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ORIGINAL PAPER

Comparison of global strain values of myocardium in beta-thalassemia major patients with iron load using specific feature tracking in cardiac magnetic resonance imaging

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Abstract

Thalassemia defined a spectrum of diseases characterized by reduced or absent production of one of the globin chains of hemoglobin. High iron deposition in the myocardium may cause functional impairment even before any changes in left ventricular (LV) ejection fraction. These impairments may appear as changes in strain values. Early detection of myocardial dysfunction is essential for improving survival and preventing further complications. Therefore, this study aims to evaluate the cardiac strain patterns by Feature Tracking -Cardiac Magnetic Resonance Imaging (FT-CMR) method and their correlation with T2* values as a new parameter in determining myocardial iron overload (MIO). In this retrospective investigation, ninety-one patients with B-thalassemia major included from May 2016 to July 2019. Twenty-three healthy subjects, also incorporated as a control group. CMR used to evaluate ventricular volumes, LVEF, and the amount of myocardial T2*. Moreover, Global Longitudinal Strain (GLS), Global Circumferential Strain (GCS), and Global Radial Strain (GRS) were measured and analyzed in both rights and left ventricles. Correlations of cardiac T2* with GLS, GCS, and GRS were evaluated. The optimal cutoff value of GLS for prediction of cardiac T2* < 20 ms (as an indicator of inadequate chelation) calculated as well. There were significant correlations between cardiac T2* with LV GLS, LV GCS, and right ventricular GLS ($p < 0.05$ for each one). Moreover, a significant difference detected between the group of TM − MIO and TM + MIO and control group in terms of GLS ($p < 0.001$). The optimal cutoff value of GLS for prediction of cardiac T2* < 20 ms was at − 16.5% with sensitivity and specificity of 73% and 63%, respectively. Our study demonstrates that strain values measured by FT and myocardial T2* values are correlated. FT-CMR can be considered as an efficient tool for early detection of iron deposition and its effects on cardiac tissue so that proper and timely modification could have applied to chelation therapy.

Keywords Thalassemia · Magnetic resonance imaging · T2* · Strain

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Introduction

Thalassemia defined a spectrum of diseases characterized by reduced or absent production of one of the globin chains of hemoglobin. Mostly beta-thalassemia is due to impaired production of beta-globin chains, which leads to a relative excess of alpha-globin chains [1–8]. Excess alpha-globin chains are unstable, incapable of forming soluble tetramers on their own, and precipitate within the cell, leading to a variety of clinical manifestations [9–14]. TM patients are anemic, which starts during the first year of life, and they will need a profound and life-long transfusion to manage their anemia [15–19].

Development of acute decompensated heart failure is the major cause of death in beta-thalassemia major [20–23]. It

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is inevitable for patients in need of life-long transfusion to develop Iron overload. Each unit of transfused red cells has 200 to 250 mg of elemental iron enters into the body. After the body abounds with this excess iron, iron accumulated and would be deposited in other viscera, usually the liver, heart, and endocrine organs [24–26]. When iron stores overwhelm the sequestration ability of reticuloendothelial cells, developing parenchymal iron overload would cause end-organ dysfunctions, especially heart, liver, and endocrine organs and finally death [27–29].

Iron chelation therapy initiated after approximately 20 to 25 units of red cells transfusion, at a time when the serum ferritin level is > 1000 ng/mL (mcg/L) and liver iron concentration is > 3 mg of iron per gram of dry weight as measured either by liver biopsy or noninvasive MRI imaging [30].

CMR is considered the "gold standard" technique for the measurement of left and right ventricular indices. Myocardial iron deposition can be quantified reproducibly with myocardial T2*, a relaxation parameter that arises on CMR principally from the local magnetic field in homogeneities that are increased with iron deposition [26, 31, 32]. Studies implicate that noticeable percentages of patients have cardiac T* < 20, which indicates inadequate chelation [33].

FT-CMR is a highly accurate tool to detect myocardial dysfunction and myocardial fiber deformation by measuring the strain values especially at the early stages of myocardial disease.

For these reasons, our study aimed to evaluate utilizing of FT-CMR method in patients with Beta-thalassemia to measure ventricular strain and investigate its correlation to CMR T2* values and its predictive value in better assessment of myocardial iron overload. FT-CMR can detect and follow over time myocardial boundaries leading to a more automatized quantification of strain parameters.

Material and methods

Study population

This retrospective investigation was conducted in Shahid Rajaei Heart Center of Iran University of Medical Sciences from May 2016 to July 2019. A total of 91 patients with a diagnosis of thalassemia major included in our study, all of them receive long-term blood transfusions and iron chelators. In all patients, myocardial iron load measured by obtaining T2* values by CMR imaging. All incorporated cases were in normal sinus rhythm. Furthermore, we assessed 23 normal subjects without any previously diagnosed cardiac conditions that may affect the myocardial function. The exclusion criteria were moderate to severe valvulopathy, presence of atrial fibrillation or flutter, and history of ischemic heart disease. All patients gave written informed consent.

CMR study performed using a 1.5- Tesla scanner (Siemens Avanto, Erlangen, Germany) with a cardiac-phased array receiver surface coil and ECG gating. Vertical, horizontal long-axis slices, and a stack of contiguous cine short-axis slices from the atrioventricular ring to the apex were acquired using a steady-state free precession pulse sequence (slice thickness = 8 mm, no interslice gap for long-axis and short-axis images; repetition time/echo time = 3−4/1.2 ms, FOV = 300, imaging matrix 156 × 192, voxel size 1.9*1.6*7 mm, depending on heart rate the temporal resolution or "reported" TR is about 31.5 ms, Siemens Avanto. Germany). T2* images acquired using gradient-echo sequence with a time repetition of 120 miliseconds (ms) and with obtaining T2* value with different echo times. Measurement of signal intensity done by putting a region of interest in the interventricular septum. TM patient categorized as MIO if T2* < 20 ms and no iron overload with T2* > 20 ms. C categorized as MIO if T2* < 20 ms and no iron overload with.

FT-CMR method and global strain analysis

Offline analysis was performed, by FT software CVI 42 system. Automatic border tracking commences after manually defining endocardial and epicardial borders at the end-diastolic image.

RV and LV strain data were collected from cine images in the 4-chamber plane to identify the longitudinal strain and the short-axis plane for circumferential and radial strain. Optimal brightness adjusted for better contrast and discrimination of endocardium from the blood pool. Outline of the endocardial borders then manually corrected, afterward, contours propagated and features detected automatically by the software throughout the cardiac cycle.

Myocardial strain described as the percentage of changes in dimensions of determined sites of myocardium from end-diastole to the one measured in end-systole. Longitudinal strain represents the longitudinal shortening of the cardiac muscle, from the base to the apex of the heart. Circumferential strain is an expression of cardiomyocytes shortening along the LV circular perimeter and calculated in the short-axis view. Radial strain represents myocardial deformation toward the center of the ventricular cavity and measure LV wall thickening during systole, hence depicted by a positive value.

Statistical analysis

SPSS software version 21.0 used for statistical analysis. Categorical variables expressed as frequency and percentage, while continuous variables with normal distribution

Table 1 Baseline characteristics

	Case		Control	
	Mean	Std. Deviation	Mean	Std. Deviation
Age (years)	24.6	6.2	23.7	5.9
LVEF (%)	52.0	12.4	60.0	3.6
LVEDVI (ml/m^2)	102.8	82.8	142.3	10.1
LVESVI (ml/m^2)	44.8	22.4	46.5	4.2
LVSV (ml)	70.3	25.4	51.9	3.4
RVEF (%)	48.4	11.4	50.5	3.6
RVEDVI (ml/m^2)	92.5	28.9	144.0	109
RVESVI (ml/m^2)	49.3	24.3	50.0	4.1
RVSV (ml)	63.2	24.7	50.9	3.24
M/F	1.1		1.28	

expressed as mean ± standard deviation (SD). Non-normal variables (T2* values) described with median and 25th and 75th percentiles. Differences between means of numerical variables assessed with Student's t-test. The Spearman's rank correlation applied to correlate myocardial deformation with T2* values. Receiver operating characteristic (ROC) curve utilized to define the sensitivity and specificity of the GLS in detecting MIO and to establish the best-cut off, the value of the tests, performed as two-sided at a significance level p = 0.05.

Results

In the represented investigation, the mean age of TM patients was 24.66 ± 6.23 years, and 57.1% of patients were male. (Table 1).

T2* median value of our TM group was 18 ms (25th quartile 9.5 ms; 75th quartile 34.9 ms). Mean T2* value for control group was 53.3 ± 3.69 ms.

62 subjects (70%) showed significant MIO (T2* < 20 ms). Mean LVEF derived by CMR was 53.80 ± 11.57%.

There was a significant difference between LV GLS of TM + MIO group and control group, as well as patients with TM – MIO and control group. (p < 0.001) (Tables 2, 3).

The analysis revealed that a significant correlation exists between LV GCS, LV GLS, RV GLS, and T2* values. GLS was significantly lower in patients with TM + MIO (p < 0.001). The only significant difference between patients with TM – MIO and control group have been revealed in RV GLS values (P = 0.004).

Analysis of the ROC curve (Fig. 1) showed an area under the curve of 0.77 (95% CI 0.678–0.861) with the best GLS cut-off: – 16.5% (73% sensitivity and 63% specificity) for the detection of significant MIO. Furthermore, it displayed areas under the curve of less than 0.7 for LV GCS and RV GLS, therefore none of these parameters were suitable for the detection of significant MIO. For RV GCS, there was not a significant predictive value (p = 0.075). Correlation plot-showing the coefficient of determination (R square = 0.023) (Fig. 2).

Table 2 Mean myocardial strain values in right ventricle and left ventricle

	Case group with MIO (n = 66)	Control group (n = 23)	P value
Mean LV global longitudinal strain (%)	– 12.90 ± 4.18	– 18.19 ± 2.07	0.005
Mean LV global radial strain (%)	36.7 ± 18.82	42.39 ± 7.14	0.003
Mean LV global circumferential strain (%)	– 13.57 ± 10.26	– 19.2 ± 2.01	0.015
Mean RV global longitudinal strain (%)	– 16.41 ± 14.73	– 23.34 ± 4.40	0.098
Mean RV global radial strain (%)	17.54 ± 11.53	21 ± 7.9	0.800
Mean RV global circumferential strain (%)	– 9.69 ± 5.41	– 12.7 ± 4.3	0.594

Table 3 Mean myocardial strain values in right ventricle and left ventricle

	Case group without MIO (n = 25)	Control group (n = 23)	P value
Mean LV global longitudinal strain (%)	– 13.81 ± 3.25	– 18.19 ± 2.07	0.093
Mean LV global radial strain (%)	40.50 ± 8.93	42.39 ± 7.14	0.807
Mean LV global circumferential strain (%)	– 17.44 ± 2.38	– 19.2 ± 2.01	0.417
Mean RV global longitudinal strain (%)	– 19.06 ± 8.09	– 23.34 ± 4.40	0.004
Mean RV global radial strain (%)	21.99 ± 11.02	21 ± 7.9	0.191
Mean RV global circumferential strain (%)	– 10.73 ± 3.61	– 12.7 ± 4.3	0.684

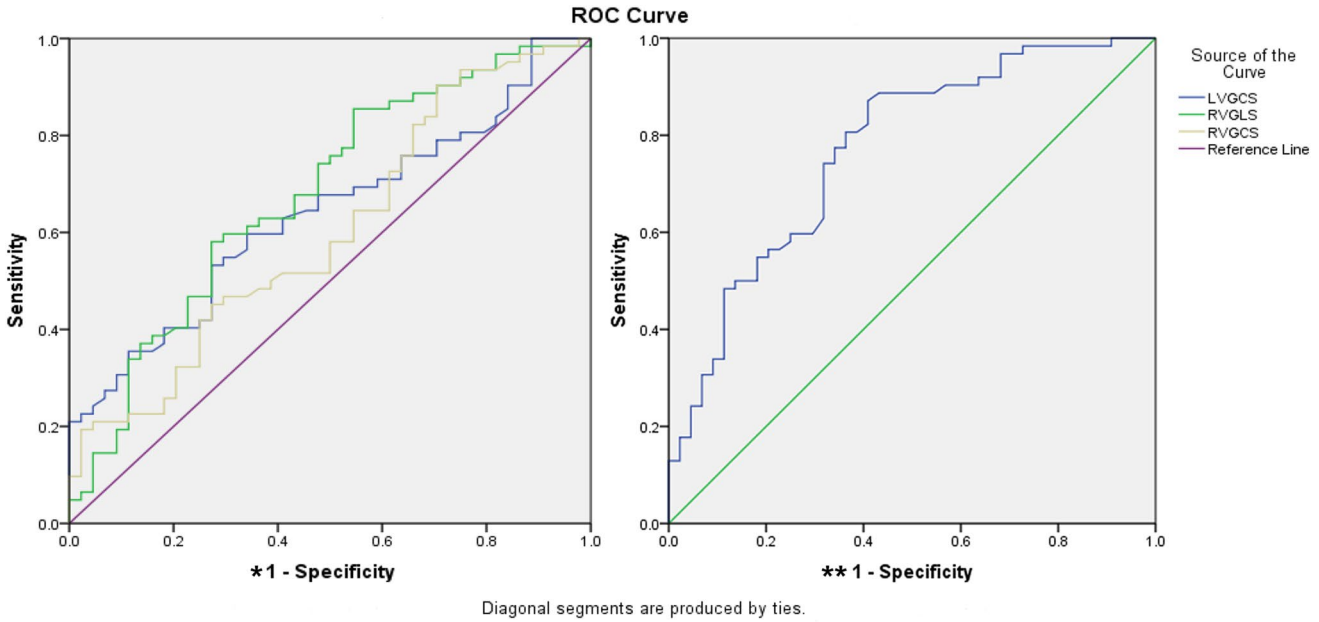

Fig. 1 ROC curve showing an area under the curve of 0.63 with LV GCS (p = 0.016), an area under the curve of 0.67 with RV GLS (p = 0.002), and an area under the curve of 0.60 for RV GCS (p = 0.75). ROC curve showing an area under the curve of 0.77 (95% CI 0.678–0.861) with a best LV GLS cut-off of − 16.5%

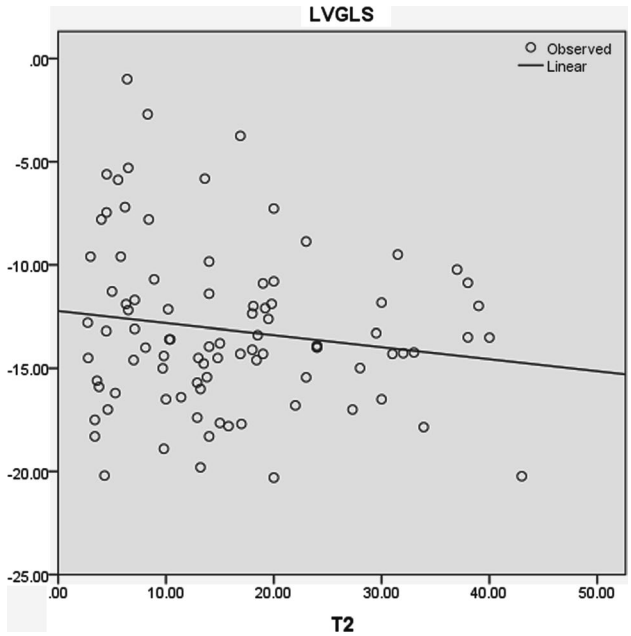

Fig. 2 Regression line drawn on scatter diagram relating LV GLS and T2* value

Discussion

Beta thalassemia major represents a disorder with either no effective production or severely decreased production of beta-globin, needs chronic blood transfusion. Essentially the most important part of therapy for beta-thalassemia major is the management of excess iron load by supportive measures [24, 25]. T2* CMR has emerged to predict an increased risk of heart failure and to be a valuable method for monitoring the efficacy of iron chelation therapy in patients with beta-thalassemia.

High iron deposition in myocardium may cause functional impairment even before LV ejection fraction decreases. Once initiated, an iron chelation program must be rigorously followed and frequently monitored using MRI T2* technique [17, 18] to prevent myocardial iron overload and subsequent myocardial dysfunction and to stabilize or improve endocrine dysfunction [30–32].

With repeated blood transfusion, changes happen in myocardial deformations and, therefore variations occur in strain values. FT-CMR is a highly accurate tool to detect myocardial dysfunction and myocardial fiber deformation by measuring the strain values especially at the early stages of myocardial disease [34, 35]. FT technique assesments in both inter and intraobserver analysis, revealed excellent reproducibility of strain measurements [36]. Furthermore, there is no need to acquire supplementary imaging series in addition to routine CMR examination. Some previous research has done to find the relationship between strain value using speckle tracking echocardiography (STE) compare with the CMR T2* method [37–40]. But there is no study to evaluate the role of FT-CMR to predict the T2* value in TM patients.

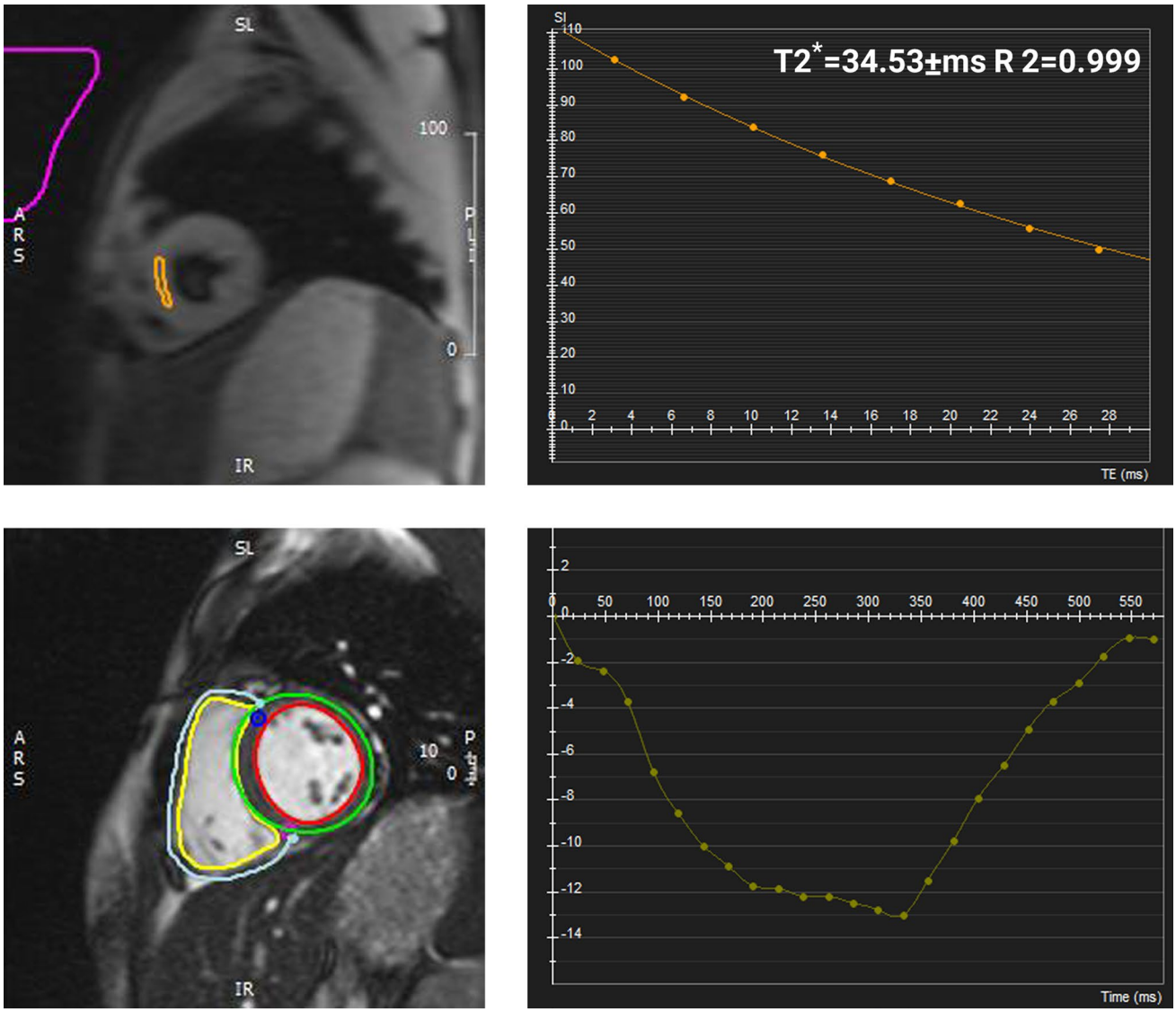

Fig. 3 13-years old boy with B-thalassemia major. GRE short axis sequence of the heart (top row) shows T2* value greater than 20, suggestive of absence of iron overload, but strain curve shows decreased global longitudinal strain of LV (bottom row)

To our knowledge, this study is the first investigation individually evaluating the correlation between myocardial iron overload, utilizing CMR T2* method with the FT-CMR technique. Summarized findings are: (1) significant correlation exists between LV GLS, LV GCS, and RV GLS, with T2* values. (2) The best GLS cut-off is − 16.5% (73% sensitivity and 63% specificity) for the detection of significant MIO. (3) There was a significant difference between LV GLS in both TM + MIO and TM − MIO relative to the control group ($p < 0.001$).

In this study, ROC Curve analysis reveals GLS of the left ventricle, has a significant prognostic value to predict T2* less than 20 ms. In a study by Parsaee et al. which conducted in 2018 with 130 patients indicated a correlation between GLS results with STE and T2* values by CMR. They determined optimal cut-off points of − 18.5% for GLS in echocardiography, comparably we found − 16.30% to be the optimal cut-off for GLS of the left ventricle using FT-CMR [2]. Temporal averaging may result in lower strain values for FT-CMR derived strain value in comparison to STE [37]. Pizzino et al. and Garceau et al. have found an absolute cut-off point of 17% by STE for determining T2* less than 20 ms [38, 39]

Even Beta-thalassemia patients without myocardial Iron overload defined as T2* more than 20 ms had a significant decrease in GLS compared to the control group. These

results suggest that possibly even minimal degrees of excess Iron, which we don't include in the iron overload spectrum, could also influence myocardial function and strain. (Fig. 3)

By correlating T2* CMR with the STE results, Parsaee et al. have shown that GLS could be valuable in the prediction of myocardial iron overload in thalassemia patients with normal LVEF. In the mentioned survey, strain values derived by STE became abnormal before any detectable impairment in myocardial function. Even the mildest degree of myocardial iron load, when raised chronically, precipitates abnormality in the ventricular longitudinal deformation [2].

One of the unique aspects of this investigation is the evaluation of all strain parameters for both ventricles. Our findings represent that although biventricular GRS is not a significant predictor for the detection of iron overload but significant correlation exists between LV GLS, LV GCS as well as RV GLS, with T2* values. Mehmet et al. have suggested that LV GCS decline earlier than other strain values but we determined that LV GLS is more superior with respect to prediction T2* values [4].

Conceivably, the size of our study group enabled us to conclude promising results, which is crucial in improvements in the management of beta-thalassemia patients at risk of evolving myocardial iron overload. We believe that the addition of strain parameter improves our knowledge about complex myocardial mechanics in this disorder. CMR feature tracking may be used more efficiently for early detection of iron toxicity and timely investigations of inadequate chelation. Moreover, further myocardial dysfunction may be prevented by modification of chelation therapy if necessary.

Because of the retrospective design of our research, some of the images may be of low quality. Consequently, our findings need to be validated by further prospective investigations, including a higher proportion of patients with the subtler or earlier disease. And lastly, further studies should be done to compare CMR derived strain value with FT compare with STE.

Conclusion

The most accurate technique for the non-invasive quantification of MIO in patients in the clinical bases is CMR. Our study demonstrated that strain values measured and calculated by CMR and myocardial T*2 values are strongly correlated. We detected decreased left ventricular GLS in TM patients even though they have normal MIO defined by $T2^* > 20$. Our findings confirm the role of GLS in detecting subclinical myocardial mechanical impairment and after further investigations FT-CMR may be used more efficiently for early detection of iron toxicity and deposition and timely investigations into origins of inadequate chelation. And further dysfunction may be prevented by modification of chelation therapy if necessary.

Study limitations

Due to retrospective aspect of our study, some of the images maybe of low quality. Consequently, our results need to be confirmed by further prospective studies with larger sample size, including a higher proportion of patients with subtler or earlier disease. And lastly further studies should be done to compare CMR-FT and other well-established imaging methods.

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Data availability The data supporting the findings of the article is available in the research deputy of Iran University of Medical Sciences.

Compliance with ethical standards

Conflict of interest The study authors declare no conflict of interest in terms of scientific collaboration and financial benefits.

Ethical approval The study protocol was approved by the ethical committee of Shahid Rajaee hospital.

Informed consent Written informed consent was acquired from all patients before including them in the study.

Research involving human participants and/or animal No Animal subjects were used in the study. All research procedures were tracked by ethical standards of the responsible committee at Iran University of Medical Sciences.

References

1. Poorzand H, Manzari TS, Vakilian F, Layegh P, Badiee Z, Norouzi F, Morovatdar N, Sani ZA (2017) Longitudinal strain in beta thalassemia major and its relation to the extent of myocardial iron overload in cardiovascular magnetic resonance. Arch Cardiovasc Imaging 5:1–5
2. Parsaee M, Akiash N, Azarkeivan A, Alizadeh Sani Z, Amin A, Pazoki M, Samiei N, Jalili MA, Adel MH, Rezaian N (2018) The correlation between cardiac magnetic resonance T2* and left ventricular global longitudinal strain in people with β-thalassemia. Echocardiography 35(4):438–444
3. Cusmà Piccione M, Piraino B, Zito C et al (2013) Early identification of cardiovascular involvement in patients with b-thalassemia major. Am J Cardiol 112:1246–1251
4. Ari ME, Ekici F, Çetin İİ et al (2017) Assessment of left ventricular functions and myocardial iron load with tissue Doppler

and speckle tracking echocardiography and T2* MRI in patients with beta thalassemia major. Echocardiography 34:383–389
5. Cheung YF, Liang XC, Chan GC et al (2010) Myocardial deformation in patients with Beta-thalassemia major: a speckle tracking echocardiographic study. Echocardiography 27:253–259
6. Hamdy AM (2007) Use of strain and tissue velocity imaging for early detect ion of regional myocardial dysfunction in patients with beta thalassemia. Eur J Echocardiogr 8:102–109
7. Fernandes JL (2012) Iron chelation therapy in the management of transfusion-related cardiac iron overload. Transfusion 52(10):2256–2268
8. Karamanou AG, Hamodraka ES, Vrakas SC et al (2014) Assessment of left ventricular and atrial diastolic function using two-dimensional(2D) strain imaging in patients with β-thalassemia major. Eur J Haematol 92:59–65
9. Carpenter JP, He T, Kirk P et al (2011) On T2* magnetic resonance and cardiac iron. Circulation 123:1519–1528
10. Aypar E, Alehan D, Hazirolan T et al (2010) The efficacy of tissue Doppler imaging in predicting myocardial iron load in patients with beta thalassemia major:correlation with T2* cardiovascular magnetic resonance. Int J Cardiovasc Imaging 26:413–421
11. Monte I, Buccheri S, Bottari V et al (2012) Left ventricular rotational dynamics in beta thalassemia major: a speckle-tracking echocardiographic study. J Am Soc Echocardiogr 25:1083–1090
12. Vogel M, Anderson LJ, Holden S et al (2003) Tissue Doppler echocardiography in patients with thalassaemia detects early myocardial iron dysfunction related to myocardial iron overload. Eur Heart J 24:113–119
13. Ramazzotti A, Pepe A, Positano V et al (2009) Multicenter validation of the magnetic resonance T2* technique for segmental and global quantification of myocardial iron. J Magn Reson Imaging 30:62–68
14. Westwood MA, Anderson LJ, Firmin DN et al (2003) Interscanner reproducibility of cardiovascular magnetic resonance T2* measurements of tissue iron in thalassemia. J Cardiovasc Magn Reson 18:616–620
15. Seldrum S, Pierard S, Moniotte S et al (2011) Iron overload in polytransfused patients without heart failure is associated with subclinical alterations of systolic left ventricular function using cardiovascular magnetic resonance tagging. J Cardiovas Magn Reson 13:23
16. Modell B, Khan M, Darlison M, Westwood MA, Ingram D, Pennell DJ (2008) Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. J Cardiovasc Magn Reson 10(1):42
17. Habibzadeh F, Yadollahie M, Merat A, Haghshenas M (1998) Thalassemia in Iran; an overview. Arch Irn Med 1:27–33
18. Chu WC, Au WY, Lam WW (2012) MRI of cardiac iron overload. J Magn Reson Imaging 36(5):1052–1059
19. Taher A, Hershko C, Cappellini MD (2009) Iron overload in thalassaemia intermedia: reassessment of iron chelation strategies. Br J Haematol 147(5):634–640
20. Baraldi-Junkins C, Levin HR, Kasper EK, Rayburn BK, Herskowitz A, Baughman KL (1993) Complications of endomyocardial biopsy in heart transplant patients. J Heart Lung Transplant 12(Pt 1):63–67
21. Liu P, Henkelman M, Joshi J (1992) Quantification of myocardial tissue iron contents using NMR relaxation. Validation in a novel murine thalassemia model. JACC 19:187A
22. Chitiboi T, Axel L (2017) Magnetic resonance imaging of myocardial strain: a review of current approaches. J Magn Reson Imaging 46(5):1263–1280
23. Pedrizzetti G, Claus P, Kilner PJ, Nagel E (2016) Principles of cardiovascular magnetic resonance feature tracking and echocardiographic speckle tracking for informed clinical use. J Cardiovasc Magn Reson 18(1):51
24. Bunn HF, Forget BG (1986) Hemoglobin: molecular Genetic and Clinical aspects. WB Saunders, Philadelphia
25. Rund D, Rachmilewitz E (2005) Beta-thalassemia. N Engl J Med 353:1135
26. Pennell DJ, Udelson JE, Arai AE et al (2013) Cardiovascular function and treatment in β-thalassemia major: a consensus statement from the American Heart Association. Circulation 128:281
27. Weatherall DJ (1994) The thalessemias. In: Stamatoyannopoulos G, Nienhuis AW, Majerus PW (eds) Molecular basis of blood diseases, 2nd edn. WB Saunders, Philadelphia, p 157
28. Adams JG 3rd, Coleman MB (1990) Structural hemoglobin variants that produce the phenotype of thalassemia. Semin Hematol 27:229
29. Forget BG, Pearson HA (2000) Hemoglobin synthesis and the thalassemias. In: Hoffman R, Benz EJ Jr, Shattil SJ, et al. (eds) Hematology: basic principles and practice, 3rd edn. Churchill Livingstone, New York
30. Kwiatkowski JL, Kim HY, Thompson AA et al (2012) Chelation use and iron burden in North American and British thalassemia patients: a report from the Thalassemia Longitudinal Cohort. Blood 119:2746
31. Ambati SR, Randolph RE, Mennitt K et al (2013) Longitudinal monitoring of cardiac siderosis using cardiovascular magnetic resonance T2* in patients with thalassemia major on various chelation regimens: a 6-year study. Am J Hematol 88:652
32. Borgna-Pignatti C, Meloni A, Guerrini G et al (2014) Myocardial iron overload in thalassaemia major. How early to check? Br J Haematol 164:579
33. Origa R, Danjou F, Cossa S et al (2013) Impact of heart magnetic resonance imaging on chelation choices, compliance with treatment and risk of heart disease in patients with thalassaemia major. Br J Haematol 163:400
34. Rachmilewitz EA, Giardina PJ (2011) How I treat thalassemia. Blood 118:3479
35. Magrì D, Sciomer S, Fedele F et al (2008) Early impairment of myocardial function in young patients with beta-thalassemia major. Eur J Haematol. 80:515–522
36. Giusca S, Korosoglou G, Zieschang V et al (2018) Reproducibility study on myocardial strain assessment using fast-SENC cardiac magnetic resonance imaging. Sci Rep 8(1):14100
37. Claus P, Omar AMS, Pedrizzetti G, Sengupta PP, Nagel E (2015) Tissue tracking technology for assessing cardiac mechanics: principles, normal values, and clinical applications. JACC Cardiovasc Imaging 8(12):1444–1460
38. Pizzino F, Meloni A, Terrizzi A, Casini T, Spasiano A, Cosmi C, Allò M, Zito C, Carerj S, Aquaro GD, Di Bella G, Pepe A (2018) Detection of myocardial iron overload by two-dimensional speckle tracking in patients with beta-thalassaemia major: a combined echocardiographic and T2* segmental CMR study. Int J Cardiovasc Imaging 34(2):263–271
39. Garceau P, Nguyen ET, Carasso S, Ross H, Pendergrast J, Moravsky G, Bruchal-Garbicz B, Rakowski H (2011) Quantification of myocardial iron deposition by two-dimensional speckle tracking in patients with β-thalassaemia major and Blackfan-Diamond anaemia. Heart 97(5):388–393
40. Muser D, Castro SA, Santangeli P, Nucifora G (2018) Clinical applications of feature-tracking cardiac magnetic resonance imaging. World J Cardiol 10(11):210–221