



Absence of cardiac siderosis despite hepatic iron overload in Italian patients with thalassemia intermedia: an MRI T2* study

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Abstract: Cardiac involvement in patients with thalassemia intermedia (TI) is characterized by a high-output state and pulmonary hypertension, with systolic left ventricle function usually being preserved. Myocardial iron overload in patients with TI has not been extensively studied. We conducted a cross-sectional study of 49 Italian patients with TI. Patient charts were reviewed and data collected for transfusion and iron chelation history, status of the spleen, and comorbid illnesses or infections. Blood samples were obtained for assessment of hemoglobin, serum ferritin and liver enzyme levels. Doppler echocardiography was done for all patients. Cardiac and hepatic iron levels were measured by MRI T2*. The mean age was 40.5 ± 8.3 years, with a male to female ratio of 29:20. A total of 34 (69.4%) patients were splenectomized and 4 patients had evidence of hepatitis C infection. Around 45% of patients were transfusion naïve while the rest received infrequent (47%) or regular (8%) transfusions. A total of 31 (63.3%) patients were maintained on iron chelation therapy. None of the patients had evidence of heart failure. Mean serum ferritin and liver iron concentration were 1060.2 ng/ml and 8.2 mg Fe/g dry weight; respectively. None of the patients had evidence of cardiac iron overload (mean cardiac T2* = 38.7 ± 11.0 ms). There were no statistically significant correlation between cardiac T2* values and liver iron concentration; serum ferritin; or any patient, disease or treatment related parameters. Patients with TI show absence of cardiac iron overload even if hepatic iron accumulation is significant.

Response to Reviewers: RESPONSE TO REVIEWER COMMENTS

"This is a well-written report on the absence of cardiac iron overload in patients with TI. Since it is a cross-sectional analysis, it is important to exclude any selection procedures whenever possible. Thus, the question which has to be answered by the authors is how patients were selected. This has to be carefully described in the methods section. The reader would like to know how many patients were eligible and how many were actually studied and why selection occurred."

We thank the reviewer for this note, the selection criteria was only based on age. In this study we only recruited adult (≥ 18 years) patients, to avoid the need for sedation to complete the MRI in children. So, out of 124 patients registered at the center, 49 were adults and hence all included in the study. This is now clearly explained in the first paragraph of the METHODS section.

"Another question to be answered is the dosage of iron chelators used."

Patients who were maintained on subcutaneous deferoxamine regimens received 20-60 mg/kg for 12 hours a day, three days a week; while patients who received the oral iron chelator deferasirox received 15-20 mg/kg/day. This was added to the first paragraph of the RESULTS section.

ORIGINAL ARTICLE

Absence of cardiac siderosis despite hepatic iron overload in Italian patients with
thalassemia intermedia: an MRI T2* study

Short title: cardiac iron in thalassemia intermedia

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Abstract

Cardiac involvement in patients with thalassemia intermedia (TI) is characterized by a high-output state and pulmonary hypertension, with systolic left ventricle function usually being preserved. Myocardial iron overload in patients with TI has not been extensively studied. We conducted a cross-sectional study of 49 Italian patients with TI. Patient charts were reviewed and data collected for transfusion and iron chelation history, status of the spleen, and comorbid illnesses or infections. Blood samples were obtained for assessment of hemoglobin, serum ferritin and liver enzyme levels. Doppler echocardiography was done for all patients. Cardiac and hepatic iron levels were measured by MRI T2*. The mean age was 40.5 ± 8.3 years, with a male to female ratio of 29:20. A total of 34 (69.4%) patients were splenectomized and 4 patients had evidence of hepatitis C infection. Around 45% of patients were transfusion naïve while the rest received infrequent (47%) or regular (8%) transfusions. A total of 31 (63.3%) patients were maintained on iron chelation therapy. None of the patients had evidence of heart failure. Mean serum ferritin and liver iron concentration were 1060.2 ng/ml and 8.2 mg Fe/g dry weight; respectively. None of the patients had evidence of cardiac iron overload (mean cardiac T2* = 38.7 ± 11.0 ms). There were no statistically significant correlation between cardiac T2* values and liver iron concentration; serum ferritin; or any patient, disease or treatment related parameters. Patients with TI show absence of cardiac iron overload even if hepatic iron accumulation is significant.

Keywords: thalassemia intermedia; iron overload; heart; liver; magnetic resonance imaging.

Introduction

In contrast to thalassemia major (TM), patients with thalassemia intermedia (TI) often have mild anemia that generally does not require regular blood transfusion therapy until later in life. However, TI patients remain at risk of the clinical sequelae of iron overload, primarily due to increased intestinal iron absorption and ineffective erythropoiesis [1]. Heart disease is the primary cause of death in TM, with myocardial iron loading observed in approximately two-thirds of patients receiving iron chelation therapy [2]. In TI, cardiac involvement is mainly characterized by a high-output state and pulmonary hypertension, with systolic left ventricle function usually being preserved [3, 4]. Myocardial iron overload in patients with TI has not been extensively studied; however, a recent report has shown no evidence of cardiac iron in a small group ($n = 20$) of patients [5]. The current study aims to further evaluate cardiac iron overload in a larger group of TI patients, and explore its correlation with liver iron concentration (LIC) and serum ferritin (SF) levels among other patient and disease characteristics.

Materials and methods

This was a cross-sectional study of ~~adult (≥ 18 years)~~ patients with TI treated at the Centro Anemie Congenite, Ospedale Maggiore Policlinico, IRCCS, University of Milan, Milan, Italy. All patients were diagnosed with TI based on criteria previously described [6, 7]. This study recruited adult patients only, to avoid the need for sedation to complete the magnetic resonance imaging (MRI) in children. Out of a cohort of 124 patients registered at the center, 49 adults (≥ 18 years) were identified. Patient charts were reviewed for data on patient's demographics (age and gender); splenectomy status; presence of comorbid illnesses or infections; and history of transfusion and iron chelation therapy. For transfusion status, patients were divided as follows: regularly transfused (2-4 times per year);

infrequently transfused (few transfusions received in the past); and transfusion naïve. Iron chelation therapy had to be administered for at least one year or else the patient was considered non-chelated. Written informed consent was provided by all patients and approval was obtained from the ethical committee at the center.

Laboratory tests

Blood samples were obtained for assessment of pre-transfusion hemoglobin (Hb), steady-state SF, and alanine transaminase (ALT) levels.

Echocardiography

Doppler echocardiography to assess left ventricular ejection fraction (LVEF) was done.

Magnetic resonance imaging

Cardiac iron levels were measured by MRI T2*. Patients were scanned with MRI 1.5 T Magnetom Avanto Siemens using a multiecho breath-hold sequence [echo times (TE) 2.58-18.9 ms] as described by Wood JC [8]. In this study, cardiac T2* > 20 ms was considered normal. LIC was calculated from liver T2* images [TE 0.99-16.50 ms] according to the formula $[1/(T2^*/1000)] \times 0.0254 + 0.202$ [9]. All T2* images were analyzed using post-processing software (CMR Tools, Imperial College, London).

Statistical analysis

Data are expressed as means \pm standard deviation (SD) or percentages where appropriate. All univariate comparisons between iron overload parameters (SF, LIC, and cardiac T2*) and continuous variables (age, Hb, LVEF, ALT) were evaluated using Spearman's (r_s) correlation coefficients. Comparisons with categorical variables (gender, splenectomy, transfusion, and chelation status) were evaluated using the independent samples *t*-test and ANOVA test. A multivariate stepwise regression analysis was done to determine significant correlations. Linear regression analysis was performed to study correlations between SF, LIC, ALT and

cardiac $R2^*$ values ($R2^* = 1000/T2^*$). All P -values are two sided with the level of significance set at < 0.05 .

Results

Data from 49 patients were included in this analysis (Table 1). A total of four patients had evidence of hepatitis C virus (HCV) infection confirmed by PCR-RNA testing. Among patients who received iron chelation therapy, 29 (93.5%) were maintained on subcutaneous deferoxamine regimens (20-60 mg/kg for 12 hours a day, three days a week) while two (6.5%) received the oral iron chelator deferasirox ~~once-daily~~ (15-20 mg/kg/day). No patient had evidence of heart failure by modified Framingham criteria [10].

The mean \pm SD of SF levels and LIC were 1060.2 ± 1090.3 ng/ml (range: 165-6361 ng/ml) and 8.2 ± 6.0 mg Fe/g dry weight (dw) (range: 1.1-26.4 mg Fe/g dw); respectively. None of the patients had evidence of cardiac iron overload (mean cardiac $T2^* = 38.7 \pm 11.0$ ms; range: 22.4-82.4 ms). On linear regression analysis, there were no statistically significant correlations between cardiac $R2^*$ and LIC ($R^2 = 0.007$; $p = 0.569$; Fig. 1) or SF ($R^2 = 0.003$; $P = 0.716$). There was a statistically significant positive correlation between SF and LIC but with poor linearity ($R^2 = 0.435$; $P = < 0.001$).

SF levels were significantly higher in splenectomized, regularly transfused and chelated patients; and correlated positively with ALT levels (Table 2). On multivariate analysis only ALT levels retained correlation with SF levels ($P < 0.001$). Similarly, LIC values were only significantly positively correlated with ALT levels (Table 2). However, ALT levels did not rise linearly with SF ($R^2 = 0.371$) or LIC ($R^2 = 0.127$). There was no statistically significant correlation between cardiac $T2^*$ values and any of the study parameters (Table 2).

Of note, there was no statistically significant differences between HCV positive and negative patients with regards to SF ($P = 522$), LIC ($P = 603$), or cardiac $T2^*$ ($P = 534$); however,

HCV positive patients had higher mean ALT levels than HCV negative patients (58.8 vs. 34.1 IU/L; $P = 0.043$)

Discussion

Data from this cross-sectional study show absence of cardiac iron overload in patients with TI, despite significant hepatic iron accumulation (> 7 mg Fe/g dw), thus providing additional insight to aid our understanding of iron deposition in this patient group.

These data, which show cardiac T2* within the normal range in all patients, support other recent findings in which cardiac T2* was > 20 ms in 20 never or minimally transfused TI patients despite elevated LIC [5]. Furthermore, they are consistent with studies showing that patients with TI are generally less prone to the cardiac iron overload associated with morbidity and mortality than patients with TM [4]. However, they contrast with other reports indicating moderate cardiac iron overload in subgroups of TI patients [11, 12]. The varying results might be explained by differences in baseline characteristics (eg, previous transfusion history and co-pathology) between patient populations.

In TI, the combination of ineffective erythropoiesis and chronic anemia/hypoxia result in hepcidin suppression, increased intestinal iron absorption and increased release of recycled iron from the reticuloendothelial (RE) system (macrophages) to the hepatocytes [1, 13, 14]. This explains the relatively low levels of SF yet high LIC (regardless of transfusion history); and confirms that SF underestimates iron burden in TI with poor correlation with LIC [15, 16]. By contrast, in transfused TM patients iron is preferentially distributed to the RE system, stimulating SF synthesis and its release to the circulation [15]. The effect of this disparity in the pathophysiology of iron overload on cardiac sparing in TI patients, and the probability of eventual cardiac iron overload with continuous transfusion therapy merits consideration in long-term follow up studies.

1 In fact, the relationship between cardiac T2* values and iron balance is quite complicated
2 because the mechanisms and kinetics of cardiac iron uptake and clearance differ from the
3 liver [17, 18]. The lack of correlation between cardiac T2* and LIC or SF in the current study
4 is consistent with data from a previous study on TI patients in which the authors found no
5 correlation between cardiac T2* and SF values [5]. Data from animal models of iron overload
6 in TI also indicate early accumulation of iron in the liver, with accumulation of iron in the
7 heart occurring over longer periods [19]. Studies on patients with TM and sickle cell disease
8 (SCD), confirm that cardiac T2* values do not correlate with SF concentration and LIC in
9 cross sectional analysis, while longitudinal studies continue to imply a causal relationship
10 [12, 17, 18, 20-22]. Wood and Noetzli [17, 20], demonstrated a significant latency to cardiac
11 T2* changes, relative to liver accumulation, suggesting a long delay between poor iron
12 control and detectable cardiac iron deposition. Other MRI work suggests that a “critical” liver
13 saturation is necessary to achieve positive cardiac iron balance [23]. This may explain
14 absence of cardiac iron overload even in patients who had LIC > 15 mg Fe/g dw in this study.
15 In conclusion, in patients with TI who had or had not received previous transfusion therapy
16 we found no evidence of cardiac iron overload although hepatic iron accumulation was
17 significant. Further research is needed to better understand if (and when) detectable cardiac
18 iron deposition can occur in patients with TI. Data also confirm that SF levels do not
19 accurately reflect the level of iron overload. Thus, recommendations for the management of
20 patients with TI should include regular assessment of LIC via biopsy or non-invasive imaging
21 methods, with iron chelation therapy being initiated in patients with LIC levels indicating
22 liver iron overload.

23 **Conflict of Interest**

24 MDC and ATT are members of Novartis Speakers' Bureau. JCW received research funding
25 from Novartis Pharmaceuticals.

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Table 1 Patients' characteristics

Parameter	Value
Mean age \pm SD, years (range)	40.5 \pm 8.3 (23-64)
Male/Female	29/20
Splenectomized, n (%)	34 (69.4)
Transfusion status, n (%)	
<i>Naïve</i>	22 (44.9)
<i>Infrequent</i>	23 (46.9)
<i>Regular</i>	4 (8.2)
Chelation received, n (%)	31 (63.3)
Mean ALT \pm SD, IU/L (range)	36.2 \pm 23.5 (9-91)
Mean Hb \pm SD, g/dL (range)	8.8 \pm 1.5 (5.3-13.1)
Mean LVEF \pm SD, % (range)	65.8 \pm 4.9 (57-79)

ALT = alanine transaminase; Hb = hemoglobin; LVEF = left ventricular ejection fraction.

Table 2 Univariate analysis showing correlations between study variables and iron overload parameters

Variable	SF (ng/mL)	LIC (mg Fe/g dry weight)	Cardiac T2* (ms)
<i>Categorical^a</i>			
Gender			
Male (n = 29)	1132.9 ± 1285.9	7.6 ± 5.8	40.8 ± 11.8
Female (n = 20)	943 ± 685.3	9.2 ± 6.4	35.6 ± 9.3
<i>P</i> -value	0.567	0.375	0.107
Splenectomy			
Yes (n = 34)	1264.1 ± 1235.4	8.5 ± 5.9	40.2 ± 12.5
No (n = 15)	579.4 ± 308.2	7.7 ± 6.6	35.3 ± 5.9
<i>P</i> -value	0.048	0.691	0.157
Transfusion status			
Naïve (n = 22)	642.3 ± 685.3	6.3 ± 5.0	37.4 ± 5.9
Infrequent (n = 23)	1341.7 ± 1265.0	10.0 ± 6.7	41.1 ± 14.5
Regular (n = 4)	1826.3 ± 1191.0	9.1 ± 5.8	32.4 ± 6.7
<i>P</i> -value	0.044	0.115	0.270
Iron chelation			
Yes (n = 31)	1313.8 ± 1233.8	9.1 ± 6.5	38.9 ± 11.8
No (n = 18)	612.5 ± 570.0	7.7 ± 6.6	38.4 ± 10.0
<i>P</i> -value	0.033	0.220	0.895
<i>Continuous^b</i>			
Age (years)	0.2	-0.023	-0.196
<i>P</i> -value	0.178	0.878	0.177
Hb (g/dL)	-0.103	-0.129	0.003
<i>P</i> -value	0.489	0.377	0.986
ALT^c (IU/L)	0.600	0.421	-0.039
<i>P</i> -value	<0.001	0.004	0.801
LVEF (%)	0.109	-0.129	0.003
<i>P</i> -value	0.464	0.377	0.986

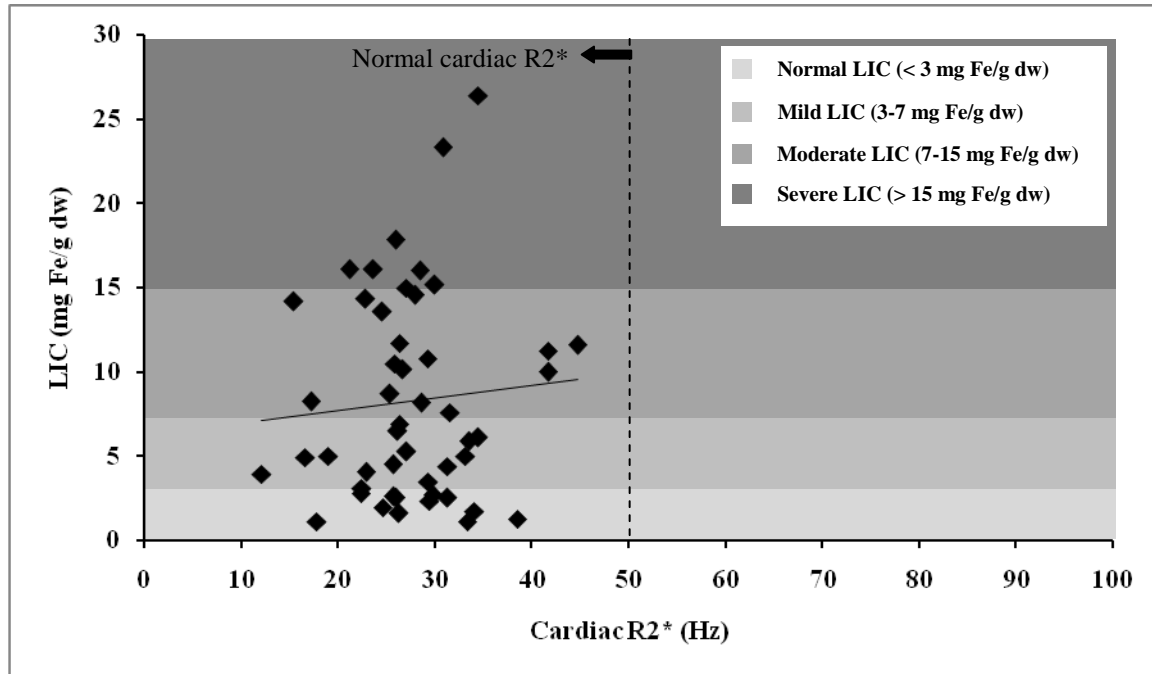
SF = serum ferritin; LIC = liver iron concentration; Hb = hemoglobin; ALT = alanine transaminase; LVEF = left ventricular ejection fraction.

^aStatistical correlation evaluated by the independent-samples *t*-test and ANOVA test; data presented as mean ± SD.

^bStatistical correlation evaluated by Spearman's Correlation; data presented as Spearman's correlation co-efficient (*r_s*).

^cExcluding the four patients with hepatitis C infection.

Fig. 1 Correlation between liver iron concentration (LIC) and cardiac R2* values



Conflict of interest

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Figure

