Myocardial iron overload assessment by T2* magnetic resonance imaging in adult transfusion dependent patients with acquired anemias

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ABSTRACT

Only limited data are available regarding myocardial iron overload in adult patients with transfusion dependent acquired anemias. To address this topic using MRI T2* we studied 27 consecutive chronic transfusion dependent patients with acquired anemias: (22 myelodysplastic syndrome, 5 primary myelofibrosis). Cardiac MRI T2* values obtained ranged from 5.6 to 58.7 (median value 39.8) milliseconds. Of the 24 analyzable patients, cardiac T2* correlated with transfusion burden (p=0.0002). No patient who had received less than 290 mL/kg of packed red blood cells (101 units=20 grams of iron) had a pathological cardiac T2* value (< 20 ms). All patients who had received at least 24 PRBC units showed MRI T2* detectable hepatic iron (liver T2* value ≤6.3 ms). Only patients with severe hepatic iron overload (T2* <1.4 ms) showed cardiac T2* value indicative of dangerous myocardial iron deposition. Serum ferritin was not significantly correlated with cardiac T2* (p=0.24). Gradient echo T2* magnetic resonance imaging provides a rapid and reproducible method for detecting myocardial iron overload which developed after a heavy transfusion burden equal to or greater than 290 mL/kg of packed red blood cell units.

Key words: cardiac iron, myelodysplastic syndromes, magnetic resonance imaging, T2*.

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Introduction

Iron-induced heart disease is the most frequent cause of death in transfusion dependent thalassemia patients. In thalassemic patients cardiac T2* Magnetic Resonance Imaging (MRI) has been recently used to evaluate myocardial iron content and it has been correlated to left ventricular ejection fraction reduction.[1] Furthermore, myocardial iron depletion has been considered a major cause of improved survival in this category of young patients.[2] So far, very limited studies addressing the issue of myocardial iron overload in adult patients with transfusion dependent acquired anemias have been published.[3-6] We, therefore, planned a pilot study to address this relevant clinical issue.

Design and Methods

Patients

From December 2005 through September 2006, 27 consecutive chronic transfusion dependent patients with acquired anemias entered the study. Twenty-two patients were affected by *de novo* myelodysplastic syndrome (20 low risk and 2 with intermediate-1 risk, according to the IPSS),[7] 5 patients were diagnosed with primary myelofibrosis.[8] All patients were transfusion dependent according to local guidelines[9] receiving a minimum of 2 packed red blood cells (PRBC) units per month. Transfused PRBC units' volume was standardized to a constant volume of 190 millilitres. A mean amount of iron intake of 200 mg was assumed for any PRBC unit.[10] Detailed clinical and transfusion data are reported in Table 1. Only 2 patients had previously received chelation therapy for at least two years and continued to receive deferoxamine subcutaneously five days a week.

Serological study

Serum ferritin levels were determined by a standard commercial method and the measurement was made within one week before or after the MRI study.

Cardiac study

Cardiac function was evaluated in all patients by electro-

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and echo-cardiography before the MRI study. Patients were considered to have cardiac disease if they required active cardiac medication (with the exception of anti-hypertensive drugs or anti-arrhythmic prophylaxis) or had a left ventricular ejection fraction less than 50%.

Magnetic resonance imaging study

All MRI examinations were performed with a validated 1.5 T scanner (GE Signa, Milwaukee, WI, USA) using a gradient echo T2* MRI technique. Our Radiology team had received specific training at the Brompton Hospital in London. Site and methodology have been validated in interscanner and intercenter validation studies.[11,12]

For the heart, a single mid-ventricular short axis slice was imaged at eight echo times (1.9 to 19.7 ms). The repeat time between each radiofrequency pulse was 30 milliseconds. For analysis, the signal intensity of a full-thickness region of the left ventricular septum was measured for each echo time. To obtain T2*value, a mono-exponential trend-line was fitted with an equation in the form y=Ke-TE/T2* where K represents a constant, TE represents the echo time and y represents the image signal intensity. For the measurement of liver T2*, a single trans-axial slice through the center of the liver was imaged at eight echo times (1.2-11.7 milliseconds). Signal intensity analysis was performed in the periphery of the liver away from the large central vessels. All MRI data were analyzed using dedicated software (CMRtools; Cardiovascular Imaging Solutions, London, UK). The signal decay curve was visually assessed by a reader and late echoes were eventually discarded to achieve a good fit. Myocardial T2* values <20 ms were indicative of iron overload, and this was considered severe when T2* was <10 ms, according to Pennell.[13] Hepatic iron overload was defined by MRI T2* values less than 6.3 ms and it was categorized as mild (6.3-2.7 ms), moderate (2.6-1.4 ms) or severe (< 1.4 ms). Patients with primary myelofibrosis (5 patients) have been excluded from analyses involving liver iron because of the presence of hepatic hemopoiesis that could interfere with the T2* signal.[14,15]

Statistical data analysis

Data with normal distribution are expressed as mean±standard deviation. Data with skewed distributions are given as median with a range. Linear relationships between variables were investigated after logarithmic transformation of T2* values by linear regression analysis (least square method) using a p value of 0.05 as the threshold for statistical significance.

The study protocol was approved by the institutional review board. Written informed consent was obtained from all patients before the MRI study.

Results

All patients regularly completed the MRI study. No complication or adverse event was registered.

Cardiac iron

At the time of the study no patient presented signs of active cardiac disease; 4 patients were on anti-hypertensive medication and one was receiving anti-arrhythmic prophylaxis for a previous episode of atrial fibrillation. Ejection fraction ranged from 54% to 70%.

Cardiac MRI T2* values obtained ranged from 5.6 to 58.7 (median value 39.8) milliseconds. A pathological cardiac T2* value (< 20 ms) was found in 3 patients (5.6, 12.4 and 8.5 ms respectively). They had received 147, 291 and 668 millilitres of PRBC units per kilogram of body weight (48, 101 and 225 PRBC units), corresponding to 9.6, 20 and 45 grams of iron respectively.

One patient showed an unexpected low myocardial T2* value having received just 48 PRBC units. In this patient homozygous polymorphism V221V of the ferroportin gene was detected. This mutation has been identified in the African-American population and it is correlated to hereditary iron overload.[16] Two patients had received chelation by subcutaneous deferoxamine. They had received 342 and 507 ml/kg (108 and 160 units) of PRBC respectively. Despite this large amount of iron intake they did not show myocardial iron deposition (MRI T2* values 43.5 and 50 milliseconds respectively). These 3 patients (ferroportin mutated and the 2 chelated patients) were excluded from further evaluations.

Figure 1 shows the relation between millilitres/kg of PRBC received and cardiac T2* value in the remaining 24 patients [r=-0.69(95%CI -0.85 to -0.38, p=0.0002)].

Excluding the patient with genetic abnormalities, no patient who had received less than 290 ml/kg of PRBC (101 units= 20 grams) had a pathological T2* value (< 20 ms). One additional patient with a T2* value close to the threshold but still in the *normal* range (20.2 ms) had received 269 mL/kg of PRBC (85 units=17 grams, 283 mg/kg of iron).

Hepatic iron

Hepatic MRI T2* values obtained ranged from 1.2 to 8.9 milliseconds (median value 1.55). Only one patient

Table 1. Patients' characteristics.

Patients	27 (18 males, 9 females)
Diagnosis	myelodysplastic syndrome 22, primary myelofibrosis 5
Age in years (median, range)	69, 46-82
Months on transfusion therapy (median, range)	27, 5-36
Packed red blood cell units received (median, range)	64, 16-225
Packed red blood cell received, mL/kg (median, range)	195, 39-668
Transfusion iron intake, mg/kg (median, range)	206, 41-703
Serum ferritin, ng/mL (median, range)	1830, 1300-6241

did not show MRI detectable hepatic iron overload (liver T2* value=8.9 ms). He had received 39 mL/kg of PRBC (16 Units=3.2 grams of iron) and surprisingly had a serum ferritin level of 2550 ng/mL. All the others, including those who had received 57 mL/kg of PRBC (24 units), presented MRI detectable hepatic iron. Hepatic iron overload was absent in 1, mild in 3, moderate in 11 and severe in 4 patients.

Relationship between cardiac and hepatic iron

No correlation was found between cardiac and hepatic iron [r= 0.4 (95%CI -0.06 to 0.70, p=0.09)]. However, none of the patients with hepatic T2* >1.3 ms (threshold for severe hepatic iron overload) showed a cardiac T2* value indicative of dangerous myocardial iron deposition (Figure 2).

Serum ferritin

Serum ferritin was not significantly correlated with cardiac T2*, r= 0.25 (95%CI -0.17 to 0.59), p=0.24.

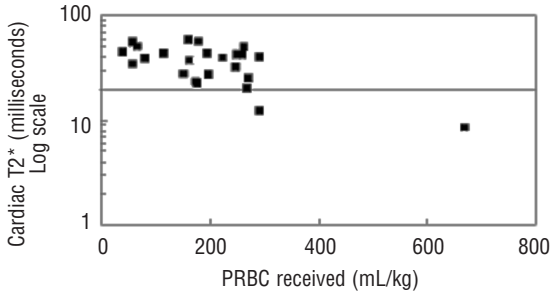

Figure 1. Correlation between log (cardiac T2*) and transfusion input expressed as mL/kg of packed red blood cells. The horizontal line indicates the threshold for MRI definition of myocardial iron deposition. Two chelated patients and the patient with ferroportin gene mutation are excluded (n=24). r= -0.69 (95% CI -0.85 to -0.38), p=0.0002.

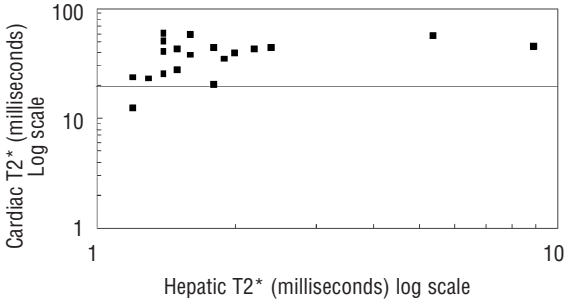

Figure 2. Correlation between log (Cardiac T2*) and log (hepatic T2*). The horizontal line indicates the threshold for MRI definition of myocardial iron deposition Chelated patients, the patient with ferroportin gene mutation and primary myelofibrosis patients are excluded (n=19). r=0.4 (95% CI -0.06 to 0.70), p=0.09.

Discussion

The role of transfusion dependency as one of the most important variables predicting survival in myelodysplastic syndromes has been recently reported by the Pavia group.[17,18]

In recent years myocardial iron assessment has been considerably enhanced in the thalassemic population. The development of the T2* MRI technique, which is today the reference standard for myocardial iron characterization, has opened up the opportunity to investigate myocardial iron overload in transfusion dependent adults in a non-invasive and reliable way.[11,19]

In our series of patients, myocardial iron deposition developed after a heavy transfusion burden equal to or greater than 290 mL/kg of PRBC units corresponding to approximately 300 mg/kg of iron (101 units of PRBC in our series). This finding confirms historical post-mortem data by Buja.[20] They showed that massive cardiac iron deposition correlated with clinical cardiac dysfunction in almost all patients who had received more than 100 units of blood.

Two recent papers using MRI T2* failed to demonstrate myocardial iron deposition in adult patients with acquired anemia.[3,5] However, these reports covered a limited number of patients and most had already been chelated. Indeed in our series, 2 heavily transfused patients (342 and 507 mL/kg of PRBC, 108 and 160 units) chelated by deferoxamine did not show either myocardial iron overload or clinical cardiac disease.

Jensen[6] used a different method distinct from T2* (based on signal intensity ratio) to evaluate cardiac iron and noted that 8 out of 11 MDS patients showed myocardial iron deposition after having received 84-420 red cell units.

Hepatic iron deposition invariably appears much sooner in a given patient's transfusion history and starts from 57 mL/kg corresponding to 60 mg/kg of iron (24 units of blood in our series). Importantly cardiac iron overload appeared only after severe hepatic iron overload was demonstrable. This observation supports the idea that the liver is primary site of iron deposition and iron-storage tissue in adult unchelated patients. The level of the serum ferritin did not predict cardiac iron overload.

Myocardial iron content cannot be predicted by conventional studies of cardiac function which detect the effects of iron deposition when disease is advanced. Adult and elderly patients with secondary iron overload are a new clinical scenario because of aging, and co-morbidity and effect of myocardial iron can be more hazardous than had been suggested by the only available clinical model (Thalassemia major). The present research project has been designed to address the issue of myocardial iron loading. Of course, cardiac function is a more complex issue involving other factors (anemia, aging etc.). A larger study dedicated to cardiac function is warranted. However, it is reasonable to state that in this category of patients myocardial iron deposition must be prevented rather than treated even before cardiac iron loading becomes detectable on MRI because other iron mediated mechanisms, such as those induced by labile plasma iron, may cause tissue cardiac damage.

The demonstration of initial hepatic iron deposition after 24 units of PRBC suggests a rational threshold to start iron chelation in this category of patients.

Authorship and Disclosures

EA and AADT participated in the design of the study, the analysis and interpretation of the data, and the writing of the manuscript; S.D, AG, CD, GC and AA participated in statistical analysis of data from this study and contributed to writing the manuscript. GM performed the MRI test and participated in the analysis and interpretation of data and writing the manuscript. All authors have seen and approved the final version. The authors reported no potential conflicts of interest.

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