Native cardiac magnetic resonance T1 mapping and cardiac mechanics as assessed by speckle tracking echocardiography in patients with beta-thalassaemia major☆

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ABSTRACT

Background: We hypothesize that cardiac magnetic resonance (CMR) native T1 is associated with myocardial deformation in thalassaemia patients. The present study aimed to compare CMR native T1 values to conventional T2* values in patients with beta-thalassaemia and to explore relationships between these CMR parameters of myocardial iron overload and left ventricular (LV) and left atrial (LA) myocardial deformation.

Methods: Thirty-four (16 males) patients aged 35.5 ± 9.2 years were studied. Myocardial T2* and T1 mapping were performed to assess the cardiac iron overload, while two-dimensional speckle-tracking echocardiography was performed to determine LV and LA myocardial deformation.

Results: T2* was 36.4 ± 8.7 ms with 3 patients having myocardial iron load (T2* < 20 ms). The native T1 was 947.1 ± 84.8 ms, which was significantly lower than the reported normal values in the literature. There was a significant correlation between T1 and T2* values (r = 0.68, p < 0.001). There were no significant correlations between T1 and T2* values and conventional and tissue Doppler parameters of left ventricular systolic and diastolic function. On the other hand, T1, but not T2*, values were found to correlate negatively with maximum LA area indexed by body surface area (r = -0.34, p = 0.047) and positively with LA strain rate at atrial contraction (r = 0.36, p = 0.04). There were no associations between either of these CMR parameters with indices of ventricular deformation.

Conclusions: In patients with beta-thalassaemia major, native T1 values are decreased, associated with T2* values, and correlated with maximum LA area and LA strain rate at atrial contraction.

1. Introduction

Cardiac failure due to iron overload remains to be the major cause of morbidity and mortality in patients with beta-thalassaemia major despite improvements in iron chelation strategies [1]. Cardiac magnetic resonance (CMR) T2* imaging is currently the standard investigation for assessment of cardiac iron overload [2]. On the other hand, emerging data suggest that native T1 mapping may be a promising new technique [3,4] as it permits noninvasive assessment of not only myocardial edema, protein and lipid deposition, but also accumulation of other T1-altering substances including iron without the need to administer gadolinium-based contrast agents [5–7]. The availability of the pixel-valued colour coding T1 map, which allows detection of relatively small variations of T1 within the myocardium [6,7], has expanded the clinical application of native T1 mapping of the myocardium.

In patients with thalassaemia major, Feng et al showed correlations between T1 and T2* measurements in thalassaemia major patients [3]. Krittayaphong et al further demonstrated progressive decrease in native T1 through the spectrum of absent, mild-to-moderate, and severe cardiac iron load [8]. While these data suggest potential value of native T1...
mapping in the detection of myocardial iron load, the functional implication of altered native myocardial T1 values in thalassaemia patients remains unclear. Whereas T2* measurements have been shown to associate with ventricular myocardial deformation in these patients [9,10,11], relationships between CMR native T1 values and parameters of myocardial deformation, the latter being regarded as sensitive measures of subclinical cardiac dysfunction, have hitherto not been explored.

Given the reported progressive decrease of native T1 with increasing myocardial iron load [8], we hypothesize that native T1 is associated with myocardial deformation in thalassaemia patients. The present study aimed to compare CMR native T1 values to conventional T2* values in patients with beta-thalassaemia major and to further explore relationships between these CMR parameters of myocardial iron overload and left ventricular (LV) and left atrial (LA) myocardial deformation.

2. Methods

2.1. Subjects

This is a prospective study of patients with transfusion-dependent beta-thalassaemia major recruited from paediatric and adult haematology out-patient clinics. There were no exclusion criteria and all of the patients who consented to the study were recruited consecutively. Patients were assessed by history and physical examination for respectively symptoms and signs of heart failure. Demographic information, type of chelation therapy, and medical and medication history were obtained from the case notes and their ferritin level and liver and renal function test results were reviewed. Cardiac magnetic resonance and myocardial deformation as assessed by speckle tracking echocardiography were performed as described below within 1.4 ± 0.5 years of each other. Echocardiographic assessment was performed within two weeks of blood transfusion so as to minimize the potential confounding influence of anaemia. Based on institutional practice, the post-transfusion haemoglobin was targeted at 14 g/dL. The Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster approved the study and written informed consent were obtained from all subjects and parents of minor.

2.2. CMR imaging

Cardiovascular magnetic resonance (CMR) was performed using Siemens Magnetom Aera 1.5 T MRI system (Siemens AG, Healthcare Sector, Germany) with 18-channel torso body array coil.

Myocardial T1 mapping was performed as previously reported [12] in the matched mid-ventricular, basal and apical short axis slices (Fig. 1). The T1 mapping sequence is a balanced SSFP, single breath hold modified inversion recovery Look-Locker sequence (MOLLI) with a 5(3) 3 image acquisition algorithm, with data acquisition period of 5 heart beats followed by recovery period of 3 heart beats and then another data acquisition period of 3 heart beats. A total of 8 images was acquired with different Inversion time (TI) via 11 heart beats. T1 mapping quantification was performed by tracing semi-automatically the epicardial and endocardial contours of the region of interest using the commercially available software (Cardiac Analysis Workflow, Syngo.via workstation, Siemens AG, Healthcare Sector, Germany). The average myocardial T1 values of the mid-ventricular, basal, and apical short axis slices was calculated and used for analysis.

For T2* measurements of myocardium, T2* mapping with single breath-hold bright blood gradient-echo sequences were used. Data acquisition involved segmented and non-segmented single breath-hold gradient-echo pulse sequence with readout for a range of respective echo times. Eight echoes were acquired for assessment of myocardial T2* relaxation time while 12 echoes were be acquired for liver T2* relaxation time. Mid-ventricular short axis slice was used for T2* measurement of myocardium, while orthogonal axial slice through segments 7 and 8 of the liver parenchyma was used for T2* measurement of liver. The corresponding image data were by CMRTtools software for pixel-wise T2* estimation using robust filling technique via fitting the signal intensities of acquired images to the T2* decay model.

2.3. Conventional and speckle tracking echocardiography

All echocardiographic assessments were performed using the Vivid E95 ultrasound machine (GE Medical System, Horten, Norway). The average value from the echocardiographic indices will be based on readings from three cardiac cycles.

Two-dimensional, M-mode and Doppler echocardiography was performed. Two-dimensional echocardiographic images were used for quantification of the maximal LA area from the apical four-chamber view. The LV end-systolic and end-diastolic dimensions, thickness of interventricular septum and posterior LV wall were measured by M-mode using parasternal short axis view. The fractional shortening and the mass of the left ventricle were calculated according to standard formulae. Left ventricular diastolic functional indices including early (E) and late (A) inflow velocities and E deceleration time were determined by pulsed-wave Doppler echocardiography. Tissue Doppler echocardiography was used to measure peak mitral annular early (e) and late (a) diastolic myocardial tissue velocity, e/a ratio, and peak systolic myocardial tissue velocity (s) and myocardial acceleration during isovolumic contraction.

Fig. 1. Native T1 mapping of basal (left), mid-ventricular (middle), and apical (right) segments of the left ventricle in a thalassaemia patient without iron load.
Two-dimensional speckle tracking echocardiography was performed to assess LV and LA deformation as reported by our group previously (Fig. 2) [9,13]. Briefly, LV global longitudinal strain (GLS) and strain rates during systole (SRs) and early (SRe) and late (SRa) diastole were determined based on the apical four-chamber view, while LV global radial and circumferential strain and strain rates were assessed from the parasternal short-axis view at mid-ventricular level. To quantify LV strain and strain rate, the entire LV contour was manually traced and tracked by the Echopac software (GE Medical Systems, Wauwatosa, WI, USA) and QRS onset was used as the reference time point [9]. Left atrial deformation was determined from the apical four-chamber view by tracing the entire LA endocardial border and using the onset of P-wave as the reference time point. The following indices of LA deformation were determined: positive, negative and total strain, and strain rates at ventricular systole (aSRs), early diastole (aSRed), and atrial contraction (aSRac) [13]. Our group has previously reported on the high reproducibility of using 2D speckle tracking echocardiography in the assessment of ventricular [9] and atrial myocardial deformation [13].

2.4. Statistical analysis

Results are presented as mean ± standard deviation. Strain parameters are expressed in absolute values to facilitate interpretation and analyses. Relationships between T1 values and T2* values, and echocardiographic indices were explored using Spearman correlation analysis. A p value < 0.05 is considered statistically significant. All statistical analyses will be performed using SPSS version 26 (SPSS, Inc., Chicago, Illinois).

3. Results

Thirty-four patients (16 males and 18 females) aged 35.5 ± 9.2 years were studied. Their demographic and clinical parameters, iron chelation therapies and other medications, ferritin levels and renal and liver function test results are shown in Table 1. Twenty-three (68%) patients reported good compliance to iron chelation therapies, while 11 (32%) reported only poor to fair compliance. Two (6%) patients had history of cardiac arrhythmias, 1 had atrial fibrillation and the other had atrial flutter, which reverted back to sinus rhythm after antiarrhythmic treatments. At the time of study, all of the patients were in sinus rhythm. Nine (26%) patients had diabetes, 3 (9%) had hypertension, 2 (6%) had hyperlipidaemia, and none were in clinical heart failure at the time of study. The serum creatinine levels were normal in all of the patients, while liver parenchymal enzymes were mildly increased in 11 (32%) patients.

Table 2 summarizes the previously reported native T1 values obtained using similar magnetic field strength and mapping sequence. The T1 value in our patients was 947.1 ± 84.8 ms, which was significantly lower compared with the published normative values based on 1.5 T CMR systems [14–16] and our previously reported normative values based on 3 T MRI system [17]. There was a significant correlation between T1 and T2* values (r = 0.68, p < 0.001) (Fig. 3). Based on a T2* value of < 20 ms, 3 (9%) patients had myocardial iron overload, 2 (6%) with moderate (T2* values of 13.7 ms and 14.1 ms) and 1 (3%) with mild (T2* value of 17.4 ms) myocardial iron overload. Based on a reported normal T1 cutoff value of 903 ms in healthy subjects [4], 5 (15%) of our patients had iron overload.
The echocardiographic findings of patients are summarized in Table 3. The LV shortening fraction was 33.9 ± 7.5% and LV end-systolic and -diastolic dimensions were within normal limits. The CMR-derived LV ejection fraction was 59.5 ± 4.8% with only 1 (3%) patient having an ejection fraction < 50%. Table 4 shows the correlations between CMR T1 and T2* values and serum ferritin levels and echocardiographic parameters. There were no significant correlations between T1 and T2* values and conventional and tissue Doppler parameters of left ventricular systolic and diastolic function. On the other hand, T1 but not T2* values were found to correlate negatively with maximum LA area indexed by body surface area (p = 0.047) and positively with LA strain rate at atrial contraction (p = 0.04). There were no associations between either of these CMR parameters with indices of ventricular deformation. Serum ferritin levels did not correlate with any of the echocardiographic parameters.

4. Discussion

The novel finding of the present study is the demonstration of associations between native T1, but not T2*, values and maximum LA area and LA strain rate at atrial contraction. Hence, the greater the myocardial iron load, the larger the LA size and the worse the LA contractile function. To our knowledge, this is the first study to interrogate the relationship between CMR native T1 values and cardiac mechanics.

In vitro studies have shown shortening of native T1 with increased myocardial iron load [18,19]. Although CMR T2* is the most used technique for quantification of myocardial iron overload and that its use has led to substantial reduction of mortality of thalassaemia patients [20], its limitations include the need for long breath-hold, susceptibility to artifacts, and reduced discrimination in mild or higher degrees of iron load [4]. With development of improved T1 mapping sequences [21,22], the use of T1 for noninvasive quantification of myocardial iron load in thalassaemia is increasing [3,4,23,24]. Our findings of decreased native T1 values, as compared to published reference values [14–17], and correlations between T1 and T2* values in patients with beta-thalassaemia major agree with those reported previously [3,8]. Interestingly, Sado et al found that about one-third of patients with various underlying causes referred for assessment of myocardial iron load had of the heart. The native T1 (953 ± 74 ms vs 935 ± 107 ms, p = 0.57) and T2* (36 ± 9 ms vs 37 ± 9 ms, p = 0.92) values and ferritin levels (4317 ± 2085 pmol/L vs 5017 ± 3683 pmol/L, p = 0.48) were similar between patients compliant versus those less compliant to iron-chelation therapy.
The other hand, the observed significant associations between native T1 and T2* MRI and occurrence of atrial fibrillation. In the present study, we did not perform 24-hour Holter monitoring. On the other hand, 2 of our patients had symptomatic atrial arrhythmias that were reverted back to sinus rhythm after antiarrhythmic treatments. Proposed mechanisms of impairment of LA mechanics and LA dilation include vulnerability of the relatively thin-walled atria to even small amounts of tissue iron [29] and development of atrial fibrosis [27]. Against this background, our novel findings of associations between native T1 but not T2* and LA strain rate at atrial contraction and LA dilation are intriguing. Importantly, LA dilation has been shown to be a risk factor for cardiovascular events in the general population [30,31], in patients with heart failure with preserved ejection fraction [32], and in those with dilated cardiomyopathy [33]. Our findings lend further support to the proposition that native T1 may be more sensitive in the detection of a lower myocardial tissue iron load, at an early stage when only atrial dysfunction begins to appear.

Several limitations to this study require comments. First, we have compared native T1 values against published normal values. It remains optimal to compare the findings in patients with study site-specific normal values derived from healthy volunteers [34]. Local references based on 1.5 T MRI systems are not available to date and we have therefore used reference values derived using similar magnetic strength and mapping sequence. [14-16] Additionally, we have compared the native T1 values of patients against our previously published local reference values based on 3 T MRI system [17], which has been shown to generate similar T1 values as that of the 1.5 T MRI system [35]. Second, this is a relatively small scale cross-sectional study that does not provide data on the longitudinal changes of T1 with alteration of atrial and ventricular mechanics. It would be interesting to monitor in a longitudinal fashion for associated changes in these parameters. Third, the small number of patients with significant myocardial iron load might have limited the power as alluded to earlier to unveil relationships between native T1 and T2* and ventricular myocardial deformation parameters.

In conclusion, in patients with beta-thalassaemia major, native T1 values are decreased, associated with T2* values, and correlated with maximum LA area and LA strain rate at atrial contraction. Native T1 may offer the potential for better detection of mild degree of iron loading and larger scale study in patient populations with myocardial iron load to confirm our preliminary findings of an association with atrial function is warranted.

CRediT authorship contribution statement

Wing-Shan See: Conceptualization, Data curation, Formal analysis, Funding acquisition, Writing – original draft. Edwina Kam-fung So: Formal analysis, Investigation, Methodology, Project administration. Gloria Yu-Yan Hwang: Resources, Writing – review & editing. Leanne Chin: Resources, Software, Visualization, Writing – review & editing. Lawrence Ip: Resources, Software, Visualization, Writing – review & editing. Wendy Wai-man Lam: Resources, Software, Visualization, Writing – review & editing. Shau-yan Ha: Supervision, Writing – review & editing. Yiu-fai Cheung: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100947.
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