Voxel-wise reproducibility of Magnetic Resonance Rheology of the liver at 3T MRI

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Introduction: Magnetic Resonance Rheology (MRR, also known as MR elastography) has the potential to serve as a surrogate marker for liver fibrosis detection and monitoring instead of liver biopsy in patients with chronic liver disease[1]. The threshold for detecting a significant change in liver elasticity and viscosity over time that predicts disease progression or regression needs to be established. Factors influencing the rheological measurement can be related to signal-to-noise ratio (SNR), day-to-day physiological changes, and anatomical location. The pattern of fibrosis is often heterogeneously distributed throughout the liver, especially at higher fibrosis grades[1]. We therefore aimed to (1) define the threshold for detecting a significant change in both liver elasticity and viscosity in repeated total-liver MRR measurements, and (2) to focus on the reproducibility of the viscoelastic pattern throughout the liver by calculating the voxel-wise reproducibility of liver MRR in relation to image resolution.

Methods: Intrascan (ISR), within-day (WDR) and between weeks (BWR) reproducibility of MRR was examined in 15 healthy volunteers and in 12 patients with viral hepatitis B/C and biopsy proven liver fibrosis (m/f 17/11; mean age 34.4, range 18-58). Patients were scanned four times: twice while in the same position (ISR), once after repositioning during the same session (WDR), and once 2-4 weeks later (BWR). MRR was performed on a 3T Philips Intera MR system adapted with experimental hardware and acquisition software; a coil-driven piston was placed against the right side of the chest, transmitting longitudinal waves of 50 Hz. A spin-echo echo-planar acquisition sequence was used to measure the 3D displacement vector of the propagating waves (TR/TE=420/40 ms, FOV 320x320x28 mm, voxel size 4x4x4 mm, acquisition matrix 80x80, acquisition time 70 s. in 6 breath holds on expiration), from which elasticity (kPa) and viscosity (Pa.s) maps were generated. Per participant, the repeated scans were registered to the first using a 2D rigid registration method. Subsequently, a ROI was manually drawn outlining the liver, avoiding boundaries and large vessels. This ROI was copied from the first scan to the registered corresponding scans. For ISR, WDR and BWR we used Bland-Altman analysis to calculate total-liver coefficients of reproducibility (CR) and voxel-wise CR (vwCR), defined as 1.96.SD of the paired differences[2,3]. CR is the threshold value below which the difference between repeated measurements is expected to lie for 95% of pairs of repeated measurements. The repeatability index (RI) was calculated as CR/mean value. CRs were compared using F-tests. To evaluate the influence of image resolution on voxel-wise reproducibility, all ROIs were spatially convolved using a Gaussian filter with step-wise increasing full width half maximums (FWHM), while correcting for boundary effects (*fig 1*). For both elasticity and viscosity, the vwCR was determined as a function of spatial resolution.

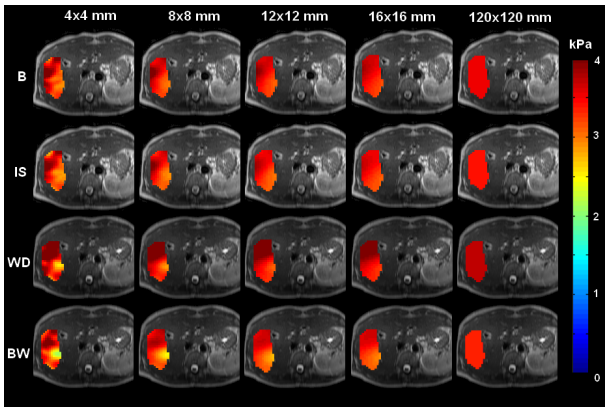

Fig 1: Axial elasticity maps (kPa) of a patient with liver cirrhosis. Horizontally: Decreasing image resolution. Top to bottom: baseline scan (B) and repeated scans ISR, WDR and BWR.

Results: Mean total-liver ROI size was 12.1 ± 3.5 cm^3. Reproducibility results are shown in *table 1*. There were no significant differences in reproducibility parameters between patients and volunteers. Elasticity showed slightly better reproducibility than viscosity. The BWR analysis shows that an over-time change in elasticity of more than ~20% indicates a significant change, which would mean disease progression or regression in patients. The mean voxel-wise reproducibility increased as a function of decreasing image resolution, as shown in *fig 2*. At the lowest resolution of 80 mm FWHM, voxel-wise reproducibility equals total-liver reproducibility analysis. For both rheological parameters, WDR and BWR reproducibility decreased significantly compared to the ISR session ($p<0.01$ for elasticity and $p=0.02$ for viscosity). WDR and BWR yielded comparable results ($p=0.31$ for elasticity and $p=0.91$ for viscosity).

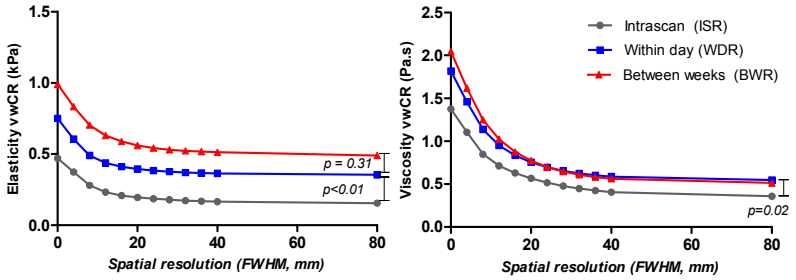

Fig 2: Voxel-wise analysis in relation to spatial resolution of all 27 participants (5085 voxels).

Table 1: Reproducibility results

		Mean elasticity ±SD (kPa)	Tot CR (kPa)	Tot RI (%)	vwCR (kPa)*	vwRI (%)*	Mean viscosity ±SD (Pa*s)	Tot CR (Pa*s)	Tot RI (%)	vwCR (Pa*s)*	vwRI (%)*
Intrascan	**Pat *(12)***	2.32±0.83	0.15	**6.5**	0.24	**10.3**	2.27±0.62	0.31	**13.7**	0.62	**27.3**
	Vol *(15)*	1.66±0.12	0.17	**10.2**	0.23	**13.7**	1.74±0.25	0.37	**21.3**	0.78	**44.8**
	Tot (27)	1.95±0.64	0.16	**8.2**	0.23	**11.8**	1.98±0.52	0.35	**17.7**	0.71	**35.9**
Within day	**Pat *(12)***	2.36±0.83	0.38	**16.1**	0.49	**20.8**	2.28±0.59	0.63	**27.6**	1.00	**43.9**
	Vol *(15)*	1.65±0.13	0.33	**20.0**	0.37	**22.4**	1.77±0.21	0.53	**29.9**	0.89	**50.3**
	Tot (27)	1.95±0.65	0.36	**18.5**	0.44	**22.6**	1.99±0.51	0.57	**28.6**	0.95	**47.7**
Between weeks	**Pat *(12)***	2.31±0.73	0.57	**24.7**	0.81	**35.1**	2.27±0.58	0.46	**20.3**	1.04	**45.8**
	Vol *(15)*	1.66±0.12	0.31	**18.7**	0.38	**22.9**	1.80±0.21	0.64	**35.6**	1.01	**56.1**
	Tot (27)	1.97±0.59	0.47	**24.0**	0.63	**32.0**	2.01±0.49	0.56	**27.9**	1.02	**50.7**

Coefficient of repeatability (CR) = 1.96 SD paired differences; Repeatability Index (RI)= CR/mean value; Tot = total liver analysis; vw = voxel-wise analysis.* ****The voxel-wise results were obtained at an image resolution of 12x12 mm FWHM.***

We found that the voxel-wise results at a spatial resolution of 12 mm FWHM yielded an acceptable trade-off between reproducibility and spatial resolution for this cohort, as presented in *fig 2* and in *table 1*.

Conclusion and Discussion: MRR is a reproducible technique for both healthy and fibrotic livers. Our results are in line with previous studies[4,5]. Between-weeks reproducibility is the most important parameter for clinical applicability. However, different factors such as SNR, day-to-day physiological variations and patient position can influence reproducibility. Intrascan reproducibility is unrelated to day-to-day variations in patient physiology or anatomical position, and thus reflects the technical reproducibility. The decrease in reproducibility of WDR and BWR scans can thus be attributed to anatomical factors (precision of repositioning). We have shown that physiological day-to-day changes play a minor role in this cohort, as WDR and BWR results were not significantly different. Our voxel-wise analyses indicate that MRR can be used for the evaluation of smaller, focal liver lesions, although there is a trade-off between reproducibility and spatial resolution.

References: [1]*Huwart, Radiology 2007;* [2]*Padhani, NMR in Biomed 2002;* [3]*Korporaal, Radiology 2010;* [4]*Hines, JMRI 2010;* [5]*Huwart, Gastroenterology 2008.*