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Running title: Cardiac MRI in males and females with thalassemia.

Key words: thalassemia, cardiac iron, MRI, T2*, sex

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Abstract

Background. It has been repeatedly reported that female patients with thalassemia major survive longer than males and that the difference is due to a lower rate of cardiac disease in females.

Design and Methods. We compared the cardiac iron load as measured by magnetic resonance imaging T2* in 776 patients (370 males) examined at the National Research Council as part of an Italian cooperative study. We also established normal left ventricular ejection fraction values for our population.

Results. Prevalence of cardiac disease was higher in males compared to females (105 males vs 69 females; p <0.0001). Cardiac T2* was significantly lower in patients with heart dysfunction (p <0.0001), but no difference was observed according to sex. Twenty males and 5 females had a history of cardiac arrhythmias. Their cardiac T2* was not significantly lower than that of patients without arrhythmias (24 ms vs 26 ms; p=0.381), nor was there a difference between sexes. Liver T2* was significantly lower in males and females with heart dysfunction compared to those without. Ferritin levels were higher in patients of both sexes with heart dysfunction without significant differences between males and females.

Conclusions. Males and females are at the same risk of accumulating iron in their hearts, but females tolerate iron toxicity better, possibly as an effect of reduced sensitivity to chronic oxidative stress.

Introduction

Survival of patients with thalassemia major has significantly improved in recent decades, due to regular transfusions and chelation therapy. This favorable trend continues, thanks to the introduction of new oral iron chelators and imaging methods, which allow better management of iron overload. However, complications are still frequent and cardiac disease remains the leading cause of death in these patients. It has been repeatedly reported that female patients have a better prognosis than males. All the studies have been concordant in documenting significantly better results for female than for male patients.1,2,3.

In a Greek study, women had 23% longer life expectancy than men1 and in a large report from Cyprus including the entire population born after 1974, a multivariate analysis demonstrated that women had less than half the risk of death compared to men.4 The difference in survival is mainly due to a lower prevalence of cardiac disease in females. Male patients were more likely to develop heart failure and arrhythmias than were female patients. An Italian cooperative study showed a highly significant association between sex and heart failure. In fact 71% of the patients with heart failure were males.2 It has been suggested that females have a better compliance than males, and therefore accumulate less iron in crucial organs like the heart and the liver. Such a hypothesis, however, is not confirmed by ferritin levels, which, in our series, were not significantly lower in females.
The aim of our retrospective study was to verify if the decreased prevalence of cardiac disease in females could be attributed to lesser iron accumulation in their hearts as measured by multislice multiecho T2* Magnetic Resonance Imaging (MRI) technique.

**Design and Methods**

The Myocardial Iron Overload in Thalassemia (MIOT) project is a network involving 57 Italian thalassemia centers and six Italian MRI sites where cardiac magnetic resonance (CMR) is performed using homogeneous, standardized and validated procedures. All centers are linked by a web-based network, configured to collect and share patients’ history, clinical and diagnostic data. At all six sites, CMR exams were performed using 1.5 T scanners. For the measurement of myocardial iron overload, we used a multislice multiecho T2* approach, as previously described. A T2* gradient–echo multiecho sequence was used for the measurement of liver iron overload. A single transverse slice through the liver was obtained at nine TEs in a single end-expiratory breath-hold. T2* image analysis was performed using a custom-written, previously validated software program (HIPPO MIOT®, IFC-CNR). The software was able to map the myocardial T2* distribution into a 16-segment LV model according to the American Heart Association/American College of Cardiology standardized myocardial segmentation. A T2* value > 20 ms was considered as a conservative cut off for all 16 segments, for the mid-ventricular septum and for the entire heart. The intra-observer, inter-observer and inter-study variability of the proposed methodology were previously assessed. The transferability of multislice multiecho T2* within the MIOT network has been previously validated.

Steady-state free procession cine images were acquired to assess ventricular function parameters (left ventricular volumes, mass and ejection fraction) quantitatively in a standard way. In brief, 9 to 14 breath-hold short-axis slices (depending on the LV size) from the atrioventricular ring to apex were acquired with a 8-mm slice thickness and a 0-mm gap. The images were analyzed using MASS software (Medis, Leiden, The Netherlands) by each site. Papillary muscles were included when measuring LV mass and excluded when measuring volumes. Thalassemia major patients undergo T2* MRI to quantify and monitor segmental and global myocardial iron overload and liver iron overload. The data collected in a specially prepared form include: age, sex, diagnosis of heart disease (in particular, heart dysfunction and arrhythmias documented by ECG and requiring medications), and mean yearly serum ferritin levels. Risk factors for heart disease (smoking, family history, hypertension, diabetes mellitus type 1 and 2, dyslipidemia, obesity) were also considered, since previous studies showed the presence of coronary artery disease in thalassemia major patients and, moreover, cardiac risk factors were reported to be significantly correlated with myocardial fibrosis.

We performed a retrospective review of the MRI results and of clinical data in thalassemia major patients having undergone at least one CMR examination at the time of the study. For patients who had undergone more than one MRI, the results of the first examination were considered in order to avoid the effect of intensive chelation started in some of patients found to have a low T2*. 
Thalassemia major patients with a normal myocardial T2* have different normal values for left ventricular ejection fraction (LVEF) compared to healthy individuals as demonstrated by Westwood et al. using the CMR tools software (Cardiovascular Imaging Solutions, London, UK). In order to avoid bias due to the use of different software, we defined our limit of normal for the LVEF. Among 776 thalassemia major patients present in the MIOT database having undergone at least one CMR examination at the time of the study, we selected 93 patients with no history of cardiac disease, normal electrocardiogram, no known risk factors, and T2* values >20 ms in all cardiac segments. Therefore, as far as it was possible to ascertain with conventional standardized non-invasive approaches, we included all thalassemia subjects with no evidence of cardiac disease. Since LV parameters can differ with age and gender, we divided the population into 3 groups of age (< 20 years, 20-30 years and > 30 years) differentiating male and female. The lower limit of normal for the LVEF within each category was defined as mean – 2 standard deviation (SD) (Table 1). Accordingly, in the present study heart dysfunction was defined as a LVEF lower than the identified thresholds and/or a history of heart failure requiring treatment.

**Patients**

All the patients were affected by thalassemia major and were on chronic transfusion regimen every 2 to 4 weeks to maintain a pretransfusional hemoglobin level greater than 95 g/L. All patients had been chelated with deferoxamine for the majority of their lives. At the time of the MRI examination 35% of the patients were on deferoxamine, 18% on deferasirox, and 22% on combination deferoxamine plus deferiprone and 5% on sequential deferoxamine-deferiprone. The study complied with the Declaration of Helsinki. All patients gave written informed consent to the protocol. The institutional review board approved this study.

**Statistical Analysis**

All data were analyzed using the SPSS version 13.0 statistical package. All continuous variables were described as mean ± SD. Categorical variables were expressed as frequencies and percentages. The coefficient of variation (CoV) was calculated as the ratio of the standard deviation (SD) of the half mean square of the differences between the repeated values, to the general mean, and expressed as percentage. Comparisons between groups were made by independent-samples t-test for continuous values with normal distribution. The Wilcoxon rank sum test was applied for continuous values with non-normal distribution (i.e. T2* data). For non-continuous variables, χ2 testing was performed. In all tests, a 2-tailed probability value of 0.05 was considered statistically significant.

**Results**

At the time of the study, 776 thalassemia major patients were present in the MIOT database having undergone at least one CMR examination. Three hundred and seventy (48%) were males and 406 (52%) females. 174 (22%) patients had a diagnosis of one or more cardiac problems, including heart dysfunction (66.6%), arrhythmias (14.4%), and both heart dysfunction and arrhythmias (19%).
The prevalence of cardiac disease (heart dysfunction and/or arrhythmias) was significantly higher in males than in females ($P<0.0001$). In fact, 105 males (28.4%) had active or prior and resolved cardiac disease as compared to 69 females (17%).

**Heart dysfunction**

The coefficient of variability among centers for the quantification of the LVEF in patients without cardiac iron or dysfunction was 6.3%, confirming the MIOT network a reliable system where cardiac function parameters were analyzed using reproducible procedures. We identified two groups of patients with heart dysfunction: patients with a history of clinically symptomatic heart failure requiring therapy with a normal LVEF at the time of the MRI (group 1) or patients with LVEF at the time of MRI below the thresholds identified in our study population with or without a history of symptomatic heart failure (group 2). When the two groups were considered together, there was a significantly higher percentage of males with heart dysfunction (23%) than females (16%) ($p=0.014$). The difference between sexes was statistically significant in the third decade of life. (Figure 1) Serum ferritin levels were higher in patients of both sexes with heart dysfunction but the difference was not statistically significant (1931 ± 1861 ng/ml vs 1588 ± 1456 ng/ml; $P=0.099$) and no significant differences between males and females were found (Table 2). Correlation between cardiac $R2^*$ and ferritin was statistically significant ($R= -0.359$, $P<0.0001$).

Global heart $T2^*$ values were significantly lower in both males and females with heart dysfunction (Table 2) compared to those without dysfunction, but no difference was observed according to sex (Figure 2). Correlation between LVEF and cardiac $R2^*$ was statistically significant ($R= -0.327$, $P<0.0001$). The percentage of patients with LVEF lower than the normal limits and a global heart $T2^* > 20$ ms was significantly higher in males (9%) than females (3%) ($P<0.0001$) (Figure 3). Within this subgroup of patients 38% showed a heterogeneous myocardial iron overload, 33% had myocardial fibrosis, 19% suffered from arrhythmias, but no differences were observed according to sex. Global heart $T2^*$ in group 1 was higher (23 ± 13 ms) than in group 2 (18 ± 14ms), although the difference did not reach statistical significance ($P=0.069$). In neither group there was a significant difference between sexes for global heart $T2^*$ values.

**Cardiac arrhythmias**

Twenty males and 5 females had a history of cardiac arrhythmias ($P=0.001$). Global heart $T2^*$ was not significantly lower in patients with arrhythmias compared to those without arrhythmias (24±14 ms vs. 26±13 ms; $P=0.381$), nor was there a significant difference between sexes (Figure 4).

**Cardiovascular risk factors**

Data on risk factors for heart disease were available for 726 (345 males, 381 females) of the 776 patients studied. 154 males and 183 females had at least one risk factor. There was no significant difference between sexes ($P=0.360$). Smoking was significantly more frequent among males than females (68 vs 40; $P= 0.001$), but there were no significant differences in LVEF in either males or females. In addition, the prevalence of
diabetes was significantly higher in patients with heart dysfunction (type 1: P=0.029 and
type 2: P=0.023), but the difference between sexes was not statistically significant
(P=0.263 and P=0.164).

**Chelation treatment**
The analysis of different chelation treatments did not demonstrate a significant difference
between patients with heart dysfunction and without heart dysfunction (P=0.604), nor
between sexes (P=0.46). In addition, there was no difference in the reported compliance
to chelation therapy between males and females (P=0.518).

**Liver iron**
Liver iron was not correlated with heart iron. Liver T2* values were significantly lower in
both males and females with heart dysfunction compared to those without dysfunction but
no difference was observed according to sex.

**Discussion**
Data from a large cohort of thalassemia major patients supports an association between
gender specific differences in survival with a lower prevalence of cardiac disease in
females.2

**MRI Results**
We compared the cardiac and hepatic iron overload in males and females by means of
T2* MRI. Our method measures the global heart iron instead of the more widely used T2*
value in the ventricular septum.11 This can be advantageous in that the distribution of iron
in the heart is heterogeneous.7,8

**Comparison between sexes**
Although the heart T2* in patients with heart dysfunction, both in group 1 or 2, was
significantly lower than in patients without this complication, there was no difference
between males and females, indicating that males and females are at the same risk of
accumulating iron in their hearts. The LVEF results can be subdivided in three zones:
>56%, considered normal, 50-56% considered mildly abnormal, but not necessarily
associated with iron, especially in men, and < 50% considered grossly abnormal and
strongly associated with iron, having a T2* generally <10. A few women were in the mildly
abnormal range and were not associated with iron, while the gender difference was largest
in the intermediate zone. In contrast, men and women showed fairly similar behavior in the
presence of severe iron overload.
The values of T2* that we observed in our patients with heart dysfunction were higher than
data reported in the literature11, where values below 20 ms were considered pathological
and associated with heart failure and arrhythmias.16 However, it can be hypothesized that
our patients in group 1 had been chelated intensively after the acute episode of heart
failure, therefore increasing their T2*, although we did not calculate the time relationship
between the past heart failure episode and the current T2* value, so no firm conclusions
can be drawn. In patients in group 2 the T2* values were lower, but still higher than expected. This finding needs to be studied further. In our large cohort of thalassemia major patients we confirmed the presence of patients with abnormal heart function and global heart T2* > 20 ms, previously reported in a small number of patients. Several explanation could account for this finding, in contrast to previous reports stressing the absence of LV dysfunction with a normal T2* value in the mid ventricular septum. First of all, our well treated study population with good compliance showed a significantly lower body iron overload and myocardial iron overload than the study population reported by Anderson LJ et al. (serum ferritin 1652 ± 1543 ng/mL versus 2095 ± 1559, P < 0.0001). Second, although iron could be removed by chelation treatment, the induced heart damage could be progressive and not totally reversible. Moreover, heart damage in thalassemia does not result only from iron overload (i.e. a consistent percentage of our chronically anemic patients showed myocardial fibrosis or arrhythmias). Nutritional deficiencies, including selenium, thiamine, vitamin D and carnitine and thyroid disease have been reported to cause heart dysfunction in thalassemia. Finally, genetically determined variables could affect susceptibility to heart dysfunction in presence of iron overload and a consistent percentage of our patients showed a heterogeneous myocardial iron burden. Global heart T2* was not significantly lower in patients suffering from arrhythmias. The lack of correlation between heart T2* and arrhythmias seems to confirm a lower magnitude of cardiac iron overload to cause arrhythmias, as previously suggested. Two children (both female) below age 10 years showed LVEF of 56% barely below the limit of the normal (57%) without heart hemosiderosis. One of the two had recently immigrated from a South American country where transfusion was erratic and no chelation was available. Also worth commenting are three patients with severe reduction of the EF, but no excessive iron overload (Figure 3). It is likely that they had severe iron deposition that had subsequently been cleared by intensive chelation. All the patients had been chelated with deferoxamine for the majority of their lives, and some had later been switched to oral chelators alone or in combination, without significant difference in compliance between males and females. The evaluation of compliance over several years, however, is always approximated, as it is based on the personal trusting relationship between physician and patient, supported by a few objective data, like the number of vials or of pills distributed by the pharmacy or checking for sites of injection. Only in the course of short-term studies it is possible to measure with some accuracy the actual adherence to therapy.

Proposed explanations
A better life expectancy in females has also been observed in sickle cell anemia and is the rule in the majority of the world populations. In the most recent update of life expectancy and mortality in 2002-2004 in the modern European Union, life expectancy was 75.1 years for men and 81.3 years for women. It has been proposed that female longevity is more essential, from a Darwinian perspective, than the prolonged survival of males. But what are the physiological mechanisms set in place to obtain this result?
The common explanation that testosterone increases deaths at a young age because it increases aggression and competitiveness does not apply, in general, to the thalassemia population where the gender gap in life expectancy is strictly correlated with the presence of heart disease. Similarly, the opposite effects of testosterone and estrogens in regulating the blood levels of LDL and HDL cholesterol, are not a good explanation for our patients who overall tend to have very low levels of total cholesterol. However, the gender difference in survival was present already in a survey performed in 1983, including patients born before 1970, when only a small proportion of patients had spontaneous puberty and very few were receiving hormonal substitutive therapy. In addition, it has been suggested that women survive longer because they have a slower metabolism rate almost from the moment of conception, when male embryos divide faster than female ones. The faster metabolic rate could make male cells more vulnerable to breakdown and therefore to disease and death. Several other hypotheses have been proposed, including more active female immune functioning, compensatory effects of the second X chromosome, reduction in the activity of growth hormone and the insulin-like growth factor 1 signaling cascade.

More interesting and to the point could be the more efficient antioxidant defenses available to females. Hydroxyl radicals notoriously implicated in vascular damage, especially in the presence of iron overload, are very damaging and ubiquitous. Their effects can be quenched by antioxidant enzymes in the mitochondria, like superoxide dismutase and glutathione peroxidase. A study comparing oxidative damage to DNA in males and females demonstrated significantly higher levels of modified DNA bases in males.

Conclusions
Our retrospective study showed that males and females with transfusion dependent thalassemia major are at the same risk of accumulating iron in their hearts, but females tolerate iron toxicity better, possibly as an effect of reduced sensitivity to chronic oxidative stress.

Authorship and Disclosures
All authors participated in the study design and read and approved the paper. MM, CBP, VC: analyzed and interpreted the data, wrote the report. AM, MCDA: provided statistical analysis and interpretation of data. AS, LP, EC, GV: provided patients, participated in the discussion of results, and reviewed the paper. ML, VP, AP: evaluated cardiac and hepatic iron of all patients, interpreted and discussed data.
The authors reported no potential conflicts of interest.
References


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undertaken on behalf of the Italian Society for Thalassemia and Hemoglobinopathies (SITE).

Tables

Table 1. LVEF thresholds calculated as a function of age and sex in patients with no history of cardiac disease, normal electrocardiogram, no known risk factors and T2* values >20 ms in all cardiac segments.

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<th>&gt;30 years</th>
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<td>62.4±3.1</td>
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<td>56</td>
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<tr>
<td></td>
<td>threshold</td>
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<td>56</td>
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<td>Without heart dysfunction</td>
<td>With heart dysfunction</td>
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<td>--------------------------------</td>
<td>----------------------------</td>
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</tr>
<tr>
<td></td>
<td>Males (N=285)</td>
<td>Females (N=342)</td>
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<td>Age (years)</td>
<td>29.1±9.1</td>
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<td>Hb pre-transfusion (g/dL)</td>
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<td>1611±1504</td>
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<td>AST (u/L)</td>
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<td>RV EF (%)</td>
<td>60.6±6.2</td>
<td>63.5±6.7</td>
<td>&lt;0.0001</td>
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Legends to figures

Figure 1. Percentage of heart dysfunction in males and females according to age. The difference between sexes was statistically significant in the third decade. (M, male; F, females). Two female patients <10 yrs of age had LVEF below normal (see text).

Figure 2. Global heart T2* values in patients with and without heart dysfunction.

Figure 3. Relationships between global heart T2* values and left ventricular ejection fraction (LVEF) in males (A) and in females (B). The broken lines represent the normal reference ranges for global heart T2* and LVEF.

Figure 4. Global heart T2* in patients with and without arrhythmias.
Figure 1
Figure 2
Figure 3
Figure 4