Cardiac magnetic resonance imaging R2* assessments and analysis of historical parameters in patients with transfusion-dependent thalassemia

Recent advances in magnetic resonance imaging (MRI) techniques allow the assessment of iron overload in tissues[1] especially the heart,[2] in transfusion-dependent thalassemia patients. The R2* value (1/T2*) recorded in the intraventricular septum of the heart indirectly measures the degree of cardiac iron load. Applying this new technology we looked at a number of historical and biochemical parameters in order to determine their relationship to cardiac iron overload and the effect of cardiac iron on functional and structural changes of the heart in transfusion-dependent thalassemics.

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Our unit manages over 400 patients with thalassemia major. The patients enrolled in this study were transfused approximately every 2 weeks and all were on regular chelation therapy with desferrioxamine, given at a dose of 30-45 mg/kg/per day subcutaneously for 5-7 days per week in infusions lasting 8-12 hours: compliance to therapy was variable. At the Athens MRI Imaging Site (Euromedica Encephalos™), 147 unselected patients and 12 with echocardiographically demonstrated reduced left ventricular ejection fraction (LVEF) were assessed for cardiac R2*. Written consent was acquired from all. The site had been validated by the Brompton Hospital for T2* compatibility.[3] A General Electric magnetometer (1.5 Tesla magnet-Signa CVI with 40 mT/m gradients with appropriate cardiac software; General Electric, Milwaukee, IL, USA) was used for the MRI. Initially only cardiac T2* studies (inverse of R2*) for iron were performed. Subsequently liver iron (144 patients) and later cardiac (structural and functional) parameters were assessed (86 patients). The results are expressed as R2* as this is the measurement that is made directly and has a more linear relationship to iron than T2*.

The mean value of the cardiac R2* was 93±80 sec^{-1} (the normal range at the center is 25.1-47.6 sec^{-1}; the cut-off value for iron load R2* >40 sec^{-1})[11] with a range of 19-500 sec^{-1}. Cardiac R2* was elevated in 68% of the whole group and in 36% (44/12) of those with a LVEF ≥60%. The hepatic R2* was 718±635 sec^{-1} with a range of 37-3030 sec^{-1}.

We analyzed the data on all the historical and biochemical parameters in the entire group against R2* and subdivided the patients into two groups. Group A consisted of the patients with normal cardiac R2* (R2* ≤40 sec^{-1}=T2* >25 msec). Group B consisted of these with cardiac iron overload (R2*>40 sec^{-1}=T2* ≤25 msec). We then compared all the parameters within these two groups.

Table 1A (*online version only*) shows the parameters that were measured, including those significantly related to cardiac R2*. None had a predictive value (r<0.5). Table 1b (*online version only*) presents the same parameters for the patients divided into the two groups (group A and B). A derived index, the iron equilibrium factor (IEF), grossly related to iron equilibrium with advancing age (multiplying the red cell consumption in mL by age and then the compliance factor, which is 1-Compliance divided by 365) was found to be statistically related to the R2* according to the *p* value for the whole group, between groups A and B (after Bonferroni's correction) and with a Spearman's correlation coefficient of 0.411. On receiver operator characteristics

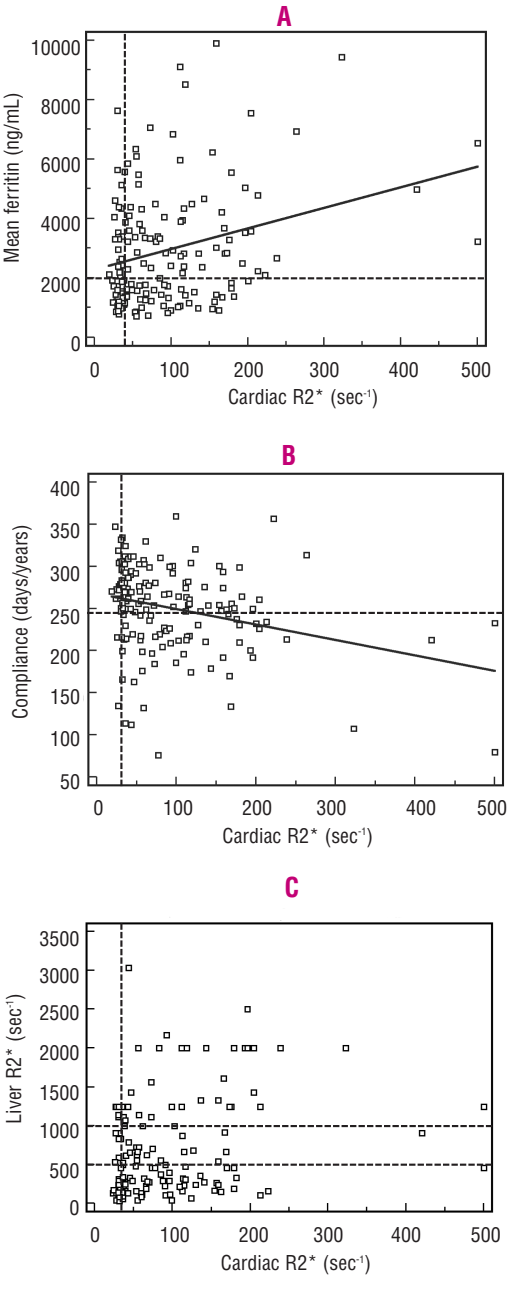

Figure 1. A. Scatter diagram and regression line of the 5-year mean ferritin compared to the cardiac R2*. The vertical dotted line indicates the R2* value above which cardiac iron is considered to be present. The horizontal dotted line represents the value above which a patient is considered to be at risk of cardiac problems. **B.** Scatter diagram and regression line of compliance compared to cardiac R2*. The vertical dotted line is the upper limit of normal for cardiac R2* and the horizontal dotted line indicates the level of compliance above which compliance is regarded as being adequate. **C.** Scatter diagram of hepatic R2* compared to cardiac R2*. The three horizontal dotted lines indicate the divisions of hepatic R2* that are associated with normal (between 0 and 190 sec^{-1}) , mild (between 190 sec^{-1} and 400 sec^{-1}), moderate (between about 400 sec^{-1} and 1000 sec^{-1}) or severe iron loading (dotted line >1000 sec^{-1}). The vertical dotted line indicates the level of cardiac R2* that differentiates a normal (≤40 sec^{-1}) from an iron-loaded heart (>40 sec^{-1}).

(ROC) curve analysis, it was highly significant, with a positive likelihood ratio of 9.31 at >2124. LVEF was also significant, with a positive likelihood ratio of 6.3 at ≤60.5% (Table 1C *online version only*). Figures 1A-1C, 2A and 2B

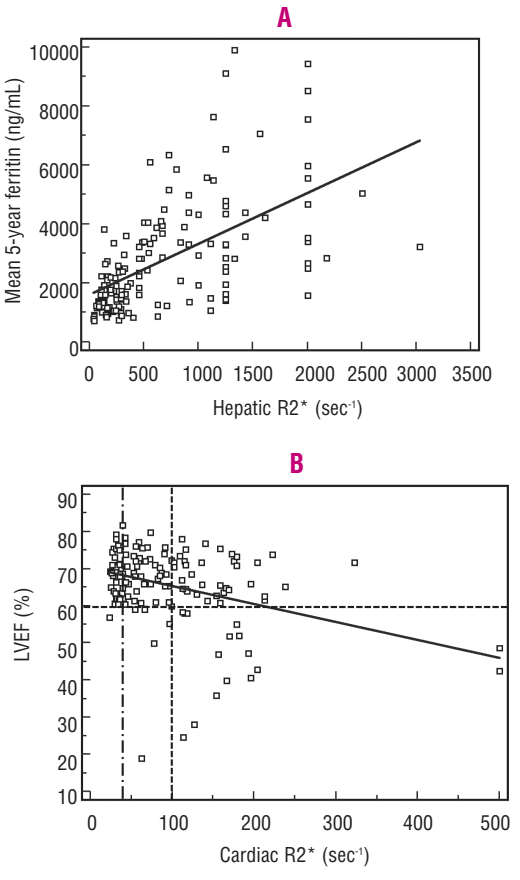

Figure 2. A. Scatter diagram and regression analysis of mean 5-year ferritin compared to hepatic R2*. **B.** Scatter diagram and regression line of the left ventricular ejection fraction (LVEF) compared to the cardiac R2*. The vertical broken dotted line is the upper limit of normal of the cardiac R2* and the horizontal line represents the level under which LVEF is now regarded as being abnormal (at the time of starting this study > 52% was considered as normal). All patients, with the exception of one, with cardiac dysfunction had cardiac iron load and in most cases the dysfunction was severe. Patients with R2* greater than 100 sec^{-1} (T2*< 10 msec) are heavily iron loaded (above dotted line). One patient with a LVEF of 57% had an R2* of 30 sec^{-1}.

show the relationships between a number of parameters and R2* of either the heart or liver and clearly demonstrate the lack of correlation between heart and liver iron.

As regards structural and functional MRI measurements in 86 patients for whom we had such data, levels of cardiac iron increased, the end systolic volume increased, whereas clear increases of end diastolic volume occurred only in cases with reduced LVEF. A reduction of LVEF (<60%)[4] occurred in all patients but one with cardiac iron load emphasizing the usefulness of MRI iron load measurements.

We demonstrated the usefulness and pitfalls of the traditional parameters, including liver iron load (Table 1D, *online version only*),[5,6] in predicting heart iron load and its risks. Cardiac iron is associated with a number of parameters, but their predictive value is low. The IEF, however, shows a very strong relationship with cardiac iron and highlights the importance of iron equilibrium. Patients with values >2124 for this factor have a 96% chance of having cardiac iron overload. The relationship of cardiac iron to structure and function, especially LVEF and end systolic volume index are clearly shown by this study. If MRI is not accessible in a center, echo derived borderline or elevated values of end systolic volume or its index, particularly their trajectory, or reduced LVEF, should be regarded as a warning sign that the patient has a significant cardiac iron load. When MRI is available, cardiac and hepatic R2* measurements to assess iron load are extremely useful for designing and tailoring personalized chelation regimes.

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**Details on the specific techniques, validation and statistical analyses are available on request from the authors.*