

Evaluation of Hepatic Iron Concentrations by R2* Magnetic Resonance Imaging in 35 Patients with Iron Overload: Comparison of R2* Measurements at 1.5T and 3T and Validation with Liver Biopsies.

C. M. Hillenbrand¹, R. B. Loeffler¹, M. McCarville¹, R. Song¹, E. Hansbury², M. Rieman², N. Mortier², M. P. Smeltzer³, C-S. Li³, F. Hoffer¹, L. Kun¹, R. Ware², and J. Hankins²

¹Radiological Sciences, St. Jude Children's Research Hospital, Memphis, TN, United States, ²Hematology, St. Jude Children's Research Hospital, Memphis, TN, United States, ³Biostatistics, St. Jude Children's Research Hospital, Memphis, TN, United States

Introduction: Certain hematological diseases such as sickle cell anemia (SCA), beta thalassemia (β -thal), or bone marrow failure (BMF) accumulate iron in the liver, heart, endocrine organs, and other tissues as a consequence of ineffective erythropoiesis or repeated red blood cell transfusions. Chronically transfused patients become iron overloaded after 18-24 erythrocyte transfusions; chelation therapy is then necessary to remove excessive accumulation. Monitoring of body iron content is therefore critical for the proper clinical management of these patients. Liver iron concentration (LIC) measured by liver biopsy has traditionally been used as the gold standard for total body iron. Biopsies bear, however, risks such as bleeding, pain, and infection. Non-invasive methods for serial quantification of body iron burden based on MR relaxometry (R2 and R2* [1,2]) have been developed, but have not been fully investigated or validated; this is especially true for 3T scanners which become increasingly available. To date the evaluation of iron burden using 3T MRI has only been investigated in a single study that indirectly calibrated R2* values acquired at 3T against R2* data from 1.5T [3]. A direct calibration of R2* measurements performed at 3T (and 1.5T) with LIC obtained by liver biopsies has not yet been demonstrated. The aim of this work was to conduct a comprehensive evaluation of LIC obtained by R2* MRI at 1.5T and 3T in patients with iron overload, and to correlate these R2* values directly with LIC measurements derived from liver biopsies. Further objectives were to study the reliability of R2* LIC measurements as a function of magnetic field strength B_0 and to establish a relationship between LIC data measured by R2*-MRI at 3T and 1.5T.

Methods: 35 patients with iron overload (SCA n=27, β -thal n=6, BMF n=2; mean \pm SD age 15.5 \pm 6.6y) were enrolled in this prospective IRB-approved study. All study participants completed R2* testing at 3T and 1.5T (Siemens, Trio and Symphony) and liver biopsy within 30 days. All liver biopsy samples were sent to Mayo Laboratories for LIC quantification. A multi gradient echo sequence (ETL 16, TE[1] 1.07ms, TE_{inter} 0.82ms) was implemented to obtain a series of T2* weighted, axial liver images at different TE in a single breathhold. Quantitative T2* maps were calculated offline using custom written MATLAB software that fitted on a pixel-by-pixel basis the signal intensity drop over the image series to a monoexponential decay. Two independent reviewers, blinded to the patients' clinical status, performed regions of interest (ROI) analysis. ROIs were drawn on T2* maps in a homogeneous area of the right hepatic lobe, avoiding blood vessels and obvious bile ducts. Mean R2* of the ROI values were calculated as $R2^* = 1/T2^*$. The association between LIC and liver R2* was calculated for both field strengths, 3T and 1.5T, using the Spearman's Rank-Order Correlation Coefficient. Due to possible leverage points or outliers in the data, robust simple linear regression methods were used to fit a regression line to scatter plots. The agreement among the 2 raters was assessed using the intraclass correlation coefficient (ICC). Finally, the 3T-R2* values for all patients were plotted against the corresponding 1.5T-R2* values and robust linear regression models were applied to study the relationship between hepatic R2* measurements from 1.5T and 3T.

Results: Both raters' R2* values were strongly associated with LIC at both field strengths; the correlation coefficients were 0.84 and 0.83 ($p < 0.00005$) for the 3T exam, and 0.97 and 0.95 ($p < 0.00005$) for 1.5T. Rater agreement was strong on R2* data with ICC 0.98 (3T) and 0.98 (1.5T). 6 subjects were excluded for the 3T analysis by rater 1 and 5 subjects by rater 2, because the T2* fit failed in liver tissue due

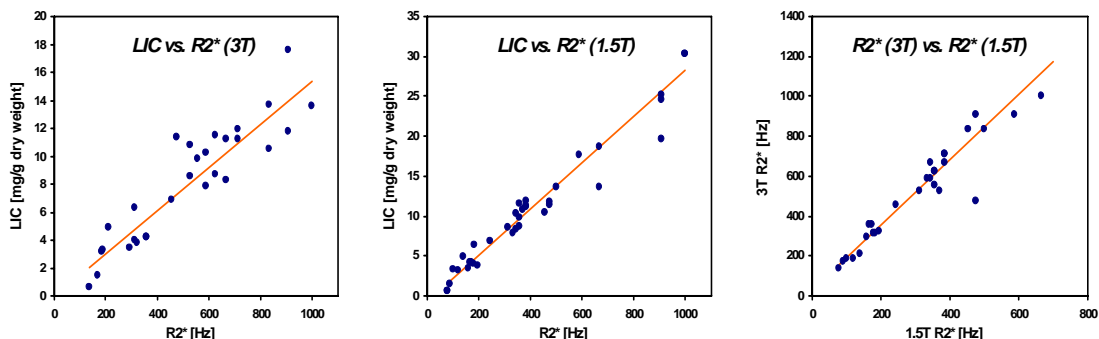


Figure 1: Correlation between LIC data from liver biopsy and hepatic R2*-ROI analysis at 3T (left) and 1.5T (center) in 35 patients with iron overload. The relationship between 3T-R2* liver data and 1.5T-R2* measurements is shown on the right.

to lack of signal. These subjects were later identified as having a very high LIC (mean \pm SD LIC (24.9/26.8 \pm 8.1/6.8)mg/g dry weight [rater 1/rater 2]). Fig. 1 shows the relationship of quantified LIC and hepatic R2*-values from 3T (left) and 1.5T (center) as analyzed by rater 1. A slope of 0.015mg/g/Hz at 3T and 0.029Hz mg/g dry weight at 1.5T (intercept -0.033 and -0.582 mg/g dry weight; R^2 0.72 and 0.67) was calculated using robust regression analysis for this rater and demonstrated a good correlation between LIC and R2* at 3T and 1.5T. The right plot of Fig. 1 shows the 3T-R2* ROI analysis of the same rater plotted against 1.5T-R2* values. The line of best fit for 3T-R2* vs. 1.5T-R2* liver data yielded a slope of 1.63/1.58Hz, an intercept of 32.8/43.3Hz, and an R^2 of 0.74/ 0.75 for rater 1 and rater 2, respectively.

Discussion: The present work is the first patient study that directly investigated the correlation of liver R2* values obtained from 3T MRI scans with LIC data from liver biopsies. It is also the first and largest study to investigate 1.5T-R2* measurements in the same cohort for indirect calibration of 3T-R2* values and direct correlation with biopsy. In our study, 3T-R2* and 1.5T-R2* liver values were highly associated with LIC in patients with iron overload. 1.5T-R2* analysis of the liver correlates slightly better with LIC values than 3T-R2* data. This finding is mainly attributed to the fact that the increased R2* sensitivity at $B_0=3T$ poses challenges to the measurement of R2* in highly overloaded patients ($T2^* < 1-2ms$). Nevertheless, the good correlation between LIC and 3T-R2* demonstrates that R2*-based LIC estimation obtained from 3T scans is sensitive enough in moderately elevated LIC values and could therefore be used for clinical purposes. Our results are particularly relevant considering the increasing number of installed 3T systems.

References: [1] St. Pierre et al. Blood 2005;105: 855-861. [2] Wood JC et al. Blood 2005; 106:1460-1465. [3] Storey P et al. JMRI 2007; 25:540-547. This work was supported in part by our institutional NHLB funded Comprehensive Sickle Cell Center.