Iron overload is the main complication in thalassemia major (TM) patients, and heart failure caused by myocardial siderosis remains the main cause of death in adults.1–3 Many questions regarding the natural history of cardiac iron overload are still unanswered. Moreover, TM patients develop a cardiomyopathy characterized by a multifactorial etiopathogenesis. Other than iron, chronic anemia, myocarditis, and endocrine abnormalities seem to be determining factors as well.4,5

Background—Cardiovascular magnetic resonance (CMR) plays a key role in the management of thalassemia major patients, but few data are available in pediatric population. This study aims at a retrospective multiparametric CMR assessment of myocardial iron overload, function, and fibrosis in a cohort of pediatric thalassemia major patients.

Methods and Results—We studied 107 pediatric thalassemia major patients (61 boys, median age 14.4 years). Myocardial and liver iron overload were measured by T2* multiecho technique. Atrial dimensions and biventricular function were quantified by cine images. Late gadolinium enhancement images were acquired to detect myocardial fibrosis. All scans were performed without sedation. The 21.4% of the patients showed a significant myocardial iron overload correlated with lower compliance to chelation therapy ($P<0.013$). Serum ferritin $\geq 2000$ ng/mL and liver iron concentration $\geq 14$ mg/g/dw were detected as the best threshold for predicting cardiac iron overload ($P=0.001$ and $P<0.0001$, respectively). A homogeneous pattern of myocardial iron overload was associated with a negative cardiac remodeling and significant higher liver iron concentration ($P<0.0001$). Myocardial fibrosis by late gadolinium enhancement was detected in 15.8% of the patients (youngest children 13 years old). It was correlated with significant lower heart T2* values ($P=0.022$) and negative cardiac remodeling indexes. A pathological magnetic resonance imaging liver iron concentration was found in the 77.6% of the patients.

Conclusions—Cardiac damage detectable by a multiparametric CMR approach can occur early in thalassemia major patients. So, the first T2* CMR assessment should be performed as early as feasible without sedation to tailor the chelation treatment. Conversely, late gadolinium enhancement CMR should be postponed in the teenager age. (Circ Cardiovasc Imaging. 2015;8:e003230. DOI: 10.1161/CIRCIMAGING.115.003230.)

Key Words: children ▪ ferritins ▪ magnetic resonance imaging ▪ thalassemia major

Received January 29, 2015; accepted July 8, 2015.

From the Centro per la Cura delle Microcitemie, Cardarelli Hospital, Napoli, Italy (M.C., A.F.); Dipartimento della Donna, del Bambino e di Chirurgia Generale e Specialistica, Seconda Università di Napoli, Napoli, Italy (M.C.); Cardiovascular MR Unit, Fondazione G. Monastero CNR-Regione Toscana, Pisa, Italy (A.M., M.G.N., V.P., A.P.); Ematologia-Emoglobinopatie, Civico Hospital-ARNAS, Palermo, Italy (L.C.); Centro Microcitemia, “Garibaldi” Hospital, Catania, Italy (V.C.); Oncoematologia Pediatria, Policlinico di Modena, Modena, Italy (G.P.); Pediatría, Adolescencología y Talasemia, Arcispedale “S.Anna”, Ferrara, Italy (M.R.G.); Ematologia II con Talassemia, Ospedale “V. Cervello”, Palermo, Italy (L.P., A.M.); Clin. di Radiologia, Policlinico “Paolo Giaccone”, Palermo, Italy (P.T., M.M.); and Radiology Department, University of Ancona, Ancona, Italy (G.V.).

Correspondence to Alessia Pepe, MD, PhD, Cardiovascular MR Unit, Fondazione G. Monastero CNR-Regione Toscana, Via Moruzzi 1, 56124 Pisa, Italy. E-mail alessia.pepe@ftgm.it

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Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org

DOI: 10.1161/CIRCIMAGING.115.003230

See Clinical Perspective
further open the prognosis in this population. Unfortunately, data about this issue are scarce and not definitive.6,7

The highly sensitive and reproducible magnetic resonance imaging (MRI) T2* technique has revolutionized thalassemia management,1 providing a direct assessment of cardiac and hepatic iron content and evaluating the effectiveness of iron chelation therapy.8–11 The multislice approach12–14 detects uneven iron accumulation in the heart and allows to identify patients at risk for cardiac complications in a precocious stage.15 Moreover, cardiovascular magnetic resonance (CMR) provides the opportunity to quantify bi-atrial and biventricular function parameters with excellent reproducibility.16 Furthermore, with the same scan, it is possible to acquire late gadolinium enhancement (LGE) images to determine the presence of myocardial fibrosis, which is still unstudied in children affected by TM.

This study aims at a retrospective multiparametric CMR assessment of cardiac iron overload, function, and fibrosis in a cohort of pediatric patients with TM enrolled in a large cooperative study, including >2000 patients with hemoglobinopathies.

Methods

Study Population

From the 2171 patients with hemoglobinopathies enrolled in the Myocardial Iron Overload in Thalassemia (MIOT) Network, we retrospectively selected 107 pediatric TM patients (age <18 years) who had undergone at least 1 MRI scan.

The MIOT Network is constituted by 9 MRI sites and 70 thalassemia centers where CMR exams are performed using standardized and validated procedures and where patients’ clinical–instrumental data are put in a centralized database via web.17 The patients were monitored for glucose dysregulation according to the current Thalassaemia International Federation (TIF) Guidelines at the time of the study.18 Even if the fasting plasma glucose was normal, all patients performed an oral glucose tolerance test at the age of puberty. The study complied with the Declaration of Helsinki. Parents gave their informed consent for all patients. The project was approved by the institutional ethics committee.

MRI

MRI was performed using a 1.5T scanner (GE Excite HD). An 8-element cardiac phased array receiver surface coil and ECG gating was used. For the measurement of myocardial iron overload (MIO), a multislice multiecho T2* approach was adopted.13 Three parallel short-axis views (basal, medium, and apical) of the left ventricle (LV) were obtained by T2* gradient-echo multiecho sequence. Each short axis was acquired at 9 echo times in a single end-expiratory breath-hold.12,19,20 For the measurement of liver iron overload, a T2* gradient-echo multiecho sequence was used. A single transverse slice through the liver was obtained at 9 echo times in a single end-expiratory breath-hold.21 T2* image analysis was performed using a previously validated software (HIPPO MIOT).4,31 In thalassemia, the LGE visualized in 2 different views. The extent of LGE areas was quantified using a previously validated software.4,11 In thalassemia, the LGE technique was proved to be safe.32

The study enrolled 107 patients (mean age 12 years, 3 girls, median body weight 36 kg) from 9 MRI centers and 70 thalassemia centers. At the first MRI examination, the 2 patients from South America were not chelated.

Statistical Analysis

All data were analyzed using SPSS version 13.0 statistical package. The normality of distribution of the parameters was assessed by using the Kolmogorov–Smirnov test. Continuous variables with normal distribution were described as means±SD, whereas non-normal variables were represented with median and 25th and 75th percentiles. Categorical variables were expressed as frequencies and percentages.

For continuous variables with normal distribution, comparisons between groups were made by independent-samples t test (for 2 groups) or 1-way analysis of variance (for >2 groups). Wilcoxon’s signed-rank test and Kruskal–Wallis test were applied for continuous values with non-normal distribution. The Bonferroni adjustment was used in all pairwise comparisons. χ2 testing was performed for noncontinuous variables.

Analysis of covariance models were used to evaluate the impact of cardiac iron on the relationship between myocardial fibrosis and cardiac remodeling. When necessary, outcomes were log-transformed to normalize the residual distributions and to equalize the residual variance.

Correlation analysis was performed using Pearson’s test or Spearman’s correlation where appropriate. Odds ratios and 95% confidence intervals were calculated. To determine the best serum ferritin and LIC cut-offs for discriminating the presence and absence of MIO, the maximum sum of sensitivity and specificity was calculated from receiver-operating characteristic curve analysis.

A 2-tailed probability <0.05 was considered statistically significant.

Results

Patient Data

One hundred and five patients were Italian, whereas 2 had recently arrived in Italy from South America. Age range was 4.2 to 17.9 years.

At the first MRI examination, the 2 patients from South America were not chelated.
Clinical data are summarized in Table 1.

**CMR Data**

MRI data are summarized in Table 2.

All MRI scans were performed without sedation. No significant correlation was found between global heart T2* values and age \((r=0.022; P=0.823)\) or sex \((P=0.288)\).

Global heart T2* values were significantly associated to midseptum T2* values, but the bias between the 2 measurements increased for values \(>20\) ms (Figure 1).

Twenty-three patients \((21.5\%)\) showed an abnormal global heart T2* value, and none of them was under 7.9 years of age (Figure 2A).

Sera ferritin was negatively correlated with global heart T2* values \((r=−0.425; P<0.0001)\). Using receiver-operating characteristic curve analysis, a serum ferritin of \(2000\) ng/mL was found to be the best threshold for discriminating the presence of cardiac iron with an area under the curve of 0.733 \((P=0.001); Figure 3A\). Odds ratios for global heart T2* values \(<20\) ms was 3.9 \((1.2–12.5; 95\%\) confidence intervals; \(P=0.023)\) for serum ferritin \(\geq 1500\) ng/mL and 4.9 \((1.7–13.8; 95\%\) confidence intervals; \(P=0.003)\) for serum ferritin levels \(\geq 2000\) ng/mL.

There was a significant negative correlation between global heart and MRI LIC values \((P=−0.436; P<0.0001)\). Using receiver-operating characteristic curve analysis, an LIC \(\geq 14\) mg/g/dw was found to be the best threshold for discriminating the presence of MIO in children with an area under the curve of 0.817 \((P<0.0001); Figure 3B\). Odds ratios for abnormal global heart T2* values was 30.08 \((3.58–252.68; 95\%\) confidence intervals; \(P=0.002)\) for patients with MRI LIC \(\geq 14\) mg/g/dw versus patients with normal MRI LIC. Out of the 23 patients with an abnormal global heart T2* value, 22 showed hepatic iron overload \((1\) mild, 4 significant, and 17 severe), and 1 had a T2* value close to the cut-off \((2.9\) mg/g/dw).

No significant correlations were found between the global heart T2* values and the biatrial areas or the LV and RV functional parameters, with the exception of the RV systolic volume index \((r=−0.232; P=0.016)\). Eighteen patients \((16.8\%)\) showed LV dysfunction. Of them, 6 \((33\%)\) had a global heart T2* value \(<20\) ms (Figure 2A). LV dysfunction was present in the youngest patient involved in this study \((a girl of 4.9 years who did not receive any chelation treatment)\). Excluding this patient, none of the patients with LV dysfunction was under 6.6 years of age. Eight patients \((7.5\%)\) showed RV dysfunction. Of them, one \((12.5\%)\) had a global heart T2* value \(<20\) ms. None of the patients with RV dysfunction was under 11.3 years of age.

No difference in the chelation regimen was found between the patients with significant heart iron \((global heart T2* \(<20\) ms) versus the patients without significant heart iron \((P=0.472)\).

Patients with global heart T2* \(\geq 20\) ms had more frequently a good/excellent compliance to the chelation therapy compared with patients with significant cardiac iron \((93.9\%\) versus 73.9\%; \(P<0.013)\).

### Table 1. Clinical and Instrumental Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>14.4 (10.2–16.1)</td>
</tr>
<tr>
<td>Sex (males/females)</td>
<td>61/46</td>
</tr>
<tr>
<td>Ferritin levels, ng/L</td>
<td>1814 (1091–2858)</td>
</tr>
<tr>
<td>Hemoglobin pretransfusion, g/dL</td>
<td>9.6 (9.4–9.8)</td>
</tr>
<tr>
<td>Transfusion starting age, y</td>
<td>1.0 (1.0–2.0)</td>
</tr>
<tr>
<td>Chelation starting age, y</td>
<td>3.0 (2.0–4.0)</td>
</tr>
<tr>
<td>Duration of transfusion therapy, y</td>
<td>13.1 (8.5–14.9)</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>27.0 (18.5–46.5)</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>26.8 (19.0–36.5)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>0</td>
</tr>
<tr>
<td>HCV-RNA positivity, n (%)</td>
<td>4 (3.9)</td>
</tr>
<tr>
<td>Chelation therapy, n (%)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Desferrioxamine</td>
<td>32 (29.9)</td>
</tr>
<tr>
<td>Deferasirox</td>
<td>49 (45.8)</td>
</tr>
<tr>
<td>Deferiprone</td>
<td>14 (13.1)</td>
</tr>
<tr>
<td>Combined desferrioxamine+deferiprone</td>
<td>9 (8.9)</td>
</tr>
<tr>
<td>Sequential desferrioxamine/deferiprone</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Dosage of desferrioxamine, mg/kg body weight/d</td>
<td>39.1±9.7</td>
</tr>
<tr>
<td>Dosage of deferiprone, mg/kg body weight/d</td>
<td>71.1±14.9</td>
</tr>
<tr>
<td>Dosage of deferasirox, mg/kg body weight/d</td>
<td>26.9±6.8</td>
</tr>
<tr>
<td>Excellent/good compliance, n (%)</td>
<td>94/105 (89.5)</td>
</tr>
<tr>
<td>Splenectomized, n (%)</td>
<td>25 (23.4)</td>
</tr>
</tbody>
</table>

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; and HCV, hepatitis C virus.

### Table 2. MRI Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global heart T2*, ms</td>
<td>32.8 (22.6–38.9)</td>
</tr>
<tr>
<td>MRI LIC, mg/g/dw</td>
<td>0.6 (0.5–1.0)</td>
</tr>
<tr>
<td>No. of segments with abnormal T2*</td>
<td>1.0 (0.0–5.0)</td>
</tr>
<tr>
<td>Mid-septum T2*, ms</td>
<td>34.0 (22.0–40.0)</td>
</tr>
<tr>
<td>MRI LIC, mg/g/dw</td>
<td>7.3 (3.3–15.1)</td>
</tr>
<tr>
<td>Left atrial area, cm²</td>
<td>16.0 (14.0–18.0)</td>
</tr>
<tr>
<td>Right atrial area, cm²</td>
<td>14.0 (13.0–17.0)</td>
</tr>
<tr>
<td>LVESVI, mL/m²</td>
<td>88.4±17.8</td>
</tr>
<tr>
<td>LVESVI, mL/m²</td>
<td>34.0 (28.2–40.0)</td>
</tr>
<tr>
<td>LV cardiac output, L/min</td>
<td>4.9 (4.2–6.2)</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>54.8±12.8</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>60 (57.0–64.0)</td>
</tr>
<tr>
<td>RVESVI, mL/m²</td>
<td>82.9±17.9</td>
</tr>
<tr>
<td>RVESVI, mL/m²</td>
<td>31.0 (26.0–37.0)</td>
</tr>
<tr>
<td>RVF, %</td>
<td>61.4±6.8</td>
</tr>
<tr>
<td>Patients with fibrosis, n (%)</td>
<td>12/76 (15.8)</td>
</tr>
<tr>
<td>Extent LGE areas, % of LV mass</td>
<td>1.3±0.7</td>
</tr>
<tr>
<td>LGE segments per patient, M/SD</td>
<td>2.0±1.0</td>
</tr>
<tr>
<td>Patients with more foci of LGE, %</td>
<td>67</td>
</tr>
<tr>
<td>Septal region involvement, % of LGE foci</td>
<td>72.0</td>
</tr>
</tbody>
</table>

CIC indicates cardiac iron concentration; LGE, late gadolinium enhancement; LIC, liver iron concentration; LV, left ventricle; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; MRI, magnetic resonance imaging; RV, right ventricle; RVESVI, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; and RVESVI, right ventricular end-systolic volume index.
Four groups of patients were identified by the segmental approach (Figure 4):

- No MIO (all segments with T2* ≥20 ms; Group A, 40 patients)
- Heterogeneous MIO (some segments with T2* ≥20 ms and other segments with T2* <20 ms) and T2* global value ≥20 ms (Group B, 44 patients)
- Heterogeneous MIO and T2* global value <20 ms (Group C, 13 patients)
- Homogeneous MIO (all segments with T2* <20 ms; Group D, 10 patients)

The clinically and instrumentally relevant findings in the 4 groups are summarized in Table 3. The mean serum ferritin levels in the last year were significantly different between groups A and C (P=0.012 and P=0.030, respectively). The groups C and D had a significantly higher MRI LIC value than the group A (P<0.0001 for both comparisons) and the group B (P=0.030 and P=0.012).

The left ventricular end-diastolic volume index was significantly higher in the group D than in the groups A and B (P=0.034 and P=0.035), whereas the left ventricular end-systolic volume index was significantly higher in the group D than in the group A (P=0.050). The group D had a significant higher LV mass index than all the other groups (P=0.026 versus group A, P=0.019 versus group B, and P=0.006 versus group C). The right ventricular systolic volume index was significantly higher in the group D than in the group A (P=0.026).

In 31 patients, the presence of myocardial fibrosis was not investigated because the parents did not give the consent to the administration of the contrast medium or because a short MRI protocol was chosen to avoid a sedation.

The youngest patient showing myocardial fibrosis had 13 years of age. No patients showed an ischemic pattern. Table 4 shows the comparison between patients with and without myocardial fibrosis. A significant higher MIO was detected in patients with myocardial fibrosis (Figure 5). The association between myocardial fibrosis and cardiac remodeling persisted also after the correction for global heart T2* values.

**Liver MRI Data**

No significant correlation was found between MRI LIC values and age (r=0.138; P=0.158). Eighty-three patients (77.6%) showed a pathological MRI LIC (Figure 2B). MRI LIC values were not significantly different between boys and girls (P=0.076). Serum ferritin was positively correlated with MRI LIC values (r=0.668; P<0.0001).

No difference in the chelation regimen was found between the patients with liver iron (MRI LIC ≥3 mg/g/dw) versus the patients with no liver iron (P=0.515).
All patients without hepatic iron had a good/excellent compliance to the chelation therapy, but the frequency of good/excellent compliance was comparable between patients without and with hepatic iron (100% versus 86.4%; \( P = 0.65 \)).

**Discussion**

Current life expectancy in TM patients is definitely improved in the last 15 years, mainly thanks to widespread use of MRI for detecting iron overload in target organs (liver and heart).\(^{11}\) Although several studies focused on adults,\(^{8-11,33}\) this is the largest report of TM children undergoing MRI assessment using a multiparametric approach. In rare diseases, collaborative projects like the MIOT Network may be useful to produce evidence that aids better management of patients.

In our series of 107 pediatric TM patients, selected retrospectively from a large cohort of thalassemia patients, sedation was never necessary because the children had been carefully prepared, thanks to the cooperation among family, nurse, and physician.

The pattern of iron loading in TM could be better revealed in children because the kinetics of iron uptake/release in different organs is not altered by multiple comorbidities, medications, or changes in chelators.\(^ {9,19,34}\) Furthermore, TM children undergo a more regular transfusion regimen, and the amount of transfused red blood cells tends to be more tailored to body weight; indeed they could represent the ideal population to study the initial stage of iron loading and the onset of its complications.

Our results show that in TM children, iron is initially and mainly stored in liver because the vast majority of assessed patients (77.6%) presented with pathological MRI LIC (the youngest 4.2 years old; Figure 2B), with moderate to severe liver iron overload in more than half of them (68%). Only 37.7% of patients showed no MIO (Figure 4), and the youngest patient with MIO was 7.9-year-old, thus suggesting that children can accumulate iron also in the heart at early age (Figure 2). Thus, the first cardiac T2\(^ *\) assessment should be performed as early as possible without sedation, as recently confirmed by other studies focused on TM children younger than 10 years.\(^ {6,7}\) To our knowledge, this is largest report about iron overload prevalence by MRI in white TM children. TM children patients with a homogenous MIO showed significantly more pronounced signs of negative cardiac remodeling and significantly higher traditional markers of cardiac risk (LIC or serum ferritin). Although nonprospective data are available in pediatric population, our preliminary prospective data on a large cohort of TM adult patients shows that a homogeneous MIO identifies patients at high risk of heart failure.\(^ {35}\) Additionally, a heterogeneous iron overload distribution in the heart, previously demonstrated in TM adults and in TM children <10 years,\(^ {6,15}\) is now reported also in pediatric patients, and a sizeable part of those with global heart T2\(^ *\) >20 ms experienced heterogeneous iron overload (group B).
It has been demonstrated that 20 ms is a conservative cut-off value for T2*. In fact, by T2* calibration data, 20 ms equates to 1.1 mg/g iron dry weight, which is approximately twice the historically reported normal mean level of human myocardial iron. Most of the patients in group B have a global heart T2* in the 20 to 30 ms range corresponding to early cardiac iron overload. In a recently published paper on a large cohort of adult thalassemia major patients, no significant differences were found. In particular, all patients with detectable cardiac iron presented moderate to severe liver iron overload. Our results concur with this hypothesis because an initial connection between hepatic and cardiac iron was demonstrated in our pediatric population where the organ-specific mechanisms of iron loading/unloading are not masked by severe iron overload or intensive chelation. MRI LIC ≥14 mg/g/dw and serum ferritin levels ≥2000 ng/mL were found to be significant risk factors for a global heart T2* value <20 ms in TM children. The role of this traditional markers could result particularly useful in pediatric population, where MRI assessment is difficult to carry out because of early age, scarce collaboration, or limited availability. The weak correlation between heart iron and LIC or serum ferritin confirms that total body iron stores do not have strong predictive value with respect to the presence of cardiac iron. Anyway, when CMR is unavailable, serum ferritin ≥2000 ng/mL and LIC ≥14 mg/g/dw predict presence of cardiac iron overload in children.

Previously, myocardial fibrosis was demonstrated as a relative common finding (>20%) in Italian TM adults, and now it appears not rare also in TM children. Extensive fibrosis replacement was shown in previous autopic studies, but little contemporary data investigates the role of myocardial fibrosis in the development of cardiac disease in TM. In adult TM population, myocardial fibrosis has been shown to be correlated with age, HCV infection, and diabetes mellitus, but no relationship has been found with MIO and LIC. Our results suggest that in TM children, cardiac iron overload is one of the main determinants of myocardial fibrosis (Figure 5), which could predispose to heart diseases. In fact, the stigma of negative cardiac remodeling are significantly more represented in TM children with myocardial fibrosis (Table 4). As our cohort is a young cohort free of complications (diabetes mellitus or HCV infection), it has been possible to find a significant link between heart iron and replacement myocardial fibrosis. However, the association between myocardial fibrosis and a negative cardiac remodeling persisted also after the correction for global heart T2* values. This datum seems to suggest that when

### Table 3. Clinical and Instrumental Findings in Group A With No Myocardial Iron Overload (MIO), in Group B With Heterogeneous MIO and Global Heart T2* Value ≥20 ms, in Group C With Heterogeneous MIO and Global Heart T2* Value <20 ms, and in Group D With Homogeneous MIO

<table>
<thead>
<tr>
<th>Group</th>
<th>Age, y (N=40)</th>
<th>Hemoglobin pretransfusion, g/dL</th>
<th>Chelation starting age, y</th>
<th>Serum ferritin, ng/L</th>
<th>ALT, U/L</th>
<th>AST, U/L</th>
<th>MRI LIC, mg/g/dw</th>
<th>Mid septum T2*, ms</th>
<th>LVEDVI, mL/m²</th>
<th>LV mass index, g/m²</th>
<th>LVEF, %</th>
<th>RVESVI, mL/m²</th>
<th>RVEDVI, mL/m²</th>
<th>RVEF, %</th>
<th>Cardiac output, L/min</th>
<th>LVESVI, mL/m²</th>
<th>LV mass index, g/m²</th>
<th>LVEF, %</th>
<th>RVESVI, mL/m²</th>
<th>RVEDVI, mL/m²</th>
<th>RVEF, %</th>
<th>Cardiac output, L/min</th>
<th>LVESVI, mL/m²</th>
<th>LV mass index, g/m²</th>
<th>LVEF, %</th>
<th>RVESVI, mL/m²</th>
<th>RVEDVI, mL/m²</th>
<th>RVEF, %</th>
<th>Cardiac output, L/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (N=40)</td>
<td>14.9 (1.3–16.2)</td>
<td>9.5 (9.2–9.8)</td>
<td>3.0 (2.0–4.0)</td>
<td>1459 (20–2151)</td>
<td>25.5 (15.3–33.5)</td>
<td>24.8 (18–30.0)</td>
<td>4.9 (2.9–8.7)</td>
<td>43.5 (39.0–46.8)</td>
<td>86.9±19.6</td>
<td>54.4±11.7</td>
<td>62.0 (57.3–64.0)</td>
<td>81.5±20.5</td>
<td>62.0±8.2</td>
<td>621±6.5</td>
<td>60.1±4.4</td>
<td>62.8±3.5</td>
<td>60.8±8.2</td>
<td>621±6.5</td>
<td>62.8±3.5</td>
<td>60.8±8.2</td>
<td>621±6.5</td>
<td>62.8±3.5</td>
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<td>621±6.5</td>
<td>62.8±3.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B (N=44)</td>
<td>12.9 (8.4–16.1)</td>
<td>9.7 (9.4–10.0)</td>
<td>3.0 (2.0–4.0)</td>
<td>1651 (1069–2594)</td>
<td>25.5 (12.3–38.0)</td>
<td>25.8 (19–35.3)</td>
<td>6.3 (2.8–12.2)</td>
<td>34.5 (28–42.0)</td>
<td>87.1±15.2</td>
<td>50.4±12.8</td>
<td>59.5 (50.5–61.4)</td>
<td>82.4±15.5</td>
<td>62.1±6.5</td>
<td>62.1±6.5</td>
<td>49.5±10.3</td>
<td>67.0±13.9</td>
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<td>Group C (N=13)</td>
<td>15.0 (12.6–16.0)</td>
<td>9.7 (9.5–9.9)</td>
<td>3.0 (1.8–4.5)</td>
<td>2453 (1898–4540)</td>
<td>48.0 (25.9–111.8)</td>
<td>37.0 (20.5–66.1)</td>
<td>18.3 (8.0–25.6)</td>
<td>18.0 (17.0–21.5)</td>
<td>85.2±13.9</td>
<td>49.5±10.3</td>
<td>59.5 (52.9–61.3)</td>
<td>35.0 (21.5–36.4)</td>
<td>31.0±13.5</td>
<td>31.0±13.5</td>
<td>49.5±10.3</td>
<td>67.0±13.9</td>
<td>5.6±8.2</td>
<td>62.1±6.5</td>
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<td>Group D (N=10)</td>
<td>14.3 (13.1–15.9)</td>
<td>9.6 (9.2–9.7)</td>
<td>2.0 (2.0–4.0)</td>
<td>2900 (1364–3981)</td>
<td>50.0 (31.8–97.5)</td>
<td>41.0 (27.5–70.5)</td>
<td>21.4 (12.9–28.3)</td>
<td>11.0 (8.0–14.3)</td>
<td>104.2±20.1</td>
<td>40.0 (34.8–46.0)</td>
<td>4.0 (3.6–5.0)</td>
<td>5.1 (4.8–71)</td>
<td>4.6 (3.9–5.9)</td>
<td>4.6 (3.9–5.9)</td>
<td>6.6±8.2</td>
<td>62.1±6.5</td>
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ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; LIC, liver iron concentration; LV, left ventricle; LVEDVI, left ventricular end-dyastolic volume index; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-systolic volume index; MRI, magnetic resonance imaging; RV, right ventricle; RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; and RVESVI, right ventricular end-systolic volume index.
the myocardial fibrosis appears, the risk of a negative cardiac remodeling is independent from the presence of iron. However, CMR LGE can be postponed until 13 years old unless HCV infection or cardiac disease is present.

In conclusion, this is the largest study about TM children using a multiparametric MRI approach. The data presented are indicative of high rate of liver iron overload at early age. TM children can also experience significant MIO with a global heart $T_2^*$ value <20 ms (21.4%) correlated with lower compliance and traditional markers of cardiac risk, such as serum ferritin $\geq 2000$ ng/mL and MRI LIC $\geq 14$ mg/g/dw. Specifically, a homogeneous pattern of MIO was associated with negative cardiac remodeling indexes and significantly higher LIC. Myocardial fibrosis is not a rare finding correlated with a negative cardiac remodeling, and iron overload is the main determinant in children.

MRI $T_2^*$ scanning should be recommended as early as feasible without sedation to tailor chelators. Conversely, LGE CMR is indicated in teenagers, particularly in those with cardiac iron.

**Acknowledgments**

We thank all the colleagues of the Myocardial Iron Overload in Thalassemia Network (https://miot.ftgm.it).

**Sources of Funding**

The Myocardial Iron Overload in Thalassemia project receives nonprofit support from industrial sponsorships (Chiesi Farmaceutici S.p.A. and ApoPharma Inc.).

![Figure 5. Global heart $T_2^*$ values in the fibrosis group and in the no-fibrosis group. The circles represent the mean values, whereas the bars are the SD.](image-url)
Disclosures
Dr A. Pepe received speaker’s honoraria from Chiesi, ApoPharma Inc., and Novartis. The other authors report no conflicts.

References


***CLINICAL PERSPECTIVE***

This multicenter study represents the largest report of pediatric thalassemia major patients undergoing magnetic resonance imaging within the myocardial iron overload (MIO) in thalassemia network using a multiparametric technique. Using this approach, a detectable cardiac damage can occur much earlier in pediatric patients. The iron burden is a time-dependent process, and there is a delay in cardiac iron uptake, although liver is primarily filled (77.6% of the patients). However, a consistent number of patients (21.4%) showed a significant MIO correlated with lower compliance to chelation therapy. Serum ferritin ≥2000 ng/mL and liver iron concentration ≥14 mg/g/dw were detected as the best threshold for predicting MIO. A homogeneous MIO was associated with a negative cardiac remodeling and significant higher liver iron concentration. This is the first study to describe late gadolinium enhancement in the pediatric thalassemia major population. Myocardial fibrosis was detected in a significant percentage of patients (15.8%, the youngest 13 years old), and it was correlated with negative cardiac remodeling. In this cohort relatively free of complications (as diabetes mellitus or HCV infection), MIO is one of the main determinants of myocardial fibrosis.
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Circ Cardiovasc Imaging. 2015;8:e003230
doi: 10.1161/CIRCIMAGING.115.003230
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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