MRI-R2* Relaxometry for cardiac, pancreatic and hepatic iron assessment in patients with Hereditary Hemochromatosis

Sarah Keller[1], Bjoern Schoennagel[1], Zhiyue Jerry Wang[2], Regine Grosse[3], Peter Nielsen[4], Gerhard Adam[1], Roland Fischer[1], and Jin Yamamura[1]

[1]*Diagnostic and Interventional Radiology, University Medicine Hamburg Eppendorf, Hamburg, Germany,* [2]*Radiology, Children's Medical Center Dallas, Dallas, Texas, United States,* [3]*Pediatric Hematology and Oncology, University Medicine Hamburg Eppendorf, Hamburg, Germany,* [4]*Institute of Biochemistry and Molecular Biology, Center of Experimental Medicine, Hamburg, Germany*

Target Audience

Clinicians and scientists dealing with the treatment of rare diseases such as Hereditary Hemochromatosis (HHC), but also diseases needing chronic blood transfusions and following excessive body iron accumulation, such as Diamond Blackfan Anemia (DBA) and ß-Thalassemia major (TM) in which the MRI can help to measure the iron content by R2* relaxometry.

Introduction/Purpose

Hereditary hemochromatosis (HH) is frequently associated with cardiomyopathy and iron accumulation in the heart beyond increased hepatic iron concentration (HIC). Measurements of cardiac iron concentration (CIC) in patients with HH are rare (Olson et al, 1987) and sporadic cases seem to be reported less frequently.

Material and Methods

So far, we investigated 7 homozygotes with HH (C282Y: n=4, H63D: n=3; age 40 – 63 y) by biosusceptometry (HIC) and qMRI (cardiac function, transverse relaxation rate R2* and relative fat/water content of heart, pancreas, vertebral marrow, liver, and spleen).

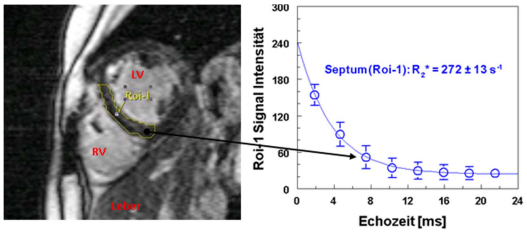

Fig. 1: Signal-intensity in heart septum of a patient with ß-thalassemia major (Roi-1) (single breath-hold multiecho method T_E=7.45 ms:1.5 T Siemens Magnetom Symphony®). The exponential fitting of the data results in the relaxation time T2*=1/R2*=3.7 ms, which are shortened due to the susceptibility effect of substantial heart iron which present in this patient. The liver iron concentration (LIC), measured by biosusceptometry (SQUID-Biosusceptometer Hamburg) is relative low (LIC(BLS)=1090 ± 114 µg/$_{liver}$.

Normal control subjects (n = 13, age 23 – 63 y) were used for comparison. Cardiac iron concentration (CIC) was calculated from septal R2* (**Fig.1**) using the reported relationship between R2* and cardio-magnetic susceptibility based on the specific hemosiderin/ferritin magnetic volume susceptibility of $1.6 \cdot 10^{-6}$ [SI-units] (Wang et al, 2010). R2* and the relative fat/water content were simultaneously achieved from chemical-shift analysis exploiting the signal magnitude characteristics as function of in phase and opposed phase echo times. Signal intensity data were assessed by CMRtools (Cardiovascular Imaging Solutions Ltd). Pancreatic and liver ROI based R2* were determined in the interventricular septum of a mid-papillary short axis slice and in a mid-vertebral slice covering the whole liver. Pancreas signal intensities were averaged from three different ROIs positioned on the tail, body and head of the pancreas. For a 2-compartment model, the signal intensities S(t) of water protons (w) with no shift relative to its resonance frequency of 63.4 MHz at 1.5 T (= 0!) and fat protons (f) with a chemical shift (water-fat shift: = 220 Hz or 3.4 ppm) are described by $S_w(t) = S_w(0) \cdot \exp(-R2_w^* t)$ and $S_f(t) = S_f(0) \cdot \exp(-R2_f^* t) \cdot [\cos(2\pi\Delta f t) + i \cdot \sin(2\pi\Delta f t)]$ with signal amplitudes S(0) and relaxation rates R2*, respectively. The signal intensity (magnitude) image from the MRI scan can be written as $|S(t)| = |S_w(t) + S_f(t)|$, with terms in the right hand side system given by the real and imaginary components of the above relations. This effective CSR approach results in different relaxation rates $R2_w^*$ and $R2_f^*$ for water and fat, respectively. In the presence of local field distortions by iron we may assume that the relaxation rates for water and fat protons are affected in a similar manner by $R2_w^* = R2_f^*$. Also taking a signal level offset (S_{LO}) into account, the final equation 1 is a robust fit function with 4 free parameters, if = const = 450 Hz. At certain echo times t = TE, the cosinus term will become positive (+1: in phase TE = 4.6, 9.2, … ms) or negative (-1: opposed phase TE = 2.3, 6.9, … ms).

(1) $S(t) = S_w(0) \cdot \exp(-R2_w^* t) \sqrt{\{1 + (S_f(0)/S_w(0))^2 + 2 (S_f(0)/S_w(0)) \cdot \cos(\Delta\Delta\Delta t)\}} + S_{LO}$.

An apparent fat content (aFC) can be calculated from the signal amplitudes $S_w(0)$ and $S_f(0)$ by equation 3:

(3) $aFC = S_f(0) / [S_f(0) + S_w(0)]$

To obtain the absolute fat content (FC), correction of equation (3) by the longitudinal relaxation rates $R1_w$ and $R1_f$ is needed. This magnitude only approach is limited to the quantification of fat fractions < 50% because of the ambiguity of fat or water dominance, i.e., inter-changing the size of the amplitudes $S_w(0)$ and $S_f(0)$ in equation 1 or 2 will result in the same fit to the signal intensity pattern with complementary fat fractions.

In tissues with no fat infiltration ($S_f(0) = 0$) or overwhelming iron concentration ($S_w(0) >> S_f(0)$), equation 1 or 2 will become the well known mono-exponential model with constant signal level offset (equation 4). This 3-parameter model was fitted to the signal intensities of heart and liver in most patients.

(4) $|S(t)| = S_w(0) \cdot \exp(-R2_w^* t) + S_{LO}$.

Levenberg-Marquardt algorithm was used to fit the beat frequency pattern.

Statistical analysis:

Linear regression was performed to estimate the relationship between the iron loading in the different examined organs. The relationship between cardiac and pancreatic iron loading as well as hepatic and pancreatic iron loading was estimated by Spearman correlation.

Results

An overview of the results is shown in **Table 1**. Hepatic iron in HH ranged from 191 to 4225 µg/g-liver (conversion factor 6 for in vitro dry HIC), while cardiac iron was determined between 47 and 140 µg/g-heart ($R2^* = 26–41\ s^{-1}$). The highest R2* was found for the patient with the highest HIC, and just above the range of our normal controls ($R2^* = 24–37\ s^{-1}$). From the normal data of Olson et al, a CIC >100 µg/g ($R2^* > 41\ s^{-1}$) may indicate cardiac iron overload, which was found in 2/7 patients but no correlation with HIC. Left ventricular ejection fraction was normal for all patients (LVEF > 56%). R2* of the spleen was found below 100 s^{-1} (controls: 30–83 s^{-1}). Pancreatic iron was found in a normal range of $R2^* = 20–71\ s^{-1}$ and seems to correlate with HIC. Increased vertebral bone marrow iron was found only in patients with the homozygous H63D mutation ($R2^* = 84–175\ s^{-1}$), in contrast to HH patients with the C282Y mutation ($R2^* < 78\ s^{-1}$) and similar to controls ($R2^* = 62–140\ s^{-1}$). These patients also suffered from hyperferritinemia (inadequately increased ferritin, and increased relative fat/water content of the liver >10%).

subject	age	sex	HFE-Mut	ferritin	LIC	Heart-R2*	LEVF	BM-R2
HR	63	m	C282Y(+/+)	62	191	39.5		77.00
SK	40	f	C282Y(+/+)	568	2402	26.4	60.88	69.80
SC	48	m	C282Y(+/+)	2551	4225	40.7	69.01	78.30
JV	45	f	C282Y(+/+)	1449	3600	26.2	60.48	56.50
GT	54	m	H63D (+/+)	47	289	31.15	64.74	84.30
HB	52	m	H63D (+/+)	1106	383	29.98	62.95	174.70
KR	63	m	H63D (+/+)	903	688	26.12	70.08	165.00

Table 1: MR-Data from subjects with homozygous C282Y for H63D-Mutations. LIC (liver iron concentration), LEVF (left ventricle ejection fraction), BM-R2 (bone marrow R2-time).

Discussion/Conclusion

Fast quantitative magnetic resonance imaging (qMRI) methods will facilitate more systematic studies of iron accumulation in different organs. Unclear at the moment is the relevance of non-liver iron storage in different diseases with iron overload. What is known in subjects under chronic transfusion treatment (e.g. ß-thalassemia major) is the clinical relevance of a life-threatening heart iron overload. In all iron overload diseases, the majority of the excess iron is stored in the liver and the SQUID-BLS-measurements of LIC is a valuable noninvasive techniques, proven in practice), to precisely quantify LIC in all kind of patients (3-89 years). Further studies with qMRI with more cases with in different iron loading diseases are clearly needed.

References

S.N Rasmussen. British Journal of Radiology 1972, 45, 579–585
K.E Brown et al. Translational Research 2006;148:55–62.
M.B Troadec et al. J Hepatol 2006; 44: 391–399.

Key words: T2*, R2*, Iron, Relaxometry, MR-Volumetry, Liver, Heart