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Key Words:	THALASSAEMIA, IRON OVERLOAD, left ventricular ejection fraction (LVEF), Cardiac Magnetic Resonance Imaging (CMR)

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CARDIAC MAGNETIC RESONANCE IN TRANSFUSION DEPENDENT THALASSAEMIA:
ASSESSMENT OF IRON LOAD AND RELATION TO LEFT VENTRICULAR EJECTION FRACTION

Running Title: T2* and cardiac dysfunction in thalassaemia

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Summary

Cardiac Magnetic Resonance (CMR) has replaced all other surrogate measurements in the determination of transfusional cardiac iron overload in patients with thalassaemia major. We aimed to determine the diagnostic value of CMR T2* with respect to cardiac dysfunction (**CD**) as determined by CMR-derived left ventricular ejection fraction (LVEF). Cardiac T2* values and LVEF measured by CMR were recorded in 303 patients with thalassaemia major, at the time of their first CMR. T2* **was correlated with** LVEF (regression coefficient: 0.57, $p < 0.001$). The prevalence of **CD** was 32.9% in patients with $T2^* \leq 8$ ms, 12.5% in patients with $T2^* > 8$ ms and ≤ 14 ms and reduced to 9.1% in patients with T2* between 14-20 ms. As the probability of CD is progressively, and not **suddenly**, reduced with increasing values of T2*, CMR has a limited diagnostic value for cardiac dysfunction (ROC Analysis, AUC = 0.68). Patients with cardiac $T2^* \leq 8$ ms require careful and intensive management. This risk decreases with increasing values of T2* but even in mildly loaded patients the probability of impaired LVEF is not negligible.

Key Words: Thalassaemia, Cardiac Magnetic Resonance Imaging (CMR), Left ventricular ejection fraction (LVEF), Transfusion Iron Overload.

Introduction

Over the last ten years, Magnetic Resonance Imaging (MRI) has been increasingly used for the assessment of transfusional iron overload (Anderson, *et al* 2001, Berdoukas, *et al* 2009).

Cardiac T2* and left ventricular ejection fraction (LVEF), derived by Cardiac Magnetic Resonance (CMR), are the indices mainly used to evaluate cardiac iron load and function.

Nevertheless, the relation between these two parameters is, as yet, not completely understood. As the major cause of premature death in patients with thalassaemia remains iron related cardiac disease, timely intervention is of vital importance (Borgna-Pignatti, *et al* 2004, Ladis, *et al* 2005). **To date there is only one large prospective study on the role of cardiac T2*, as a prognostic factor of cardiac failure (Kirk, *et al* 2009). However, studies showing the distribution of CMR-derived LVEF in thalassaemia major patients are sparse.**

As there is increasing access to CMR-derived LVEF, such information comparing it to cardiac T2* may be indispensable in implementing the best therapeutic iron chelation approach. In this single institution study we evaluated the distribution of CMR-derived LVEF in thalassaemia major patients as well as the relation of cardiac T2* to CD.

Patients and Methods

In this cross sectional study, we have retrospectively recorded the results of the first-ever CMR (T2* values and LVEF) performed in patients with thalassaemia major, who have been followed in our unit. The clinical management of these patients includes regular blood transfusions at 14-21 day intervals and chelation therapy. Pre-transfusion haemoglobin (Hb)

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3 levels are maintained above 95g/l. Chelation regimes include **deferoxamine**, deferiprone,
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6 combination of **deferoxamine** and deferiprone and deferasirox.
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9 Patients under the age of 18 were excluded from the analysis. There were no patients with
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11 congenital heart defects. The Ethics Committee of the hospital approved permission for
12
13 medical review, waiver of informed consent and anonymous publication of data according to
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15 the Declaration of Helsinki.
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20 Magnetic resonance studies were performed using a cardiac-dedicated 1.5 Tesla magnet
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22 (Signa CVI, GE, Milwaukee, USA) with 40 mT/m gradients and appropriate cardiac software.
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24 For cardiac T2* determination a single breath multi-echo fast gradient-echo sequence was
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26 used with a fixed TR of 25.6 ms, with 10 echoes acquired in the range of 2.2-22.6 ms and an
27
28 inter-echo spacing of about 2.2 ms. Additional imaging parameters included 1 excitation,
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30 matrix of 160x256, bandwidth 62.5 KHz, slice thickness of 8 mm, ECG-gating and total
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32 acquisition time ranging from 15-20 msec. The calculation of T2* was made off line by an
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34 exponential least-squares fit of the multi-echo signal intensity data (SI) versus echo time (TE),
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36 with the use of a PC and standard fitting programs (GRAFIT or SigmaPlot 2001).
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44 Ejection fractions were calculated at a separate workstation (Windows Advantage 4.3, GE,
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46 Milwaukee, USA) and GE proprietary software (MASS 6). A FIESTA multi-phase sequence was
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48 used in the 2-chamber and 4-chamber long axis views (mid slice) and in the short axis view
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50 (10-12 multi-phase slices). No statistically significant differences were found for the LVEF
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52 calculated in the short (one multi-phase mid slice) and long axis (multi slice, multi-phase)
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54 views.
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3 In order to establish LVEF reference limits for thalassaemia major patients without cardiac
4 iron overload, we assessed the distribution of LVEF in patients with $T2^* > 20$ ms, which is
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6 currently considered, **arbitrarily**, the lower limit of the normal values (Anderson, *et al* 2001).
7
8 Cardiac dysfunction (CD) was defined as LVEF below $-1.96 \times SD$ from the mean of the
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10 population without cardiac iron overload. Subsequently, the relation between LVEF and $T2^*$,
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12 in those patients with $T2^* \leq 20$ ms, was evaluated. In addition, we assessed the percentage of
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14 patients with cardiac dysfunction, in each group of cardiac iron load according to their $T2^*$,
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16 namely $T2^* \leq 8$ (severe iron load), >8 and ≤ 14 (moderate iron load), >14 and ≤ 20 (mild iron
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18 load). Finally, the ability of $T2^*$ to discriminate between patients with and without cardiac
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20 dysfunction (among those with cardiac iron overload) was also evaluated.
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36 Statistical analysis

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39 Continuous variables are presented as mean \pm standard deviation (SD), while categorical
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41 variables are described by absolute (n) and relative frequencies (%). The reference range of
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43 LVEF in the cardiac iron-free patients ($T2^* > 20$ ms) was determined by the mean- $1.96 \times (SD)$
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45 which corresponds to the lower 2.5% of subjects in that population. Means were compared
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47 by Student t- test or analysis of variance (ANOVA, applying the Bonferroni correction for
48
49 multiple comparisons) in cases of more than two groups, while percentages were compared
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51 by Fisher's exact test. Correlations between continuous variables were assessed by
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53 Pearson's coefficient (r). Linear regression analysis, reporting β coefficients and p-values, was
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55 used to evaluate the effect of different factors on LVEF. The relative risk of having CD
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3 between the three groups defined by T2* was estimated by logistic regression analysis.
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5 Results are presented as odds ratios (OR) and p-values. The probabilities of having CD for
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7 every distinct value of T2* were also estimated by logistic regression analysis. Finally,
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9 receiver operating characteristic analysis (ROC) was used to evaluate T2*'s ability to
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11 discriminate between CD and CD-free patients. **The ROC analysis allows the evaluation of**
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13 **T2* in distinguishing between CD and non-CD patients characterized according to the LVEF.**
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15 **The measure of accurate classification by T2* is the area under the ROC curve (AUC). The**
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17 **results for AUC lie between 1 (perfect classification) and 0.5 (of information, which is**
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19 **equivalent to classifying individuals by chance). Confidence intervals (95% c.i) are provided**
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21 **along with the estimation of AUC. Data were analyzed using Stata 11.2 statistical software**
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23 **(Stata Corporation, College Station, Texas, USA).**
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34 Results

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37 A total of 303 patients (48.2% males) with a mean age of 29.4 ± 5.6 years were included in
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39 the analysis. **Figure 1 shows the relationship of LVEF to T2*.**
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44 According to the >20 ms threshold, 128 patients (46.9% males) were cardiac iron-free at the
45
46 time of their first CMR. The mean value of LVEF in that group was $67.8 \pm 5.3\%$. Cardiac iron-
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48 free males had lower LVEF compared to females (66.7 ± 5.1 vs 68.8 ± 5.3 , respectively,
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50 $p=0.026$). The lower limit for LVEF in cardiac iron-free patients was 56.7% for males and
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52 58.4% for females, thus we set different lower LVEF limits according to gender. This finding of
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54 small gender-related differences is in accord with a previous report, which has also shown
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56 that women with thalassaemia major exhibit higher levels of LVEF (Westwood, *et al* 2007). In
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3 **the 128 cardiac iron free patients**, age and T2* values did not affect LVEF as assessed by
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6 Pearson's r ($r=0.08$, $p=0.3$ and $r=-0.06$, $p=0.6$, respectively).
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10 In the patients with cardiac iron overload ($T2^* \leq 20$ ms), LVEF was significantly related to T2*
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12 values. Linear regression revealed that an increase of T2* by 1 ms increases the LVEF by
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14 0.57% ($\beta=0.57$, $p<0.001$), while in the same regression model age had also a borderline
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16 positive effect on LVEF ($\beta=0.21$, $p=0.060$). Gender was not statistically significant.
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20 **The mean values of LVEF and the ratio of patients with CD to those without CD differed**
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22 **significantly between the four groups of cardiac iron load as shown in table 1.** Logistic
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24 regression analysis showed that patients with severe cardiac iron load had **4.9 and 3.7** times
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26 higher probability of exhibiting CD compared to mild and moderate cardiac iron load,
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28 respectively (**OR=4.8**, **p=0.008** and **OR=3.7**, **p=0.005**, respectively, results adjusted for age).
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32 The odds of having CD between the mild and moderate iron load group did not differ
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34 significantly.
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38 Compared to the non-loaded population ($T2^*>20$ ms) patients with $T2^*\leq 8$ ms were **13.0**
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40 times more likely to have impaired LVEF (**OR=13.0**, $p<0.001$). The respective relative risks for
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42 those with moderate (8-14 ms) and mild (14-20 ms) iron overload were 4.3 (OR=4.2,
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44 $p=0.014$) and 3 (OR=3, $p=0.1$).
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50 With respect to the capability of T2* to discriminate between CD and CD-free patients
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52 among those with cardiac iron overload, the ROC analysis estimated an area under the curve
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54 equal to 0.68 (figure 2, 95% c.i. 0.58-0.77). At T2* cut-off values of 14, 10 and 8 ms, the
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56 percentages for sensitivity/specificity were 88.6/27.9, 77.1/50.7 and 65.7/67.1 %
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3 respectively. The variation of the probability of CD at various levels of T2* is demonstrated in
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6 figure 3.
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10 11 12 Discussion

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16 This analysis confirms that the risk of cardiac dysfunction steadily increases with the greater
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18 deposition of iron as determined by CMR. It concurs with the recently published, prospective
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20 study, from London, in which patients with excessive cardiac iron had a marked increase in
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22 the risk of developing cardiac failure (Kirk, *et al* 2009). Previous, smaller studies have also
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24 shown a strong correlation between cardiac T2* and CMR-derived LVEF in thalassaemic
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26 patients (Anderson, *et al* 2001, Patton, *et al* 2009).
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32 Our evaluation was based on a single time point in a patient's life and indicates that
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34 undoubtedly there is a relationship between the degree of cardiac iron load and the cardiac
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36 status at a particular point in time. For those patients with a T2* <8ms the probability of
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38 having cardiac dysfunction is 32.9% and is **13.0** times more likely than in those with T2* >
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40 20ms. This is also demonstrated by the probabilities estimated by the regression analysis.
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42 From 20 ms to 8ms there is an increase in risk from 5.7% to 21.0%. It is apparent that the risk
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44 of CD rises in a steep fashion, 5.7% to 11.3% as the T2* decreases from 20 to 14 ms and
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46 continues to rise, from 9.4% to 21.0%, as the T2* decreases further (from 14ms to 8ms).
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49 Below 8ms the risk reaches its maximum of approximately 35%. This gradual increase of the
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51 risk throughout the range of abnormal T2* values is in contrast with the results of the
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53 prospective study by Kirk *et al* (Kirk, *et al* 2009) who identified 10 ms as the threshold above
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55 which the risk of heart failure drops rapidly and that is practically minimized. Our results
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3 indicate that a non-negligible risk exists even for values proximal to the lower normal level
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6 of 20 ms. Another observational study (Patton, *et al* 2009), also, identified that 50% of
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8 patients with $T2^* > 10\text{ms}$ had $\text{LVEF} < 58\%$.
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11 This difference could be attributed to the different outcome assessed by Kirk *et al*. An
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13 abnormally low LVEF may precede clinically evident heart failure for long periods of time.
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15 Therefore, the possibility that a proportion of the patients with $T2^* > 10\text{ms}$ may have
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17 impaired LVEF in the absence of heart failure cannot be excluded. In addition, moderate
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19 cardiac iron overload may require substantially more time in order to cause the damage
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21 necessary for symptoms of heart failure to appear. The relatively short period of follow up (1
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23 year) in the above mentioned study may have not permitted this effect to become apparent.
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30 These reasons could, also, explain the high percentage (approximately 70%) of patients with
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32 $T2^* \leq 8\text{ms}$ who were CD-free. It may take a period of time before the excessive iron overload
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34 can result in clinically obvious cellular dysfunction or there may be a protective effect of
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36 ongoing chelation in the clearance of toxic free iron (Esposito, *et al* 2003, Maggio, *et al* 2009).
37
38 In addition, genetic factors and susceptibility to excess iron are likely to play a role
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41 (Economou-Petersen, *et al* 1998, Ferrara, *et al* 2001). However, as it is still possible and even
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43 likely that these patients could progress to cardiac dysfunction or even sudden cardiac death,
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45 it is essential that they are prescribed intensive chelation in order to clear cardiac iron.
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51 It is clear that the amount of cardiac iron load **is related to the prevalence of cardiac**
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53 **dysfunction at a particular point in time.** However, the exact level of iron load at which the
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55 risk of cardiac dysfunction is minimized cannot be identified by this analysis and as shown,
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57 this minimum level may vary according to the definition of cardiac dysfunction. In terms of
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59 impaired LVEF, our results indicate that even mildly loaded patients could benefit from a
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3 further reduction of their cardiac iron load. **As this is a cross sectional analysis it does not**
4 **provide prospective risk for the development of cardiac dysfunction.** As the probability of
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6 CD is progressively, and not rapidly, reduced with increasing values of T2* the ROC analysis
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8 showed that T2* has limited ability in predicting the risk of abnormal LVEF. In order to obtain
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10 a sensitivity > 90%, it would require a cut off value of T2* = 15ms. Such a cutoff would
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12 reduce specificity to a non-acceptable level (23%), which would lead a significant number of
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14 non-loaded patients being subjected to unnecessary intensive chelation.
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22 As with any cross sectional study, the main drawback is that results are drawn from a static
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24 picture of our population and correlations are based on characteristics that could be present
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26 for an undetermined period of time. In addition, the analysis was not performed according to
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28 chelation regime which may be related to the prevalence of cardiac dysfunction.
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33 Another issue with our study was related to the determination of the LVEF. To date there
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35 has not been standardization of the methodology for this measurement. The method used in
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37 our centre is different to that previously described, which resulted in higher normal values
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39 than ours (Westwood, *et al* 2007). Our method may not be ideal, as it is based on the
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41 assumption that CD is solely due to cardiac iron overload. However, as we used the same
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43 analysis in assessing LVEF in "normal" individuals (patients with T2*>20ms) the
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45 determination of CD or non CD would be expected to be appropriate for the purposes of this
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47 analysis.
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54 **CMR, providing both T2* values and LVEF,** is an essential tool for evaluating patients with
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56 transfusion dependent thalassaemia. This study provides strong evidence that even low
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58 levels of cardiac iron may be related to cardiac dysfunction and efforts should always be
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3 made to achieve levels of T2* > 20ms. Patients with T2* ≤ 8ms are at great risk of having
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5 cardiac dysfunction and require reversal of such iron load without delay.
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10 11 12 Authorship and Disclosures 13

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16 All authors contributed in study design and writing of the manuscript. GC and VB were
17
18 involved in data entry. GC performed the statistical analysis.
19

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21
22 GC, SM and EG have no interests to declare.
23

24
25 AK has participated in study monitoring committees for Novartis and has also participated at
26
27 Exjade speaker Bureau for Novartis. He has attended sponsored meetings from Novartis and
28
29 ApoPharma
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32
33 VB is a remunerated consultant with ApoPharma Inc and a consultant with Novartis Inc with
34
35 respect to the development of deferasirox. He has received honoraria from Demo AE
36
37 (Greece) and served on the Advisory Board of ApoPharma and has attended Novartis
38
39 sponsored meetings on iron chelation.
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45 VL has been remunerated for clinical trials from both ApoPharma Inc and Novartis Inc and
46
47 has attended sponsored meetings from both. VL has also served on an ApoPharma advisory
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49 board.
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Table 1. Proportion† of patients with and without cardiac dysfunction and left ventricular ejection fraction (LVEF) according to cardiac iron load at the time of their first CMR

	Cardiac T2* values			
	≤ 8 ms	>8 & ≤14 ms	>14 & ≤20ms	> 20 ms
Cardiac dysfunction free, n (%)	46 (66.7)	55 (87.3)	39 (90.7)	123 (96.1)
Cardiac dysfunction, n (%)	23 (33.3)	8 (12.7)	4 (9.3)	5 (3.9)
Total, n (%)	69 (100)	63 (100)	43 (100)	128 (100)
LVEF*, mean (SD)	60.8 (10.6)	65.6 (6.3)	67.5 (5.9)	67.8 (5.3)

†Comparison of ratio CD to CD-free between T2* groups: Fisher's exact, p-value<0.001

* ANOVA F-test†, p<0.001. Significant comparisons (considering p=0.009 as the level of significance according to the Bonferroni correction): severe vs moderate p<0.001, severe vs mild p<0.001, severe vs normal p<0.001.

For Peer Review

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4 Figure 1. Scatter plot and fitted regression lines, of left ventricular ejection fraction according
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6 to cardiac T2* for patients with ($T2^* \leq 20$ ms, black dots) and without ($T2^* > 20$ ms, grey
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8 squares) cardiac iron overload
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14 Figure 2. Receiver operating characteristic (ROC) curve for T2* values in discriminating
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16 between CD and CD-free patients.
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24 Figure 3. Showing the estimated probability of having cardiac dysfunction according to T2*
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26 values. The probabilities were estimated by logistic regression analysis.
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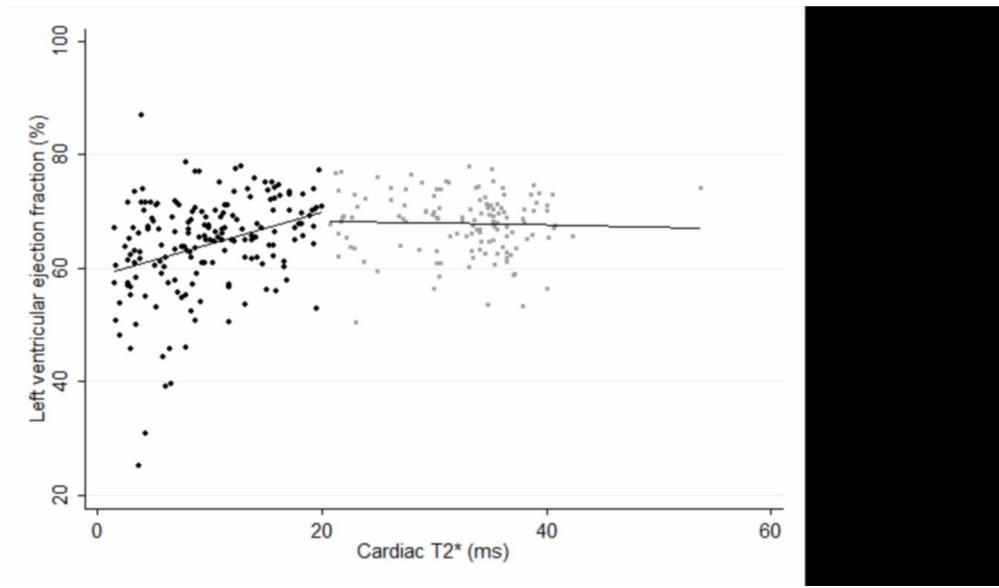


Figure 1. Scatter plot and fitted regression lines, of left ventricular ejection fraction according to cardiac T2* for patients with ($T2^* \leq 20$ ms, black dots) and without ($T2^* > 20$ ms, grey squares) cardiac iron overload
56x33mm (600 x 600 DPI)

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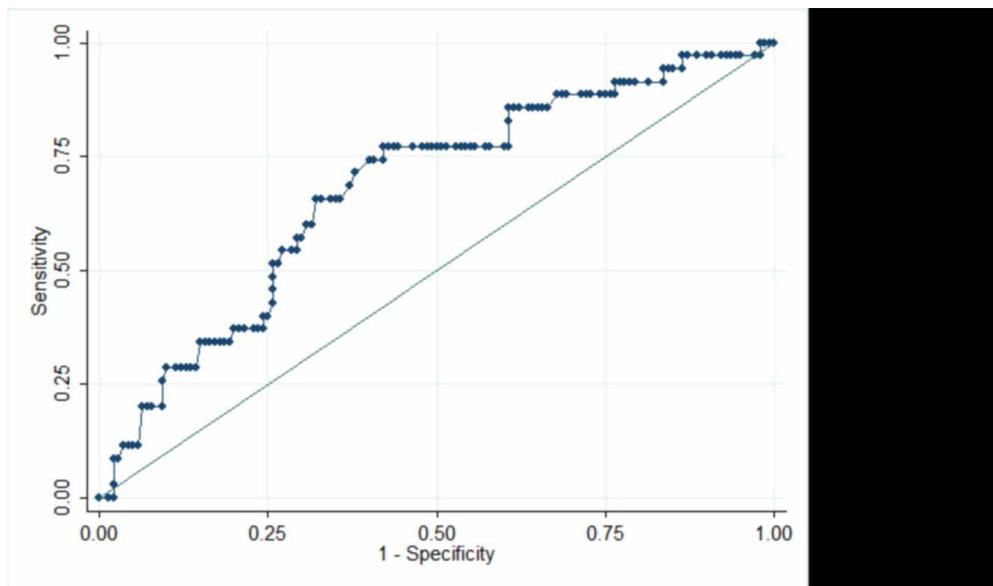


Figure 2. Receiver operating characteristic (ROC) curve for T2* values in discriminating between CD and CD-free patients.
56x33mm (600 x 600 DPI)

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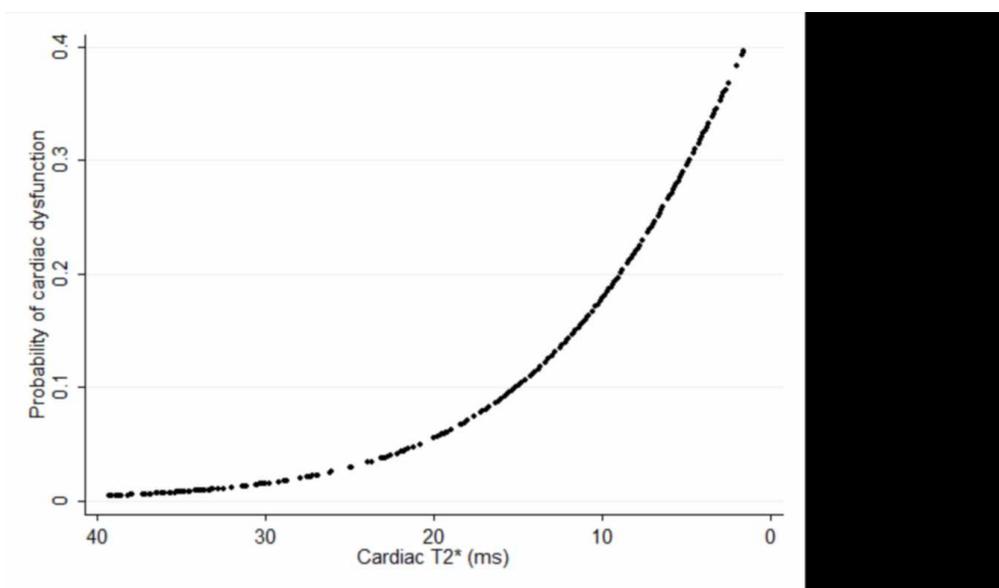


Figure 3. Showing the estimated probability of having cardiac dysfunction according to T2* values. The probabilities were estimated by logistic regression analysis. 56x33mm (600 x 600 DPI)

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