Spleen R2 and R2* in iron overloaded patients with sickle cell disease and thalassemia major

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Introduction: Thalassemia major (TM) and sickle cell disease (SCD) are the two most common genetic diseases in the world. Severe forms require chronic transfusion therapy. Each tri-weekly blood transfusion delivers ~400 mg of iron into the patient, nearly 400 times the normal daily absorption. Thus, these patients develop massive iron overload. Transfusional iron initially loads in the spleen and the Kupffer cells of the liver. Subsequently, iron redistributes from the reticuloendothelial system (RES) to hepatocytes, bone marrow, heart, liver, and endocrine system. The iron hormone, hepcidin, limits this redistribution and may be elevated in SCD patients. MRI has been used to characterize the iron stores in many of these tissues, but little study has been done on the spleen (1). We sought to find a relationship between spleen, liver and cardiac iron loading and whether there is a difference in SCD and TM. We also wanted to determine whether spleen R2 and R2* relaxation rates had similar relationships compared with the liver. We hypothesized that SCD patients would have more splenic iron than TM patients. Also, since iron deposits are larger in the spleen than in the liver, we hypothesized that splenic R2 relaxivity would be attenuated relative to R2*.

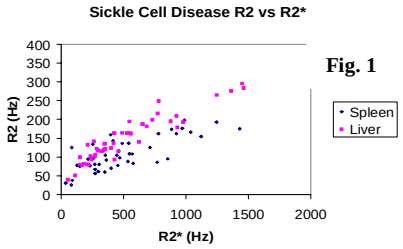

Fig. 1

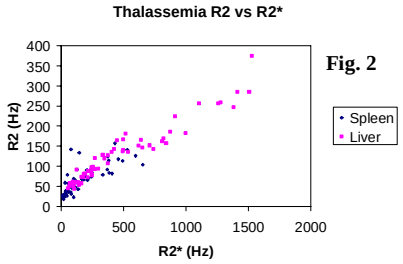

Fig. 2

Methods: MRI of the liver, heart and pancreas are routinely performed for clinical care purposes at Childrens Hospital Los Angeles. Hepatic iron concentrations (HIC) were estimated from previously validated axial R2 and R2* acquisition protocols (2). Spleen R2 and R2* were calculated from the same spin-echo and gradient-echo images. Retrospective analysis was done on 103 TM and 75 SCD patients. Of these, 43 TM patients had prior splenectomy, while 31 SCD patients had badly infarcted spleens with relaxivities that could not be accurately measured. Relaxivities were calculated pixelwise to an exponential plus constant using custom Matlab routines. Spleen R2* values were then compared to R2* values generated for heart, liver, pancreas, and kidneys by linear regression.

Results: SCD patients were younger than TM patients (11.6 ± 5.4 years versus 15.9 ± 8.1 years, $p < 0.001$), but well matched for gender (43% male versus 52% male). HIC, a good indicator of total body iron, was severely elevated in both groups but slightly higher in the SCD patients (14.1 ± 9.9 mg/g versus 12.4 ± 12.0 mg/g dry weight, $p < 0.001$). Liver and spleen demonstrated different relationships between R2 and R2*. At low R2* values, the two organs showed comparable R2-R2* behavior, but once R2* values rose to ~300 Hz, spleen R2 values became lower than those of the liver. This was true in patients with SCD (Fig. 1) and those with TM (Fig. 2). Splenic iron-loading in TM and SCD was similar when HIC was < 7mg/g. Above this HIC, splenic R2* plateaued between 300 and 600 Hz in TM patients, while R2* continues to rise in SCD patients (Fig. 3). In some patients with SCD, R2* values were so high that they could no longer be quantified (>1500 Hz). When spleen R2* values were compared to those of heart, pancreas, and kidneys, it was found that spleen iron levels had little predictive value for iron levels in these organs.

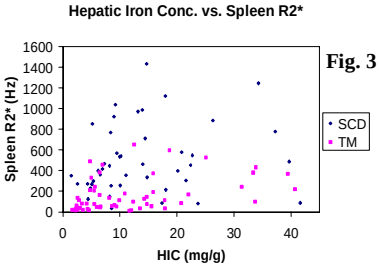

Fig. 3

Discussion: R2 loses sensitivity to splenic iron at high concentrations, representing static refocusing from larger length scale of iron deposits. In hepatocytes, iron deposits have a mean diameter of approximately 1 µm and are well tuned for R2 signal decay (3). Although iron deposits are of similar size in RES cells, the inter-particle distance is so small in these cells that the entire cell behaves as one large paramagnetic bead, having an effective diameter of 15-20 µm. Magnetically, fully saturated RES cells will have large length scale magnetic disturbances, causing static refocusing in spin echo experiments and lower R2 values. R2* techniques remain linearly proportional to iron in this scenario. The liver contains only 20% RES cells while the spleen is almost entirely composed of RES cells. Thus, for spleen and liver tissue with the same R2* value, splenic R2 was expected to be significantly lower than hepatic R2. This was found to be true in both SCD and TM patients (Fig. 1 and 2). However, this effect was seen only once R2* values had risen above ~300 Hz (Fig. 1 and 2). Similar magnetic properties at low iron levels are probably observed because this is when both organs are loading iron into their RES cells. This is supported by the fact that a R2* value of 300 Hz is representative of ~7mg of iron/g of tissue (2), which is approximately the amount of iron it would take to completely load the RES of the liver. After this point, the liver would start depositing iron into its parenchymal tissue. Interestingly, TM patients stop loading iron into their spleens at a HIC of ~7mg/g (Fig. 3). Perhaps this is because the RES of the liver loads in parallel with the RES of the spleen – once the liver RES is saturated, the body may keep more iron from being loaded into the RES of the spleen.

The spleen has not been thought of as a natural depot for iron storage (4). When iron is absorbed from the gut it is bound by transferrin (Tf), which shuttles iron safely to the liver and bone marrow (Fig. 4). The bone marrow utilizes iron to produce hemoglobin, while the liver stores iron in ferritin molecules. Iron is redistributed from these storage sites to maintain body iron homeostasis under the control of hepcidin (5). The iron of the erythron is sent to the RES when red blood cells are broken down. Tf quickly picks up the iron that is released by the RES so it can be sent back to the bone marrow or liver. When iron overload occurs, Tf molecules become saturated and toxic non-transferrin bound iron (NTBI) gets picked up by the parenchymal tissue of the liver, heart, and endocrine system (Fig. 4). There are three possible reasons why SCD patients show spleen R2 and R2* values indicative of iron-loading. First, their sickle-shaped red blood cells are rigid, causing them to lodge in splenic blood vessels. Thus, the spleen becomes infarcted and builds up a large amount of iron. Secondly, inflammation caused by sickled cells increases hepcidin levels, blocking iron absorption from the gut and locking iron in the RES cells of the spleen (5). Third, because infarcted spleens tend to decrease in volume, it may be that an increase in splenic iron concentration is the consequence of a decrease in splenic volume. This possibility is going to be examined by measuring the splenic volumes of all of the patients.

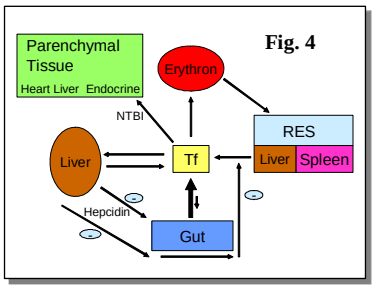

Fig. 4

Acknowledgements: GCRC (RR00043-43), NIH (1 R01 HL75592-01A1)

References: 1) Wood JC, Curr Opin Hematol 2007;14:183-90
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