Improvement of heart iron with preserved patterns of iron store by CMR-guided chelation therapy

Antonella Meloni1, Vincenzo Positano1, Giovan Battista Ruffo2, Anna Spasiano3, Domenico Giuseppe D’Ascola4, Angelo Peluso5, Petra Keilberg1, Gennaro Restaino6, Gianluca Valeri7, Stefania Renne8, Massimo Midiri9, and Alessia Pepe1

1CMR Unit, Fondazione G. Monasterio CNR-Regione Toscana, Area della Ricerca S. Cataldo, Via Moruzzi, 1, Pisa 56124, Italy; 2U.O.C. Ematologia con Talassemia, Ospedale Civico, Palermo, Italy; 3U.O. Microcitemie, Ospedale Civico, Palermo, Italy; 4U.O. Microcitemie, A.O. ‘Bianchi-Melacrino-Morelli’, Reggio Calabria, Italy; 5Microcitemia-Azienda Unità Sanitaria Locale TA/1, Presidio Ospedaliero Centrale, Taranto, Italy; 6Centro di Ricerca e Formazione ad Alta Tecnologia nelle Scienze Biomediche ‘Giovanni Paolo II’, Università Cattolica del Sacro Cuore, Campania, Italy; 7U.O. Radiologia, Azienda Ospedaliero-Universitaria Ospedali Riuniti ‘Umberto I-Lancisi-Salesi’, Ancona, Italy; 8U.O. Ospedale ‘Giovanni Paolo II’, Lamezia Terme, Italy; and 9Istituto di Radiologia, Policlinico ‘Paolo Giaccone’, Palermo, Italy

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Aims

$T_2^*$ multislice multiecho cardiac magnetic resonance (CMR) allows quantification of the segmental distribution of myocardial iron overload (MIO). We evaluated whether a preferential pattern MIO was preserved between two CMR scans in regularly chelated thalassaemia major (TM) patients.

Methods and results

We evaluated prospectively 259 TM patients enrolled in the MIO in Thalassaemia (MIOT) network with a CMR follow-up (FU) study at 18 ± 3 months and significant MIO at baseline. The $T_2^*$ in the 16 segments and the global value were calculated. Four main circumferential regions (anterior, septal, inferior and lateral) were defined. We identified two groups: severe ($n = 80$, global $T_2^* = 10$ ms) and mild–moderate MIO ($n = 179$, global $T_2^* = 10–26$ ms). Based on the CMR reports, 56.4% of patients changed the chelation regimen. For each group, there was a significant improvement in the global heart as well as in regional $T_2^*$ values ($P < 0.0001$). At the baseline, the mean $T_2^*$ value over the anterior region was significantly lower than the values over the other regions, and the mean $T_2^*$ over the inferior region was significantly lower than the values over the septal and the lateral regions. The same pattern was present at the FU, with a little difference for patients with mild–moderate MIO.

Conclusion

A preferential pattern of iron store in anterior and inferior regions was present at both CMRs, with an increment of $T_2^*$ values at FU due to a baseline CMR-guided chelation therapy. The anterior region seems the region in which the iron accumulates first and is removed later.

Keywords

Cardiac magnetic resonance • Myocardial iron overload • Preferential pattern • Thalassaemia major

Introduction

Thalassaemia major (TM) is an inherited disorder of haemoglobin synthesis that results in chronic haemolytic anaemia. Regular blood transfusions are mandatory for long-term survival, but they can cause a secondary state of tissue iron overload since humans have no physiological mechanism for active elimination of excess iron. The iron-induced cardiomyopathy is treatable and reversible if intensive chelation treatment, aimed to remove the iron excess, is instituted in time. Three chelators with differentiated mechanism of action and tissue sensitivity are currently available worldwide: deferoxamine (DFO), deferiprone (DFP), and deferasirox (DFX). To improve compliance, minimize/reduce toxicity, and enhance iron removal if an additive or synergistic effect occurs, two chelators can be used either sequentially (on different days) or in combination (both given on the same day). However, drug toxicity from...
overdosing of chelation therapy has to be avoided. Therefore, the direct monitoring of cardiac iron overload is the nodal point in the management of TM patients.

To date, cardiac magnetic resonance (CMR) is the only technique that quantitatively and non-invasively assesses cardiac iron burden. Cardiac iron is indicated by a decrease in relaxation time values, determined by the paramagnetic properties of iron compounds. The most relevant relaxation parameter is the T2* and, two validated approaches generally used in the clinical arena are the single-slice and the multislice approach. In the single-slice approach, the T2* value evaluated in a single region of interest drawn in the mid-ventricular septum is taken as representative of the T2* value for the whole heart. The multislice approach allows a global analysis of the left ventricle (LV) and consequently the identification of a heterogeneous iron distribution, demonstrated in primis by histological studies performed on haemochromatotic hearts. Importantly, it was shown that the heterogeneity of T2* values represented true heterogeneous iron density and could not have been generated by geometric and susceptibility artefacts or by myocardial fibrosis and blood oxygenation. So, the multislice, multiecho T2* CMR is ideally suited to non-invasively detect preferential patterns of myocardial iron deposits. A preferential pattern of iron store in the anterior and inferior regions was previously detected in TM patients with severe and mild–moderate iron overload. The prospective evolution of the iron store distribution has never been investigated in patients under chelation therapy.

The multislice multiecho T2* approach showed a good reproducibility, making it valuable for serial monitoring over time. This study aimed to determine whether a preferential pattern of myocardial iron overload (MIO) was preserved between two CMR scans in regularly chelated TM patients.

**Methods**

**Study population**

The Myocardial Iron Overload in Thalassaemia (MIOT) network was built in Italy in 2006 and has gradually grown, reaching the size of 69 thalassaemia centres and 8 CMR centres where exams are performed using homogeneous, standardized, and validated procedures. An online database was developed to allow the centres to collect and share patients’ data. The database is able to map myocardial iron quantitatively and non-invasively detect preferential patterns of myocardial iron deposits. A preferential pattern of iron store in the anterior and inferior regions was previously detected in TM patients with severe and mild–moderate iron overload. The prospective evolution of the iron store distribution has never been investigated in patients under chelation therapy.

The multislice multiecho T2* approach showed a good reproducibility, making it valuable for serial monitoring over time. This study aimed to determine whether a preferential pattern of myocardial iron overload (MIO) was preserved between two CMR scans in regularly chelated TM patients.

**Cardiac magnetic resonance**

CMR exams were performed on 1.5-T scanners (GE Signa/Excite HD, Milwaukee, WI, USA) using an eight-element cardiac phased-array receiver surface coil for signal reception.

Three parallel short-axis views (basal, medium, and apical) of the LV were obtained by a T2* gradient-echo multiecho sequence with electrocardiogram triggering. Each single short-axis view was acquired at nine echo times (TEs, 2.0–22 ms with an echo spacing of 2.26 ms) in a single end-expiratory breath-hold.

Acquired images were analysed by expert CMR operators in each of eight CMR centres using a previously validated, custom-written software (Hippo-MIOT®). The software is able to map myocardial T2* distribution in a 16-segment LV model according to the American Heart Association standardized segmentation. Six equiangular segments were used in the basal and medium slices and four in the apical slice (Figure 1A). For each segment, the mean value of the signal intensity along all the TEs was calculated, and the assessed decay curve was fit to the single exponential model. In heavily iron-overloaded hearts, a truncation model was applied to delete the late points with a low signal-to-noise ratio. An appropriate correction map built using the data of healthy volunteers scanned in the CoreLab of the MIOT Network was implemented within the software to correct for susceptibility artefacts.

The inter-site, inter-study, intra-observer, and inter-observer variabilities of the proposed methodology had been previously assessed. The global T2* value averaged over all 16 segmental T2* values and the T2* value in the mid-ventricular septum evaluated by averaging the T2* values in segments 8 and 9 were automatically provided. Four different main circumferential regions, such as anterior, septal, inferior, and lateral, were defined by averaging the correspondent T2* values (Figure 1B).

Cardiac iron concentration (CIC) was derived from T2* values using the formula described by Carpenter et al.

The lower limit of normal was taken as 26 ms for global heart and 24.4 ms for mid-ventricular septum T2* value. MIO was considered severe when T2* value was <10 ms.

**Statistical analysis**

All data were analysed using SPSS v.13.0 (Chicago, IL, USA) statistical package. All continuous variables are expressed as the mean and standard deviation. Correlation analysis was performed using Spearman’s test. Comparisons between groups were made by an independent sample t-test or the Mann–Whitney test. A χ2 test was performed for non-continuous variables.

Reproducibility of the T2* technique was evaluated using the coefficient of variation (CoV) and the intra-class correlation coefficient (ICC). Within-group comparisons between baseline and FU T2* data were performed by the paired t-test.

The analysis of variance (ANOVA) or the Kruskall–Wallis test in case of no-normal distribution was used to detect the presence of a significant difference among regional T2* changes.

One-way repeated-measures ANOVA was used to evaluate whether there was a significant difference between different T2*/CIC measurements. Mauchly’s test was used to test assumption of sphericity, and when sphericity could not be assumed, Greenhouse–Geisser-corrected results were taken. The Bonferroni adjustment was used in all pairwise comparisons.

A two-tailed P-value of <0.05 was considered statistically significant.

**Results**

**Characterization of the study population**

The analysis was focused on the 259 patients with significant MIO at baseline (global T2* <26 ms). One-hundred and forty-nine patients...
were females, and mean age was 29.5 ± 7.8 years. Baseline clinical data of the analysed patients are summarized in Table 1. The selected patient population was divided into two groups: severe (n = 80, baseline global $T_2^*$ between 10 and 26 ms) and mild–moderate MIO (n = 179, baseline global $T_2^*$ < 10 ms) and mild–moderate MIO (n = 179, baseline global $T_2^*$ between 10 and 26 ms). The two groups were not different regarding age (severe MIO 29.1 ± 6.7 years vs. mild–moderate MIO 29.6 ± 8.2 years; $P = 0.613$) and sex (severe MIO M/F 39/41 vs. mild–moderate MIO 71/108; $P = 0.172$).

Table 2 reports the chelation treatment performed at both CMRs. With only one exception, all patients were under chelation treatment at both the scans. The exception was a patient who at the first CMR had temporarily interrupted the DFO therapy due to a cataract. The percentage of patients who maintained the same therapy between the two scans was significantly different among the regimens (none: 0/1 (0%), DFO: 30/97 (30.9%), DFP: 12/19 (63.2%), DFX: 49/65 (75.4%), sequential DFO/DFP: 12/17 (70.6%), combination DFO + DFP: 39/58 (67.2%), sequential DFP/DFX: 1/1 (100%), and combination DFO + DFX: 0/1 (0%); $P < 0.0001$). Although the therapy was the same, 30 patients (21%) changed dosages/frequency after the baseline CMR scan. Among the 116 (45%) patients who changed chelation therapy according to the baseline CMR exam, 61 (52.6%) switched to a dual therapy (i.e. sequential or combined). Globally, based on the CMR reports, 56.4% of patients changed the chelation regimen (dosages/ frequency or drug). Of the 80 patients with severe MIO at baseline, 56 patients (70%) changed the chelation regimen.

The percentage of patients with excellent/good levels of compliance to the active chelation treatment was 87.7% at the baseline and 93.7% at the FU ($P = 0.030$).
Table 2  Chelation treatments at the baseline and FU CMRs

<table>
<thead>
<tr>
<th>Chelation at the FU</th>
<th>None</th>
<th>DFO</th>
<th>DFP</th>
<th>DFX</th>
<th>Sequential DFO/DFP</th>
<th>Combined DFO + DFP</th>
<th>Sequential DFP/DFX</th>
<th>Combined DFO + DFX</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
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<td>8</td>
<td>18</td>
<td>15</td>
<td>25</td>
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<tr>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>49</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>0</td>
<td>1</td>
<td>12</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Combined DFO + DFP (n = 58)</td>
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<td>8</td>
<td>1</td>
<td>7</td>
<td>3</td>
<td>39</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sequential DFP/DFX (n = 1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Combined DFO + DFX (n = 1)</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total at the FU</td>
<td>0</td>
<td>47</td>
<td>22</td>
<td>77</td>
<td>31</td>
<td>80</td>
<td>2</td>
<td>0</td>
</tr>
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</table>

Numbers in italic represent the number of patients who maintained the same therapy.

$T_2^*$ changes

The mean intra-observer variability assessed by CoV from one well-trained operator in each of eight sites was $7.37 \pm 4.42\%$. There was high correlation between the $T_2^*$ values calculated from images obtained in Pisa and at the other seven MRI sites concerning the global heart ($R = 0.95$). The CoV and ICC for the global heart considering all the $T_2^*$ values independently from the sites were, respectively, 8% and 0.97.

Table 3 summarizes the global heart and the regional $T_2^*$ and CIC values at both baseline and FU CMRs for the whole selected patient population. A significant increase was detected for all $T_2^*$ values ($P < 0.0001$ for all the pairwise comparisons). Accordingly, there was a significant reduction in all the regional CIC values ($P < 0.0001$ for all the pairwise comparisons). The $T_2^*$ improvement was not different among the four regions ($P = 0.398$).

A significant correlation between the global $T_2^*$ value and the $T_2^*$ value in the mid-ventricular septum was present at both basal and FU CMRs ($r = 0.955$ and 0.962, respectively, $P < 0.0001$). At the baseline, 29 (11.2%) of the 259 patients with significant global heart iron overload had a normal mid-ventricular septum $T_2^*$ value. For these patients, the mean global heart $T_2^*$ was $24.18 \pm 1.79$ ms, and the mean mid-ventricular septum $T_2^*$ was $28.15 \pm 2.87$ ms ($P < 0.0001$). Of the 29 patients with significant global heart iron overload and a normal mid-septum $T_2^*$ value, the 37.9% changed the chelation regimen, and while three patients had an insufficient compliance at the baseline, at the FU only one had an insufficient compliance.

At the FU, 182 of 259 patients (70%) had still a pathological global heart $T_2^*$ value and out of them, 12 (7%) had a normal mid-ventricular septum $T_2^*$ value.

For each group, cardiac segments were sorted by a mean $T_2^*$ value (Table 4). At the baseline as well as at the FU in both groups, the lowest $T_2^*$ value was detected in the medium anterior segment and the highest in the basal inferoseptal segment. For each group, the segment order was significantly preserved between the two scans (severe MIO: $r = 1.00$, $P < 0.0001$ and mild–moderate MIO: $r = 0.935$, $P < 0.0001$).

For each group, there was a significant improvement in the global heart as well as in regional $T_2^*$ values ($P < 0.0001$ for all the pairwise comparisons; Table 3). Accordingly, for each group, there was a significant reduction in all the regional CIC values ($P < 0.0001$ for all the pairwise comparisons). Of the patients with mild–moderate iron at baseline, 73 (41%) had a normal global heart $T_2^*$ at the FU. The $T_2^*$ improvement was not statistically different among the regions in either the severe MIO or mild–moderate MIO group ($P = 0.263$ and 0.719, respectively). The decrease in CIC was significantly higher in the group with severe MIO than in the group with mild–moderate MIO ($P < 0.0001$ for all the regions).

Patterns of MIO

At the baseline, as well as the FU CMR, a significant circumferential variability was detected in the whole patient population ($P < 0.0001$ for both CMRs) and the pattern was the same. Specifically, the mean $T_2^*$ value over the anterior region was significantly lower than the mean $T_2^*$ values over the other regions, and the mean $T_2^*$ over the inferior region was significantly lower than the $T_2^*$ values over the septal and the lateral regions. A significant circumferential variability was also preserved within each single slice at both the CMRs ($P < 0.0001$). A significant slice-to-slice variability was found at both the CMRs ($P < 0.0001$). A $T_2^*$ value was significantly lower in the medium and in the apical slices than in the basal slice.

A significant circumferential variability was present at the baseline and at the FU CMR in both groups ($P < 0.0001$; Figures 2A and 3A). At baseline, the mean $T_2^*$ value over the anterior region was significantly lower than the mean $T_2^*$ values over the other regions, and the mean $T_2^*$ over the inferior region was significantly lower than the $T_2^*$ values over the septal and the lateral regions. Exactly the same pattern was present at the FU for the group with severe MIO. The group with mild–moderate MIO showed a little difference: the mean $T_2^*$ value over the inferior region was lower than that one over the lateral region, but statistical significance was not reached. In each single slice, the significant circumferential variability was preserved in
both groups at both the scans ($P < 0.0001$ for all the comparisons; Figures 2B and 3B). A significant slice-to-slice variability was present. For patients with severe MIO, the $T_2$ value was significantly lower in the medium and apical slices than in the basal slice at both the scans ($P < 0.0001$; Figure 2C). For patients with mild–moderate MIO at baseline, only the $T_2$ value in the medium slice was significantly lower than that in the basal slice ($P = 0.019$), while at the FU, both the mean and the apical slices presented a significantly lower $T_2$ value than the basal slice ($P = 0.001$; Figure 3C).

**Discussion**

The introduction of the multislice multiecho $T_2$ CMR has made it possible to extend myocardial iron evaluation from the mid-ventricular septum to the entire LV by a segmental approach. This approach has been demonstrated to have a good intra-observer, inter-observer, and inter-study reproducibility, and it has been shown to be transferrable among the first six MRI sites enrolled in the MIOT network. Also the intra- and inter-observer variability tested in the eight MRI centres that enrolled patients in this study were demonstrated to be good and concordant with the previously published data.

Since possible bias due to susceptibility artefacts can be corrected by applying one standardized $T_2$ map of normal human hearts and since anyway the artefacts are additive in the $T_2^*$ ($1/T_2$) domain and vanish with the progression of iron overload, the multislice approach can account for the heterogeneous myocardial iron distribution. Postino et al. investigated the heterogeneity of compensated $T_2$ values in a cohort of 230 TM patients, finding a significant increase in $T_2$ value heterogeneity moving from a normal state to a condition of iron overload. In the wake of this study, Meloni et al. looked for the presence of regions with higher iron deposition. A preferential pattern of iron store in the anterior and inferior regions was detected in TM patients with severe and mild–moderate iron overload.
at their first CMR. On the basis of these findings, the aim of this study was to determine whether a preferential pattern of MIO was preserved between two CMR scans in TM patients regularly transfused and chelated. According to our protocol, the FU CMR was performed after 18 ± 3 months from the baseline CMR. This timing was a compromise between the monitoring guidelines according to the basal cardiac iron status and the real availability of CMR scans in Italy.

Our study prospectively demonstrated a significant increment of global and regional $T_2$ values at the FU. Based on the CMR using a segmental approach report, 56.4% of the patients changed chelation regimen (drug or frequency or dosage). Moreover, the discrepancy between global and mid-septum $T_2$ values present in one-tenth of the patients strengthens the added value of the multislice approach. In fact, 37.9% of the patients with a normal mid-septum $T_2$ value, but a pathological global heart $T_2$ value and heterogeneous MIO have changed the chelation regimen, and while three patients had an insufficient compliance at the baseline, at the FU only one had an insufficient compliance.

At the FU, we registered a significantly higher level of compliance to the chelation therapy, probably thanks to the opportunity for the patients to ‘touch’ directly the iron status of their hearts. Thus, the significant reduction in the cardiac iron burden was likely due to a baseline CMR-guided chelation therapy and to the improvement of the compliance to the chelation therapy.

As cardiac complications in well-chelated, well-monitored TM patients are significantly rarer than previously reported, the pattern of MIO can emerge as the sensitive predictor of cardiac complications in well-chelated TM populations to detect iron overload early and to identify borderline patients, who could particularly take advantage of tailoring chelation therapy for preventing iron-related heart damage.

DFP has been proved to be superior to DFO at removing cardiac iron, and clinical data support the dose-dependent efficacy of DFX in removing and preventing myocardial iron accumulation. This explains while the percentage of patients who remained on DFO was lower than that of patients who continued the two oral monotherapies between scans. It should be pointed out that several patients refused to change the DFO therapy. To our knowledge, low cardiac $T_2$ assessed at the first CMR triggered intensification of chelation regimens in ~20% of patients. The association between DFP and DFO has been shown to be the most effective means of reducing cardiac iron loading and, in fact, after the first CMR 61 patients switched to a combined therapy.

In the whole selected patient population as well as in both groups, the anterior region showed the lowest improvement, although a significant difference in the $T_2$ increase among the four regions was not detected. Converting the $T_2$ values to CIC, the decrease in heart iron burden was significantly higher in the group with severe MIO than in the group with mild–moderate MIO ($p < 0.0001$ for all the regions). Due to the inverse exponential relationship between $T_2$ and heart iron, a small improvement in $T_2$ values in severely iron-loaded hearts corresponds to a significant clearance of cardiac iron. The finding indirectly reflects also the higher percentage of changes in the chelation regimen based on the CMR reports among the patients with more severe iron deposition.

In this study, we reconfirmed at the baseline the same pattern of MIO detected in a previous study. Most importantly, we found out that the circumferential variability was preserved at the FU,

<table>
<thead>
<tr>
<th>Segment</th>
<th>Severe MIO at baseline</th>
<th></th>
<th>Mild–moderate MIO at baseline</th>
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<tbody>
<tr>
<td></td>
<td>$T_2$</td>
<td>Order</td>
<td>$T_2$</td>
<td>Order</td>
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<tr>
<td>---------------</td>
<td>------------</td>
<td>---------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td>Basal anterior</td>
<td>6.44 ± 1.96</td>
<td>4</td>
<td>9.46 ± 6.02</td>
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<tr>
<td>Basal anteroseptal</td>
<td>8.7 ± 2.98</td>
<td>15</td>
<td>13.12 ± 9.24</td>
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<tr>
<td>Basal inferoseptal</td>
<td>8.91 ± 2.67</td>
<td>16</td>
<td>12.92 ± 8.19</td>
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<tr>
<td>Basal inferior</td>
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<td>10.24 ± 6.57</td>
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<tr>
<td>Basal inferolateral</td>
<td>8.60 ± 2.99</td>
<td>14</td>
<td>12.58 ± 6.58</td>
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<tr>
<td>Basal anterolateral</td>
<td>8.37 ± 2.49</td>
<td>13</td>
<td>11.52 ± 5.68</td>
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<td>9.99 ± 6.34</td>
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<td>11.72 ± 6.74</td>
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<td>6.96 ± 1.93</td>
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<td>10.29 ± 5.02</td>
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<tr>
<td>Apical anterior</td>
<td>6.02 ± 1.76</td>
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<td>7.25 ± 2.15</td>
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<td>10.21 ± 5.96</td>
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<td>7.35 ± 2.18</td>
<td>10</td>
<td>11.89 ± 8.41</td>
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despite the $T_2^*$ increase. To be more precise, for the group with mild–moderate MIO at the FU, the difference between the inferior region and the lateral region lost the statistical significance. It should be pointed out that many patients with mild–moderate MIO at baseline had at the FU normal global and segmental $T_2^*$ values. This finding strongly supports the independence of the patterns from artifactual sources.

Moreover, at both the scans, the circumferential pattern was highly conserved across slices. In a histological study performed on one freshly deceased, unfixed, iron-loaded heart, Ghugre et al. also
reported a slice-to-slice reproducibility. This conservation of the relative relationship among regional $T_2^*$ values also within each single slice seems to indicate the absence of a variable regional response to chelation treatment.

Carpenter et al.\cite{4} reported no systematic variation in mean iron concentration between different LV segments or from base to apex in their $T_2^*$ CMR study against human hearts. Among the patients with severe MIO, the significantly higher myocardial iron burden in their 10 vs. our 80 patients ($5.26 \pm 0.87$ vs. $7.29 \pm 1.74$, $P = 0.0005$) may explain the differences found in our study and in Ghugre’s data.\cite{31} We found a significantly lower iron content in the basal slice vs. the medium and apical slices at both basal and FU CMRS.

**Figure 3** Baseline and FU CMR results in the patients with mild–moderate MIO at baseline. (A) Circumferential $T_2^*$ variability. (B) Mean circumferential $T_2^*$ values in each slice. (C) Slice-to-slice variability.
Limitations
It was not possible to compare CMR findings with other imaging techniques (i.e., echocardiography), because they were performed with different fixed intervals in several patients.

Due to the lower rate of cardiac complications in the last years in the thalassaemia population, prospective studies with a significant longer follow-up times are recommended to focalize about the clinical relevance of the $T_2^*$ segmentation approach in management of the chelation therapy.

Conclusions
A preferential pattern of iron store in anterior and inferior regions was present at both basal and FU CMRs, with an increment of $T_2^*$ values at FU due to both a baseline CMR-guided chelation regimen and the improvement of the compliance to the chelation therapy. The anterior region seems to be the region in which the iron accumulates first and is removed later. Our data seem to suggest that the $T_2^*$ cardiac MR approach could be useful for identifying early iron deposit and for tailoring chelation therapy in each patient to better prevent cardiac complications.

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References
A 23-year-old female, as diagnosed with complex cyanotic congenital heart disease in infancy, admitted to the emergency department with acute chest pain and shortness of breath on exertion. At the age of 3 and 7 years, she underwent right bidirectional Glenn anastomosis and extracardiac Fontan operation, respectively, because of the diagnosis of double inlet left ventricle, right ventricular hypoplasia, and ventriculoarterial discordance. Since then she was lost in follow-up.

The initial chest X-ray showed an oval, well-defined opacity with smooth contours causing dilatation of the mediastinal shadow. A chest computed tomography scan demonstrated a contrast-enhancing fusiform sac, suggesting a giant superior vena cava (SVC) aneurysm measuring $5.7 \times 8.1$ cm with no significant stasis and no evidence of thrombus or filling defects in the pulmonary arteries (Panels A–E, and see Supplementary data online, Video S1). A catheterization study revealed a large SVC aneurysm measuring 5.7 cm (Panel F, and see Supplementary data online, Video S2). Mean superior-inferior caval and right-left pulmonary artery pressures were $<6$ mmHg and no clinically significant fistula was detected. Medical therapy was recommended.

Aneurysmal dilation of the SVC is a rare anomaly. To the best of our knowledge, there has been only two cases following Glenn anastomosis, and there have been no reports after Fontan operation. The exact pathogenesis of SVC aneurysm is not known and the possibility of the deficiency of longitudinal muscle layer of the adventitia has been reported. The common feature in all reported patients was the region of the aneurysm. (Panel A) Chest X-ray, arrow shows a mediastinal shadow. (Panel B) axial multiple detector computed tomography (MDCT) image. (Panel C) oblique coronal thin maximum intensity projection MDCT image. (Panel D) anterior volume rendering MDCT image. (Panel E) posterior volume rendering MDCT image. (Panel F) the angiogram demonstrating the fusiform aneurysm of superior vena cava. Ao, aorta; LIV, left innominate vein; LPA, left pulmonary artery; RIV, right innominate vein; RPA, right pulmonary artery; SVC, superior vena cava.

Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.