T_1, T_2 and T_2^* relaxation time measurements in the liver: Reproducibility, inter- and intra-observer variability

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Introduction: Liver tissue NMR relaxation times have been shown to correlate well with histopathology of liver biopsies. T_1 has been shown to correlate with advanced fibrosis and cirrhosis [1,2] and T_2/T_2* with iron accumulation [1,3]. A recent application of respiratory triggered echo-planar imaging allowed for T_1, T_2 and T_2^* across the whole liver to be acquired in under 10 minutes with excellent patient compliance [4]. However, the reproducibility and inter- and intra-observer variability of these parameters has yet to be determined. The reproducibility of these measurements is critical for assessing the power of the method and the intra- and inter-observer variability is critical to the transferability of the technique to other centres.

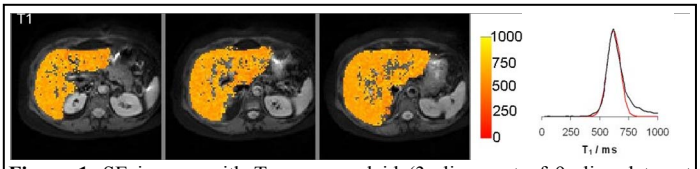

Figure 1. SE images with T_1 map overlaid (3 slices out of 9 slice data set shown). Corresponding histogram (black curve) from 9 slice data set and Gaussian curve fitted to central peak (red curve). Colour overlay displays only pixels where the red curve is non-zero.

Aim: To investigate the reproducibility of T_1, T_2 and T_2* measurements of liver tissue using respiratory-triggered EPI data, and assess the inter- and intra-observer variability of the data analysis.

Methods: *Reproducibility Study:* The study was approved by the local University Ethics Committee, and all volunteers gave written informed consent. Eight healthy volunteers (4 male, mean age 29 yrs, range 26-35 yrs) were scanned on 2 separate occasions after an overnight fast (Mean time between visits 21 days, range 7-81 days). (Healthy volunteers were used to minimise biological differences between visits, as the liver patients' condition may alter over time). Volunteers were scanned on a 1.5 T Philips Achieva scanner, with a body transmit coil and 5-element SENSE cardiac receive coil. All relaxation maps were generated from EPI data (a volume of 9 slices, 3x3x8 mm^3 voxels, 4 mm slice gap, to cover the whole liver, 96x96 image matrix, SENSE 2, SPIR fat saturation (T_2/T_2*), water only spectral excitation (T_1)). Data were acquired with respiratory triggering, during the expiration phase of the breathing cycle with a minimum TR of 3s (T_2/T_2*) or 4s (T_1). Further details on data acquisition can be found in [4].

	T_1	T_2	T_2^*
Mean CV (%)	1.5	3.1	4.3
SD CV (%)	1.7	3.8	3.7
CV 95% CI (%)	4.8	10.7	11.8
Pearson CC *	0.907	0.891	0.935

Table 1. Summary of the reproducibility of relaxation times measured in healthy volunteers.* Pearson correlation coefficient was statistically significant for all parameters ($p<0.01$, N=8).

	T_1		T_2		T_2^*	
	Inter-obs	Intra-obs	Inter-obs	Intra-obs	Inter-obs	Intra-obs
B-A Mean diff (ms)	1	1	-0.4	-0.3	-0.17	-0.05
B-A 95% UB (ms)	10	9	1.6	1.5	0.69	0.14
B-A 95% LB (ms)	-8	-8	-2.4	-2.1	1.02	-0.23
Mean CV (%)	0.33	0.30	0.96	0.92	0.65	0.23
SD CV (%)	0.36	0.32	1.62	1.47	0.89	0.17
CV 95 % CI	1.06	0.93	4.2	3.87	2.44	0.56
ICC*	0.998	0.998	0.992	0.993	0.999	1.000

Table 2. Summary of inter- and intra-observer variability data. * Intra-class correlation coefficient was statistically significant for all parameters ($p<0.001$, N=20).

Data analysis: A mask was drawn around the liver (observer dependent) from a single TE/TI volume and each voxel in the mask was fitted. For the SE-EPI/GE-EPI data, the signal from the voxels were fitted for T_2/T_2* using a weighted least squares fit with 1/TE as the weighting factor to generate a 9 slice T_2/T_2* map. For IR-EPI data, voxels were fitted to a 3 parameter model for M_0, T_1 and α (allowing for imperfections in the inversion pulse) using the Powell algorithm. If respiratory triggering was poor, some through-plane misalignment between slices occurred and these volumes were discarded from the analysis (observer dependent). Histogram analysis was used to eliminate the influence of the longer relaxation times of blood in vessels [4], preventing the need to mask to exclude these voxels, and a Gaussian curve fitted to the central region (observer dependent) to determine the mode of the relaxation time distribution (figure 1). The coefficient of variance (CV) (stdev(σ)/mean) was calculated for the modal measurements of T_1, T_2 and T_2^* from the 2 visits; a Pearson correlation coefficient between visits was also determined.

Inter-observer and Intra-observer variability of data analysis: Data from 20 chronic liver disease patients who were scanned once using the same protocol as the reproducibility study were used to determine inter- and intra-observer variability in the observer dependent components of the data analysis (patient data used to provide realistic biological variation). For the inter-observer measurements, two observers carried out the data analysis; for the intra-observer measurements, one observer carried out the data analysis on two separate occasions at least 3 months apart. Inter- and intra-observer variability was determined for T_1, T_2 and T_2^* using the 95% confidence intervals on a Bland-Altman (B-A) plot [5]. The reproducibility CV and the intra-class correlation coefficient (ICC) for both inter- and intra- observer measures were determined.

Results: Table 1 summarises the CV and correlation coefficient of the reproducibility data in healthy volunteers. Table 2 summarises the inter- and intra-observer variability results in the liver disease patients. The reproducibility data showed good agreement between visits, with a mean CV of 1.5 %, 3.1% and 4.3% for T_1, T_2 and T_2* measures respectively, and a statistically significant correlation coefficient. The inter- and intra-observer variability had similar CV and ICC, with a mean CV % of 0.3 % for T_1, 1 % for T_2 and 0.7 % for T_2^* (inter-observer data).

Discussion and Conclusions: The CVs for intra- and inter-observer repeatability data were much lower than the CV of the reproducibility data, suggesting that biological variability and scanner related noise (e.g. removal of volumes due to poor triggering) dominated the variability observed in the reproducibility data. In conclusion, the reproducibility of NMR relaxation measurements of the whole liver in healthy volunteers was extremely good, with the inter- and intra-observer variability being low. This suggests that measuring liver relaxation times from respiratory-triggered EPI at a single visit has the potential to be a robust non-invasive biomarker for liver fibrosis and iron accumulation.

References [1] Hoad C.L. et al. Gut 2011:60:A55. [2] Keevil S. et al. Brit. J. Radiol. 1994;67;1083-1087 [3] Wood J. et al. Blood 2005;106;1460-1465. [4] Hoad C.L. et al. ISMRM 2010 p2603 [5] Bland J.M. et al. Stat. Methods Med. Res. 1999:8:135-160

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