No evidence for significant myocardial iron overload in genetic hemochromatosis and multitransfused patients

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Purpose

The aim of this study was to compare the heart and liver iron stores with the use of T2* magnetic resonance imaging in hereditary hemochromatosis and multitransfused patients.
Fig. 4: Iron levels were measured using Multiple-Gradient Echo T2* sequence. Axial images of the upper abdomen and short-axis T2 images of the heart and liver, and the equivalent T2*-map and R2*-map of a patient with Thalassemia major, showing normal intensity and T2* value of the interventricular septum (41 msec) and decreased intensity of the liver (7 msec) suggesting iron loading only in the liver.

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Methods and Materials

Patients

From December 2007 through September 2011, 326 consecutive patients entered the study. 142 polytransfunded patients (72 with thalassemia, 43 hemolytic anemias, and 27 with acquired anemias) and 115 with genetic hemochromatosis. MRI also was performed in 23 healthy volunteers and in 46 hyperferritinemias.

Four patients had evidence of hepatitis C infection.

The mean age was 48.55 +/- 19.5 yr (2-87yr), with a male to female ratio of 15:8.

Magnetic resonance imaging study

All MRI examinations were performed with a validated 1.5 T scanner (GE Signa EXCITE, Milwaukee, IL, USA, with appropriate cardiac software) using a gradient echo T2* MRI technique, using a dedicated eight-channel cardiac phased-array coil.

Each scan included cardiac and liver. Iron levels were measured using a 10-15 sec breath-hold multiple-gradient echo T2* sequence, cardiac gated (Fig. 1 on page 7) (1). The following parameters were used: TR 33-35 msec, flip angle 30°, 128 x 256 matrix, FOV 36 cm, sampling bandwidth of 125 kHz, SW 8-10 mm, 1 NEX, 8 echoes for the liver, and 16 echoes for the heart (TE 1.6-16, spacing 1.7-2 msec) with minimum TE being 1.6 msec or less, minimum echo spacing 1.7 msec (Fig. 2 on page 7) (2,3).

Average T2* values of the heart were estimated at selected regions of interest (ROI) located on SAO midventricular slices positioned between the base and the apex of the left ventricle at the cardiac septum (Fig. 3 on page 8) (4-6). Liver ROIs (at the same slice) were located at a homogenous area of subphrenic liver parenchyma without blood vessels (Fig. 4 on page 9). The average signal intensity of cardiac and liver ROIs in all images in the echo train were measured as a function of TE. T2* values were calculated by fitting the data to monoexponential decay curve using Functool research tools on the GE Advantage 4.5 workstation (Fig. 5 on page 10). The signal decay curve was visually assessed by a reader.

We also performed GRE sequences of the upper abdomen with a TR of 120 ms and with different TE « in phase » (4-21 ms) and two pulse angles (20°-90°) in order to get T1, proton density (PD) and T2 images. The selected TE must be "in-phase" (4,9,14 and 21) (Fig. 6 on page 11) (7).
Signal intensity measurements are done by means of ROIs (« Region Of Interest ») of usually about 1cm². We placed 3 ROIs on the right part of the liver avoiding artifacts, liver vessels, or heterogeneous areas, and 2 ROIs on the paraspinous muscles (right and left). These ROIs, plotted for each sequence, were placed on the same image in order to avoid global signal intensity variations between images (Fig. 7 on page 12) (8-11).

Myocardial T2* values <20 ms were indicative of iron overload, and this was considered severe when T2* was <10 ms (Fig. 8 on page 13) (12).

Hepatic iron overload was defined by MRI T2* values less than 6.3 ms and it was categorized as mild (6.3-2.7 ms), moderate (2.6-1.4 ms) or severe (< 1.4 ms). When we used signal intensity ratio model, values higher than 4 mg Fe per gram dry weight (mg/g) were indicative of iron overload, and it was categorized as mild (4-7 mg/g), moderate (7-14 mg/g) or severe (>14 mg/g) (Fig. 9 on page 14) (13,14).

**Serological study**

Haemogram, hepatic enzymes, trasferrin saturation and serum ferritin levels were determined by a standard commercial method and the measurement was made within one week before or after the MRI study.

**Cardiological study**

Cardiac function was evaluated in all patients clinically by electro and/or echocardiography. Patients were considered to have cardiac disease if they required active cardiac medication (with the exception of antihypertensive drugs or anti-arrhythmic prophylaxis) or had a left ventricular ejection fraction less than 50%.

A diagnosis of heart failure was made only if the patient complained of worsening dyspnea at rest or during exercise, and objective left ventricular dysfunction was present with an ejection fraction of less than 56%, and the caring clinician made the clinical diagnosis of heart failure. A diagnosis of arrhythmia was made only if the patient complained of palpitations, and arrhythmia.

**Statistical data analysis**

Data with normal distribution are expressed as mean±standard deviation and also percentages. Data with skewed distributions are given as median with a range. Linear
relationships between variables were investigated after logarithmic transformation of T2* values by linear regression analysis (least square method) using a $p$ value of 0.05 as the threshold for statistical significance. Spearman's rank correlation coefficient and Pearson's coefficient of correlation was used to assess the degree of association between myocardial T2* and liver iron concentration, transferrin saturation, serum ferritin, patient, disease, and treatment-related parameters. T2* values measured in healthy volunteers showed a normal distribution and are expressed with 95% reference ranges.
**Fig. 1**: Cardiac MRI, Gradient echo (T2*) imaging. Short-axis T2 images of the heart and liver with different TE showing normal intensity of the interventricular septum and decreased intensity of the liver suggesting iron loading only in the liver.

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Multiple GE T2* sequence

TR 33-35 msec
Flip angle 30°
128 x 256 matrix
FOV 36 cm,
Sampling bandwidth of 125 Hz
SW 8-10 mm
1 NEX
16 echoes for the heart
minimum TE 1.6 msec or less,
minimum echo spacing 1.7 msec

Fig. 2: Parameters. Multiple-gradient echo T2* sequence. A short-axis T2 image of the heart and liver, and the equivalent T2*-map of a patient with MDS, showing normal intensity and T2* value (37 msec) of the interventricular septum and decreased intensity of the liver suggesting iron loading only in the liver.

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Fig. 3: A short-axis T2 image of the heart (arrow) and liver, and the equivalent T2*-map, showing normal intensity and T2* value (64 msec) of the interventricular septum and decreased intensity T2* value of the liver suggesting iron loading only in the liver.

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Fig. 4: Iron levels were measured using Multiple-Gradient Echo T2* sequence. Axial images of the upper abdomen and short-axis T2 images of the heart and liver, and the equivalent T2*-map and R2*-map of a patient with Thalassemia major, showing normal intensity and T2* value of the interventricular septum (41 msec) and decreased intensity of the liver (7 msec) suggesting iron loading only in the liver.

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Fig. 5: Gradient echo T2* MRI technique. Cardiac iron overload were calculated using Functool research tools on the GE Advantage 4.5 workstation.

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Fig. 6: Using this type of sequences, the liver is usually hyperintense to the muscle. A liver hypointense to the muscle indicates a liver iron overload. Axial T2*-weighted GRE MR images show progressive darkening of the liver with increasing TE, which is suggestive of iron overload.

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Fig. 7: Quantification of hepatic iron deposition, Signal/intensity ratio method. Iron overload imaging of the upper portion of the abdomen. Axial T2*-weighted GRE MR images show progressive darkening of the liver with increasing TE, which is suggestive of iron overload.

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Fig. 8: A short-axis T2 image of the heart and liver, and the equivalent T2*-map of a patient with MDS, showing T2* value (21 msec) of the interventricular septum and decreased intensity of the liver suggesting severe iron loading in the liver.

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Fig. 9: Transverse MR images of the liver in four patients with different degrees of iron overload shown with various MR sequences.

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Results

We studied 326 subjects, 49 with thalassemia major (14.8%), 23 thalassemia intermedia (7.1%), 27 myelodysplastic syndrome (8.28%) 43 hemolytic anemias (13.19%), 115 genetic hemochromatosis (35.27%), 46 hyperferritinemas (14.11%) and 23 healthy volunteers (7.05%).

Around 6.5% politrasfunded patients received 2 Units per month, 19.8% 2-4 Units/m, 5.6% >4 Units/m. A total of 88 (26.1%) patients were maintained on iron chelation therapy following blood transfusion, 15.4% with Deferasirox and 10.7% Deferoxamina or both. 39.8% of hereditary hemochromatosis needed periodic phlebotomies.

The mean hemoglobin level was 9.0 g/dL. The mean serum ferritin, and TAT were 786.57 ng/mL, and 54.52% respectively.

40.2 % MRI showed no significant liver siderosis (<4 mg Fe/g dw), 21% Showed mild overload (4-7 mg Fe/g dw), 21.9 % had moderate (7-14 mg Fe/g dw), and 16.6 % demonstrated severe liver siderosis (>14 mg Fe/g dw) (Fig. 10 on page 18).

7.7% patients had iron deposition in the pancreas, all of them politransfused patients (Fig. 11 on page 18 ) and 4.8% (all of them hemolytic anemias) in the renal cortex (Fig. 12 on page 19 ). 29% of the patients had spleen iron deposition (Fig. 13 on page 20 ). A total of 29 (8.6%) politrasfunded patients were splenectomized.

None of the patients had evidence of cardiac iron overload (mean cardiac T2* = 44.24+-9.9 ms; range: 19-69 ms).The mean value in healthy volunteers are 51+-7.8 ms, 44.4+-9.2 ms in hyperferritinemas, 44.21+-10.1ms in politransfused patients and 42.6+-9.8 ms in hemochromatosis (Table 1 on page 21).

None of the patients had values less than 10 ms, 0.6% showed moderate overload (10-20 ms), they were 2 patients with myelodysplastic syndrome, 36.4% had mild (2.6-1.4 ms ) and 62.7% had no iron deposition (Fig. 14 on page 21, Table 2 on page 22). None had evidence of heart failure. No left ventricular dysfunction, neither supraventricular arrhythias were reported in our patients including heavily transfused patients (14-16).

There was also no statistically significant correlation between cardiac T2* values and any of the study variables. No direct correlation was found between trasferrin saturation, serum ferritin levels and T2* relaxation values, both in the liver and the heart as we show in Table 3 on page 23 (17).
The results of this study could be due to an optimal management and follow up of the patients, since we Know better iron overload pathology and we are able to detect and measure iron depositions. And also to an optimal designing and tailoring chelation therapy after trasfusions or due to plebotomys in hereditary hemochromatosis. Other mechanisms may also be involved, including potential genetic variations in function of cardiac iron transport channels (18,19). It is possible that in our subjects more transfusions are required to induce iron accumulation in the myocardium, or not if the follow up and treatment is appropriate.

Physicians have a pressing clinical need for quantitative means of measuring body storage iron that are noninvasive, safe, accurate, and readily available to improve the diagnosis and management of patients with iron overload. Accurate assessment of the body iron burden is essential for managing those pathologies and to manage the therapy to prevent iron toxicity while avoiding the adverse effects of excess chelator administration. And in hereditary forms of hemochromatosis, determination of the magnitude of body iron stores permits identification of individuals at risk of iron-induced organ damage that would benefit from phlebotomy therapy.

Therefore, cardiac MRI may not serve as a diagnostic tool to assess if and when iron chelation is indicated. While no evidence of cardiac iron deposition was found, the rationale for iron chelation therapy is supported by the presence of toxic iron species in their plasma to avoid malignance transformation and tissular damage.

It is very important to be familiarized with iron overload diseases and to work with a group composed of members (radiologists, hematologists, internal physicians and cardiologists) with varied but complimentary experiences, qualifications and skills that contribute to the achievement of the specific objetives.

Magnetic resonance imaging assessment of tissue iron is becoming increasingly important in the management of transfusional iron load because it is noninvasive, relatively widely available and offers a window into presymptomatic organ dysfunction. The techniques are highly reproducible within and across machines and have been chemically validated in the liver and the heart. These techniques will become the standard of care as industry begins to support the acquisition and postprocessing software (20).

The availability of T2* MR, and the existence of a specialized erithro-pathological group at our institution has had a significant impact on patient management and quality of life of those.
**Fig. 10:** Transverse MR images of the liver in four patients with different degrees of iron overload shown with various T2 GRE sequences. Percentages are shown.

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Fig. 11: Axial GRE T2*weighted MR images shows that the liver, spleen, and bone marrow demonstrate decreased signal intensity. The pancreas has low signal intensity. The abnormal low pancreatic signal intensity suggests that the amount of transfused iron has exceeded the storage capacity of the RE cells. We also show different levels of deposition as + mild, ++ moderate and +++ severe.

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**Fig. 12:** Intravascular hemolysis and iron deposition in the renal cortex. Axial GRE T2-weighted MR images shows that the renal cortex is hypointense, with lower signal intensity than that of the medulla, causing reversed corticomedullary differentiation. Coronal single-shot fast SE T2-weighted MR image shows the accentuated low signal intensity of the renal cortex. The coronal and axial FGRE images showing notably low signal intensity of the renal cortex. Note the medullary area is not affected by the iron deposition. Also we shown different iron levels as: + mild, ++ moderate and +++ severe. Note liver iron overload.

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Patients who receive multiple blood transfusions develop iron deposition in the RE cells of the liver, spleen, and bone marrow. Splenic iron has no known clinical relevance; the spleen has low signal intensity on T2-weighted images.

**Fig. 13:** The spleen has low signal intensity on T2-weighted images secondary to iron accumulation.

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**Table 1:** T2* MRI Values of Heart

<table>
<thead>
<tr>
<th>MYOCARDiUM ms</th>
<th>Minimum ms</th>
<th>Maximum ms</th>
<th>Mean ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy volunters</td>
<td>39</td>
<td>65</td>
<td>51.3+-7.8</td>
</tr>
<tr>
<td>Hyperferritinemia</td>
<td>25</td>
<td>67</td>
<td>44.4+-9.2</td>
</tr>
<tr>
<td>Posttransfusional</td>
<td>19</td>
<td>69</td>
<td>44.2+-10.1</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>22</td>
<td>66</td>
<td>42.6+-9.8</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>19</strong></td>
<td><strong>69</strong></td>
<td><strong>44.2+-9.9</strong></td>
</tr>
</tbody>
</table>

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Fig. 14: None of our patients had significant myocardial overload. We show the percentages of myocardial iron deposition. Short-axis T2 images of the heart and liver and the equivalent T2*-map of different patients with different iron overload levels. Discordance of liver and heart iron deposition.

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Table 2: Myocardial overload. Percentages and number of patients (between parentheses) base on pathology and different iron overload levels.

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Table 3: Spearman's rank correlation coefficient $\rho$ - non-parametric measure of statistical dependence between myocardial T2* and liver iron concentration, trasferrin saturation, and serum ferritin. There was also no statistically significant correlation between cardiac T2* values and any of the study variables.

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Conclusion

Our study confirms that none of the patients had evidence of cardiac iron overload, even in subjects with significant transfusion burden, or severe systemic and hepatic iron overload.

There were no statistically significant correlation between cardiac T2* values and liver iron concentration, serum ferritin, or any patient, disease, or treatment-related parameters.

An optimal follow-up of patients and a tailor-made chelation therapy or plebotomys leads to better results, with less iron accumulation.

Further research is required to reach a consensus and serve as clinical guidelines to diagnose and manage iron overloaded patients.
Fig. 15: No myocardial iron overload in our subjects, no correlation with cardiac T2* values and liver iron concentration, serum ferritin, or any patient, disease, or treatment-related parameters.

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**Fig. 16:** T2* MR gradient echo images that shows discordance of liver and heart iron deposition in a politrasfunded patient and in a hemochromatosis. No myocardial iron overload, liver, kidney and pancreatic shows iron accumulation.

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