggressive chelation therapy and quantitative monitoring of therapeutic outcome.[15]

Magnetic resonance evaluation of tissue iron deposition is done by assessment of T2* relaxation time. With increasing TE, all tissues become progressively darker and those with iron deposit darken more rapidly. T2* is the TE for a tissue to become twice as dark.[1] Normal T2* reference values at the level of muscular IVS range from 33.3 ± 7.8 to 52 ± 16 ms.[16,17] Anderson *et al.* first assessed T2* values of thalassemia patients and reported that there was a progressive decline in ventricular performance (ejection fraction) with decreasing T2* values, especially in patients with T2* <20 ms.[16]

Labile iron is magnetically silent, whereas ferritin is weakly detectable on MRI. T2* values measure tissue concentration of hemosiderin which is a breakdown product of ferritin. Since labile iron is in dynamic equilibrium with ferritin and hemosiderin, cardiac T2* can serve to act as a gauge for clinical iron toxicity.[15] Estimation of T2* value has been done by MRI in most of the studies by obtaining a cardiac-gated, single breath-hold, eight-echo sequence of a mid-ventricular short-axis slice. ROI drawn to calculate T2* value in most of the studies is limited to mid-anterior septum or mid-inferior septum. However, because of patchy distribution of iron deposition, calculation of T2* time of a single myocardial segment can underestimate or miss the overall myocardial burden. Magnetic resonance "sampling" of more areas is thus required for complete myocardial iron burden assessment. Unfortunately, T2* measurements of thin atrial septum and lateral myocardial wall are difficult to assess accurately as they are limited by partial volume effects. Various studies have shown that although atrial arrhythmias are more common in cardiac iron overload, iron deposition is greater in the ventricles.[18,19] Pepe *et al.* propose a "global T2* value" by averaging T2* value of all the American Heart Association cardiac segments after obtaining a scan at three parallel short-axis views (basal, medium, and apical) of the left ventricle.[20] However, calculation of T2* value of 16 segments of heart is a time-consuming process. Moreover, averaging the T2* value might normalize cardiac deposition limited to a small area and result into a false-negative result. In this study, we have included an eight-echo sequence of a four-chambered view in the imaging protocol and have drawn ROI over the MIVS. The results of this study show that MIVS might be a more sensitive location of early cardiac iron overload. Moreover, liver iron concentration was more significantly correlated with the T2* values of MIVS in this study, compared to muscular IVS. Furthermore, this study confirmed the patchy deposition of iron in the myocardial tissues as there was no correlation between T2* relaxation times of membranous and muscular iron.

Our study supports the fact that low value of serum ferritin does not preclude the risk of iron overload cardiomyopathy. We could not find a significant correlation between serum ferritin and MRI-estimated liver and cardiac iron (at both the locations). Various researchers have tried to find the relationship between serum ferritin with MRI-estimated liver and cardiac iron in patients with thalassemia major and the results have been highly inconsistent, ranging from mild to no correlation.[11,21-23]

We observed a weak correlation between LIC and T2* value of muscular IVS. T2* of MIVS better correlated with LIC which further improved on addition of nonlinear effect, that is, T2* value declined more rapidly as LIC increased. The ability of LIC in predicting cardiac iron load (cardiac T2*) has also been challenged in various MRI studies.[1,24] Noetzli *et al.* suggested that although there is no linear relation between LIC and cardiac T2* measurements made at the same time, a clear relation exists if a third variable, that is, time, is included in the analysis by longitudinal monitoring of liver and heart iron. They proposed that there is a time lag between loading and unloading of iron in heart with respect to the liver in response to chelation therapy.[25]

Excessive myocardial iron can hinder the electrical function of heart and consequently lead to various arrhythmias. Various arrhythmias that have been reported to occur in cardiac iron overload include atrioventricular block, conduction defects, brady and tachyarrhythmias, and QT prolongation.[26,27] These ECG abnormalities have been attributed to various mechanisms such as increased intracellular iron, production of free radicals, selective dysfunction of Na channels, apoptosis, and fibrosis.[28] Various investigators have evaluated the ability of cardiac T2* value in prediction of these ECG abnormalities with variable results. Kayrak *et al.*, in his study of 22 patients, could not demonstrate any significant difference in transmyocardial repolarization parameters in patients with T2* >20 ms and those with T2* <20 ms.[28] Magri *et al.* demonstrated significant correlation between T2* value and QT variability index but not QTc.[29] A study by Datterich *et al.* showed that cardiac iron overload was associated with statistically significant lower heart rates, QTc prolongation, and leftward shift of the P- and T-wave axis. They also observed high rate of ECG abnormalities in patients with T2* <20 ms, such as nonspecific ST–T wave changes, sinus bradycardia, symmetric T-wave inversions, and left ventricular hypertrophy.[30] In the present study, although there was no correlation between T2* values of muscular and MIVS, there was a statistically significant difference in QTc values of patients with cardiac T2* <20 ms and T2* ≥20 ms with QTc prolongation in iron overload category.

We realize that there are several limitations of this study. First was the choice of T2* threshold to define cardiac iron overload. A T2* value of 20 ms for muscular IVS is imprecise and some patients with 20–25 ms also have mild cardiac iron overload.[25,31] Moreover, due to lack of literature, we could not assign a T2* threshold value of MIVS to demarcate the onset of iron accumulation. A second major limitation was a small sample size. The statistical analysis provided in our study should be interpreted very cautiously as it may be an over- or underestimation owing to small sample size. Third limitation of this study was the lack of control group because of financial limitations. Another limitation of our study was that the interobserver variability and reproducibility of the data could not be assessed as all of the patients were scanned only once using a single scanner and were analyzed by two radiologists in tandem. Lastly, we did not perform a follow-up ECG evaluation of the patients, which can potentially result into underestimation of ECG abnormalities as the literature shows that there is a time lag in loading of cardiac iron.

Conclusion

In conclusion, the present study shows that MIVS may be a more sensitive location for assessment of iron overload on MRI, in comparison with muscular IVS. Second, we also show that T2* value of MIVS better correlates with the liver iron concentration in comparison with T2* of muscular IVS. Third, in assessment of predictive capabilities for arrhythmias, T2* values of both these locations might have different electrophysiological implications. It would still be required to see whether the results of this study are reproducible in another and a larger cohort.

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Conflicts of interest

There are no conflicts of interest.

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