

CARDIOMYOPATHY

Myocardial Iron Loading in Patients with Thalassemia Major on Deferoxamine Chelation

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ABSTRACT

Background: Heart failure secondary to myocardial iron loading remains the leading cause of death in thalassemia major (TM). We used cardiovascular magnetic resonance (CMR) to assess the prevalence of myocardial iron overload and ventricular dysfunction in a large cohort of TM patients maintained on conventional chelation treatment with deferoxamine. **Methods:** A mobile CMR scanner was transported from London, UK, to Sardinia, Italy where 167 TM patients were assessed for myocardial iron loading, B-natriuretic peptide (BNP), and ferritin. In patients with myocardial iron loading CMR assessments of ventricular function were also made. **Results:** Myocardial iron loading ($T2^* < 20$ ms) was present in 108 (65%) patients, which was severe ($T2^* < 8$ ms) in 22 (13%). Impaired ($< 56\%$) left ventricular (LV) ejection fraction (EF) was present in 5%, 20% and 62% of patients with mild, moderate or severe iron loading. Increasing myocardial iron was related to impaired LVEF ($R_s = 0.57$, $p < 0.001$), weakly related to serum ferritin ($R_s = -0.34$, $p < 0.001$), and not related to liver iron ($R_s = 0.11$, $p = 0.26$). BNP was weakly related to myocardial iron ($R_s = -0.35$, $p < 0.001$) and was abnormal in only 5 patients. **Conclusions:** Myocardial siderosis was found in two-thirds of thalassemia major patients on maintenance deferoxamine treatment. This was combined with a high prevalence of impaired LV function, the severity of which tracked the severity of iron deposition. BNP was not useful to assess myocardial siderosis.

Keywords: $T2^*$, Magnetic Resonance, Thalassemia, Heart Failure, Chelation.

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INTRODUCTION

Beta-thalassemia major (TM) affects approximately 60,000 newborns/year worldwide (1). A mutation in the β -globin gene results in defective erythropoiesis leading to a progressive anemia, rendering the individual dependent upon life-long blood transfusions. Total body iron loading occurs mainly as a consequence of the catabolism of transfused red blood cells. With no effective physiological mechanism for iron excretion, tissue iron overload occurs. Cardiac siderosis can result in a progressive dilated cardiomyopathy, with heart failure accounting for up to 71% of all deaths in TM (2–4). Treatment with the iron chelator, deferoxamine, has been in use since the 1970s. Whilst this has dramatically improved morbidity and mortality, long term survival remains poor, with recent data from the UK thalassemia registry showing 50% of patients dead by the age of 35 (5, 6).

The high mortality results from a number of factors. First, administration of deferoxamine is uncomfortable and requires lengthy subcutaneous or intravenous infusions frequently leading to inadequate compliance (3, 6). Second, despite treatment with deferoxamine, patients may have cardiac iron loading (7). Third, the early detection of cardiac iron loading has proved problematic (8). It is highly desirable to identify those patients with significant cardiac iron loading prior to the development of LV dysfunction, which typically presents late in the disease process, because once symptomatic heart failure occurs, the mortality is very high (9, 10). These problems have encouraged considerable efforts to improve the detection of pre-clinical cardiomyopathy.

Cardiovascular magnetic resonance (CMR) is a new technology which has resulted in improved understanding of the cardiological problems in TM. It is established as the gold standard for quantifying left ventricular (LV) and right ventricular (RV) function, for which it has excellent interstudy reproducibility (11–13). CMR can also measure myocardial $T2^*$, which is a fundamental magnetic relaxation property that is highly sensitive to tissue iron overload. CMR $T2^*$ has been demonstrated to be a highly reproducible technique for the non-invasive assessment of myocardial and hepatic iron (14, 15). CMR therefore permits the simultaneous assessment of both myocardial iron loading and cardiac function making it well suited to the further understanding of iron and its cardiac consequences in patients with thalassaemia.

This study describes the prevalence of myocardial iron loading, and ventricular dysfunction in an adult thalassaemic population maintained on conventional deferoxamine chelation therapy.

METHODS

Overall study performance

This study was performed in collaboration between London, UK and Cagliari, Sardinia, Italy. A mobile CMR scanner (1.5 Tesla, Sonata, Siemens, Erlangen, Germany) based in London was transported to Cagliari to allow specialized CMR proto-

cols for patient assessment with experienced research staff. The study volunteers were recruited from 12 thalassemia centers in Sardinia as part of a screening process for a randomized controlled trial (16). All TM patients maintained on deferoxamine chelation, >18 years, and without contraindications to CMR were invited to participate.

Assessment of myocardial $T2^*$, serum ferritin, and BNP (Biosite Diagnostics Inc, San Diego, CA, USA) was performed in 167 patients with TM (males 75, females 92; aged 18–42, mean 30 ± 5.3 years). Those patients with cardiac iron loading (myocardial $T2^* < 20$ ms) (7) were invited for further CMR for assessment of ventricular function and liver $T2^*$ (15).

Cardiovascular magnetic resonance

Myocardial $T2^*$ was assessed using the single breath-hold multi-echo technique, and the entire CMR scan can be completed in 5 minutes as previously described (15). In brief, for the measurement of myocardial $T2^*$, a single 10 mm thick short axis mid-ventricular slice of the left ventricle was acquired at eight echo times (2.6–16.7 ms, which increased in 2.02 ms increments) with standard shimming in a single breath-hold. For analysis, a homogeneous, full-thickness region of interest was chosen in the left ventricular septum. The signal intensity of this region was measured for each image using in-house designed software (CMRtools, Cardiovascular Imaging Solutions, London, United Kingdom). Ventricular volumes were determined using steady state free precession cines, with contiguous short axis slices from base to apex as previously described (17). Ventricular volumes were analyzed using CMRtools. An LV ejection fraction (EF) of <56% was considered to represent impaired systolic function, as based upon locally derived normal values.

Statistical analysis

The baseline variables are presented with scatterplots. The significance of the relation between parameters was assessed using Spearman rank correlation in all cases because data was not normally distributed. Tests of proportions were performed with chi-square analysis. A p value of <0.05 was considered significant.

RESULTS

Prevalence of myocardial iron loading

Of the 167 subjects screened, 108 (65%) had cardiac iron loading ($T2^* < 20$ ms), of whom 22 (13%) had severe cardiac iron loading ($T2^* < 8$ ms). All 108 individuals with myocardial iron loading were invited for further CMR assessment, with 8 subjects declining for personal reasons.

$T2^$, ejection fraction and ferritin*

There was a significant relation between myocardial iron and LV EF ($R_s = 0.57$, $p < 0.001$, Fig. 1). Impaired left ventricular EF (<56%) was present in 5%, 20% and 62% of patients

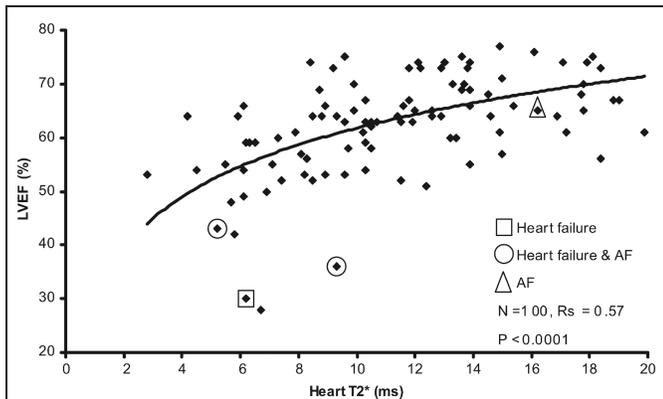


Figure 1. The relation between myocardial T2* and LV EF. There is a significant reduction in LV function with increasing myocardial siderosis (reduced T2*). Total number of subjects equals 100; of the 167 patients screened, all 108 with myocardial iron loading were invited for CMR evaluation of LV function, with 8 subjects declining. At the time of screening, 5 patients were hospitalized as a consequence of cardiac complications. Four of the 5 patients are highlighted on the graph (the fifth patient declined assessment of LV volumes and is not shown).

with mild, moderate and severe myocardial iron loading, respectively (T2* 12–20 ms, 8–12 ms, <8 ms, respectively; $p < 0.001$, Fig. 2). The likelihood of cardiac dysfunction was highest in subjects with severe myocardial iron loading (T2* < 8 ms; odds ratio =33.3, 95% CI 6.3–177 as compared with patients with T2* > 12 ms). Serum ferritin ranged from 200–7600 $\mu\text{g/L}$ (median 1640). There was no relation between myocardial iron and liver iron ($R_s = 0.11$, $p = 0.26$, Fig. 3). Of the 5 subjects with an LVEF of <45%, only 1 subject had severe hepatic iron loading (T2* < 1.4 ms), 3 had mild-moderate hepatic iron (T2* 1.4–6.7 ms), and 1 had no hepatic iron loading. Serum ferritin was negatively correlated with liver T2* ($R_s = -0.62$, $p < 0.001$, Fig. 4) and weakly correlated with myocardial T2* ($R_s = -0.34$, $p < 0.001$, Fig. 5).

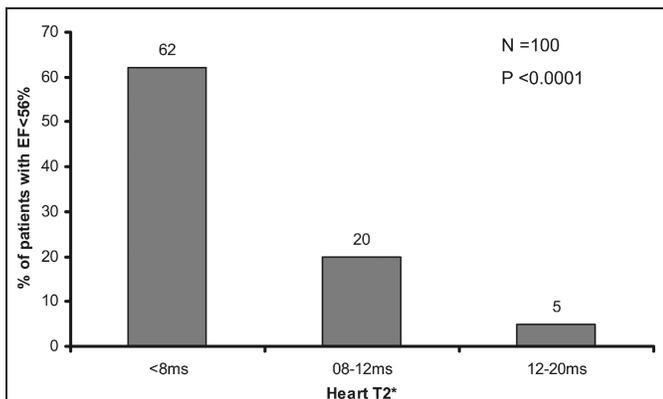


Figure 2. The prevalence of left ventricular dysfunction (EF < 56%) according to terciles of myocardial T2*. There is a substantially increased prevalence of dysfunction in the myocardial T2* < 8 ms group.

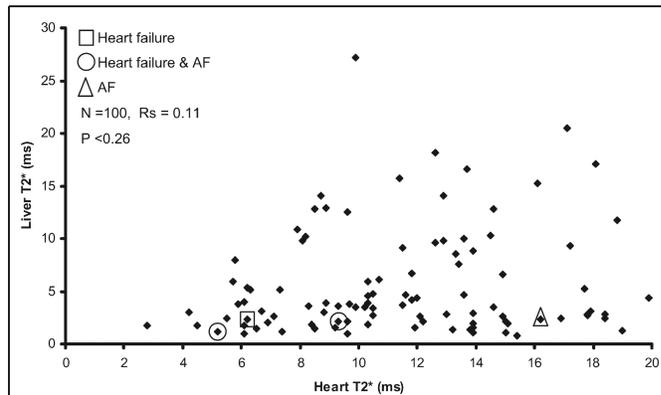


Figure 3. The relation between heart and liver T2*. There was no significant relation between heart and liver T2*, indicating that it is not possible to predict heart loading from the liver measurement. One hundred subjects are shown; of the 167 patients screened, the 108 with myocardial iron loading were invited for assessment of liver T2*, with 8 subjects declining.

Myocardial T2* and BNP

There was a weak inverse relation between plasma BNP and myocardial iron ($R_s = -0.35$, $p < 0.001$, Fig. 6). There were 5 patients with raised BNP all of whom had significant iron loading. As a predictor of myocardial iron loading, BNP had poor sensitivity (4.6%) with a negative predictive value of only 36%.

DISCUSSION

These results illustrate several important findings in a large adult TM population in a consistent protocol with state-of-the-art CMR techniques. The prevalence of myocardial iron overload (myocardial T2* < 20 ms) was 65% in TM patients on routine maintenance deferoxamine treatment. These subjects were believed to have a broad range of compliance with chelation

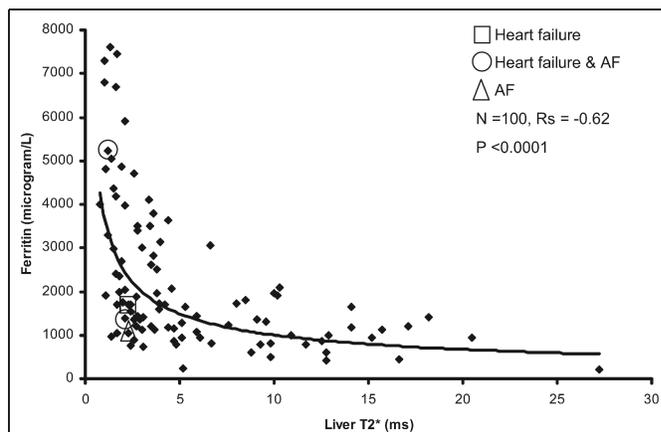


Figure 4. Relation between liver T2* and ferritin. There is a significant increase in liver iron, measured by liver T2*, associated with increasing ferritin. One hundred subjects shown (see Fig. 3 for explanation).

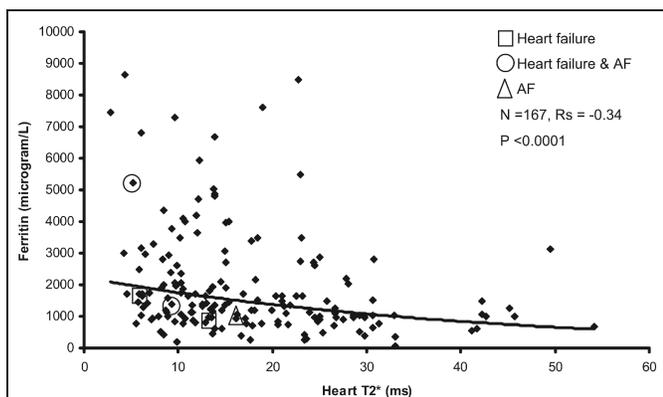


Figure 5. Relation between heart T2* and ferritin. Despite being significant, the relation is weak, with a wide scatter of values indicating that it is not reliable to predict heart iron loading from the ferritin measurement. All subjects screened (167) are shown.

(ferritin 200–7600 $\mu\text{g/L}$, median 1640) and as such are likely to be fairly representative of the TM population as a whole in Sardinia. A very similar prevalence of cardiac iron loading was also reported in a smaller UK population with broadly comparable demographics (7). Taken together, these results indicate that myocardial iron levels are inadequately controlled on conventional chelation management with deferoxamine, and that 1 in 7 patients (13%) would be considered at high risk of cardiac complications due to high levels of myocardial iron ($T2^* < 8$ ms).

The previously reported relation between myocardial siderosis and impaired LV EF has been confirmed in this study, suggesting that iron deposition in the myocardium is responsible for the cardiomyopathy. However, although this is true for the population as a whole, there is significant variation in EF between patients with similar levels of iron loading. Thus, a once-off EF measurement may be inadequate for assessing the cardiac risk resulting from myocardial siderosis. Although value has been shown for sequential LVEF monitoring (18), there was no sig-

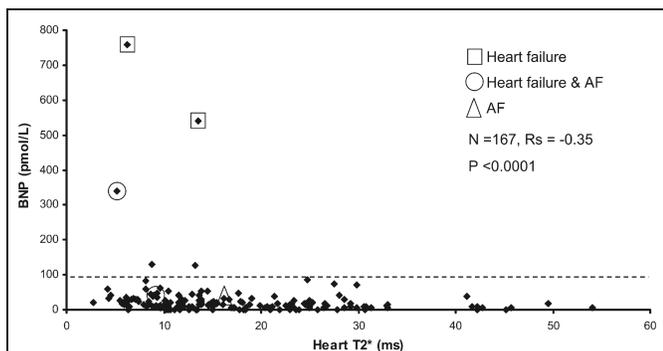


Figure 6. Relation between heart T2* and B-natriuretic peptide (BNP). Only 5 patients (3%) had an abnormal BNP (above 100 pmol/L, dotted line). The BNP, therefore, has limited value in predicting myocardial siderosis. The highlighted points represent the five patients hospitalized with cardiac complications. The 167 subjects shown represent the entire screened population.

nificant correlation between myocardial and liver iron. Thus, while liver biopsy has been regarded for some years as the gold standard in assessing body iron burden, the discordance we have reported between liver and myocardial iron indicates that the risk of heart complications cannot be managed solely from liver iron measurement. Similarly, the relation between serum ferritin and myocardial iron loading indicates that whilst a high ferritin may be bad, a low ferritin cannot be taken as reassuring.

Of significant interest is the new finding that BNP had very limited value in identifying myocardial siderosis. No previous studies at the time of writing have reported BNP measurements in thalassemia. Although the 5 patients with a raised BNP all had significant myocardial iron loading, its sensitivity of just 4.6% precludes its use as a screening test for myocardial siderosis. The statistically significant relation between T2* and high BNP was driven by the few patients with very high values, and in an asymptomatic group, it is likely that no significant or useful relation would be found. It remains to be seen however whether serial BNP measurements have any role in monitoring response to therapy in a given individual.

CONCLUSIONS

In this large cohort of patients maintained on conventional deferoxamine therapy, we have demonstrated a high prevalence of myocardial iron loading and a decline in ventricular function proportional to the severity of myocardial iron. These findings suggest that deferoxamine monotherapy may not adequately control myocardial siderosis and its adverse effects on ventricular function.

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