MR Elastography of the Liver: Defining Thresholds for Detecting Viscoelastic Changes[1]

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Purpose: To define thresholds for detecting significant change in liver viscoelasticity with magnetic resonance (MR) elastography, both for whole-liver measurements and for voxel-wise measurements in relation to spatial resolution.

Materials and Methods: This prospective study was approved by the institutional review board, and all participants provided written informed consent. Thirty participants (16 volunteers and 14 patients with hepatitis B or C; 18 men; median age, 30.4 years; age range, 18.9–58.6 years) underwent imaging twice while in the same position (intraimage reproducibility), after repositioning (within-day reproducibility), and 1–4 weeks later (between-weeks reproducibility). MR elastography parameters comprised elasticity, viscosity, attenuation parameter α, and propagation parameter β. Bland-Altman analysis was used to calculate repeatability indexes for each parameter. Analyses were performed in a region-of-interest and a voxel-by-voxel level. Voxel-wise results were calculated in relation to spatial resolution by applying Gaussian filtering to establish the optimal trade-off point between resolution and reproducibility.

Results: For elasticity, α, and β, within-day and between-weeks results were significantly lower than intraimage results ($P \leq .018$ for all). Within-day and between-weeks results did not differ significantly. Over-time changes of more than 22.2% for elasticity, 26.3% for viscosity, 26.8% for α, and 10.1% for β represented thresholds for significant change. The optimal trade-off between spatial resolution and reproducibility was found at a filter size of 8-mm full width at half maximum (FWHM) for elasticity and propagation parameter β and at 16-mm FWHM for viscosity and attenuation parameter α.

Conclusion: Repositioning causes a significant decrease in the reproducibility of MR elastography. The propagation parameter β is the most reliable parameter, with an over-time threshold for significant change of 10.1% and the ability to reproduce viscoelasticity up to a resolution of 8-mm FWHM.

Supplemental material: *http://radiology.rsna.org/lookup/suppl/doi:10.1148/radiol.13122669/-/DC1*

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Magnetic resonance (MR) elastography is a rapidly developing technique that is used to quantify the viscoelastic properties of tissue, which change under pathologic conditions. In the liver, the technique has the potential to serve as an alternative to liver biopsy in the staging and monitoring of liver fibrosis in patients with chronic liver disease (1–4). Revealing the viscoelastic properties of liver tumors is another area in which the technique holds promise (5). Although the exact acquisition and postprocessing methods of MR elastography may differ between different sites, the common feature of these methods is that low-frequency mechanical waves are sent into the tissue of interest, inducing shear stresses while propagating. Motion-sensitive MR imaging sequences are used to measure the resulting displacement fields. From these displacement fields, the viscoelastic shear properties of the tissue are analyzed (6–9).

Shear properties can be described as a complex number: the shear modulus G^*. The real part of G^* is the storage modulus (G'), and its imaginary counterpart is the loss modulus (G''): $G^* = G' + iG''$. The storage modulus G' and loss modulus G'' relate to shear elasticity and shear viscosity, respectively, when invoking a Voigt model (5). When assuming that the wave propagates through a linear, incompressible, and viscoelastic medium, the derivation of G^* can be simplified (9–11) to $G^* = \rho\omega^2/k^2$, where ρ represents the density of the material and ω the angular frequency of the vibration. The wave-vector k is also a complex quantity, describing the spatial behavior of the wave when considering a plane-wave. Wave-vector k consists of a real part β, representing propagation (in mm^{-1}), and an imaginary part α representing attenuation (in mm^{-1}): $k = \beta + i\alpha$. From here, both elasticity and viscosity can be derived separately, as explained in more detail in Appendix E1 (online). These relationships demonstrate that robustness of both attenuation parameter α and propagation parameter β are of crucial importance to a reliable reconstruction of elasticity and viscosity in MR elastography.

Defining thresholds for detecting significant changes in the liver with MR elastography, both globally and focally, is an important step toward clinical implementation of the technique. For the evaluation of liver fibrosis with MR elastography, a large portion of the liver is included, which is considered a major benefit compared with liver biopsy and transient elastography (Fibroscan; Echosens, Paris, France) (12). However, by calculating the average liver viscoelasticity, focal heterogeneities are not considered. Liver fibrosis has a heterogeneous distribution throughout the liver (13), and MR elastograms also exhibit a heterogeneous pattern. Whether this pattern is reproducible—and thus reflects real focal viscoelastic variability—has not been investigated. To achieve this, a voxel-based reproducibility analysis in relation to spatial resolution is required. In other words: At what spatial resolution can focal fibrotic areas be detected and reproduced with MR elastography?

The aim of this study, therefore, was to define thresholds for detecting significant change in liver viscoelasticity with MR elastography, both for whole-liver measurements and for voxel-wise measurements in relation to spatial resolution.

Advances in Knowledge

- Patient repositioning is the main determinant of variation when repeating MR elastography: Within-day reproducibility differed significantly from intraimage reproducibility with regard to elasticity ($P = .001$), attenuation parameter α ($P = .018$), and propagation parameter β ($P = .001$).
- Between-weeks reproducibility did not differ significantly from within-day reproducibility for any MR elastography parameter ($P = .109$–$.598$), which suggests that physiologic day-to-day variations play a minor role in MR elastography.
- Propagation parameter β is the most reproducible MR elastography parameter, with an over-time threshold for significant change of 10.1%; corresponding results were 22.2% for elasticity, 26.3% for viscosity, and 26.8% for attenuation parameter α.
- Elasticity and propagation parameter β are reproducible up to a resolution of 8-mm full width at half maximum.

Implication for Patient Care

- In the longitudinal evaluation of liver fibrosis with spin-echo echo-planar MR elastography, the defined thresholds for significant change of 22.2% for elasticity, 26.3% for viscosity, 26.8% for attenuation parameter α, and 10.1% for propagation parameter β should be taken into account.

Materials and Methods

This study was funded by Nuts Ohra Foundation, the Netherlands. Nuts Ohra Foundation was not involved in designing and conducting this study, did not have access to the data, and was not involved in data analysis or preparation of this article.

Published online before print
10.1148/radiol.13122669 **Content code:** GI

Radiology 2013; 269:768–776

Abbreviations:
FWHM = full width at half maximum
RI = repeatability index
ROI = region of interest

Author contributions:
Guarantors of integrity of entire study, A.E.B., A.D.N., R.S., A.J.N.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, A.E.B., A.D.N.; clinical studies, A.E.B., A.D.N., A.J.N.; statistical analysis, A.E.B., P.G., A.D.N., R.S., A.J.N.; and manuscript editing, A.E.B., P.G., A.D.N., R.S., J.S., A.J.N.

Conflicts of interest are listed at the end of this article.

Participants and Study Procedures

This prospective study was approved by the institutional review board, and all participants provided written informed consent. From December 2010 until April 2012, 32 participants aged 18 years and older were included. An equivalence test for paired means (Schuirmann two one-sided test approach) was performed to establish the number of participants needed. On the basis of test data in a healthy volunteer who underwent imaging twice on different days (mean elasticity of 1.67 kPa and 1.73 kPa), a sample size of 15 pairs gives 83% power to detect equivalence in means. We finally included 16 patients with chronic liver disease and 16 healthy volunteers. Patients were eligible if they had chronic viral hepatitis B or C and if results of liver biopsy were available. Volunteers were eligible if they had no history of liver disease and if they were not using any medication with the exception of oral contraceptives. Exclusion criteria for patients and volunteers were as follows: alcohol consumption of more than 3 units per day for men and more than 2 units per day for women, known hemochromatosis, or contraindications to MR imaging.

Patients were consecutively recruited from an ongoing MR elastography study that included patients with chronic viral hepatitis B or C who underwent a liver biopsy. All patients, therefore, met the inclusion and exclusion criteria. All approached patients agreed to participate in this study, which consisted of a single extra visit to the hospital to acquire reproducibility data. A total of 17 volunteers were recruited. One volunteer had a contraindication to MR imaging and did not participate in this study.

Participants underwent imaging four times to obtain three different types of reproducibility data: intraimage reproducibility, within-day reproducibility, and between-weeks reproducibility. For intraimage reproducibility, two MR elastography images were acquired immediately after one another while the participant remained in the same position in the MR unit. The first image was used as the baseline image for further reproducibility analyses. For within-day reproducibility, participants took a 5–10-minute break outside the MR imaging room after undergoing the intraimage reproducibility study. Then, the participant was repositioned in the MR unit to obtain a third MR elastography image. For between-weeks reproducibility, a fourth MR elastography image was acquired 1–4 weeks later.

The intraimage session reflects the technical reproducibility of MR elastography. Variability owing to repositioning is introduced during the within-day session, and day-to-day physiologic variation in the liver is added as a possible source of variation during the between-weeks session.

MR Elastography: Image Acquisition and Postprocessing

MR elastography was performed with a 3.0-T MR system (Intera; Philips Healthcare, Best, the Netherlands). For MR elastography planning, nondiagnostic anatomic images were acquired in the transverse, coronal, and sagittal planes with a single-shot fast spin-echo sequence (repetition time msec/echo time msec = 632/70, 90° flip angle, 450 × 450-mm field of view, and 0.7 × 0.7 × 4.0-mm voxel size). Subsequently, for MR elastography acquisition, harmonic mechanical waves of 50 Hz were applied to the liver with a portable electromechanical transducer, which was placed on the right side of the chest. Synchronous motion-encoding bipolar gradients were added to a motion-sensitive two-dimensional spin echo–based echo-planar imaging sequence with the following parameters (5): 560/40, 90° flip angle, seven sections, 320 × 320-mm field of view, and 4 × 4 × 4-mm^3 voxel size. Phase images were acquired in three orthogonal motion-encoding directions, and phase sampling consisted of eight points per vibration period. The total MR elastography acquisition time was 78 seconds, divided over six breath holds on expiration of 13 seconds each. Transverse sections of the liver were obtained. Screenshots of the MR elastography planning in the transverse, sagittal, and coronal planes were saved to facilitate planning of the repeat MR elastography images at the same anatomic location. Thoracic vertebrae were used as anatomic landmarks to this purpose (Fig 1a–c). Elastograms of the liver were reconstructed by using dedicated postprocessing software (11). Per participant, each repeated image was registered to the baseline image in the x-y plane by using a two-dimensional rigid body registration method in Matlab (MathWorks, Natick, Mass), with in-plane translations and rotations. For reliable MR elastography reconstruction per voxel, a minimum of two neighboring voxels in each direction is required. This means that only the middle three of the seven acquired transverse sections contain reliable MR elastography results. These three sections were merged into a single 12-mm-thick section for all further analyses.

Reproducibility Analysis

On the baseline anatomic MR image, a single region of interest (ROI) was manually drawn in the right liver lobe by a physician experienced in MR elastography (A.E.B., with 3 years of experience). For ROI placement, care was taken to *(a)* avoid liver margins and large vessels (Fig 1d) and *(b)* include sufficient wave penetration within the entire ROI. Areas with sufficient wave penetration were selected by analyzing the displacement maps (Fig 1e). Tissue displacement in the splenic region was measured in each individual and considered to be "noise" because the mechanical waves induced by the transducer do not penetrate this far. Three times this noise value was consequently used as the lower threshold value for sufficient wave penetration within the liver.

Consequently, the selected ROI was automatically transposed onto the corresponding, registered MR elastography images. The ROIs were visually inspected to ensure that they fulfilled the earlier ROI criteria, and ROI placement was adjusted if necessary. Finally, one identical ROI per participant was used for all four repeated MR elastography images. Mean elasticity (in kilopascals), viscosity (in pascal-seconds), attenuation

Figure 1

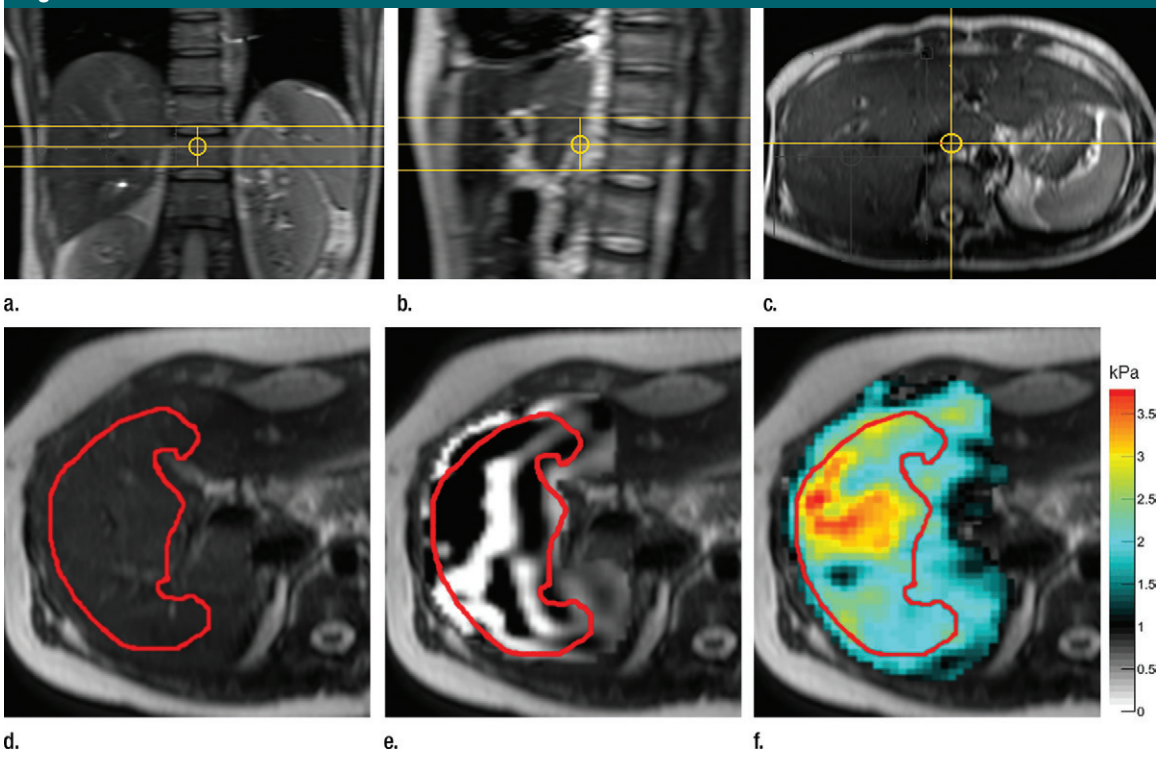

Figure 1: Acquisition and postprocessing of images from MR elastography. **(a–c)** Examples of MR elastography planning with **(a)** coronal, **(b)** sagittal, and **(c)** transverse MR images. Thoracic vertebrae are used as anatomic landmarks to retrieve the same anatomic location during the repeated imaging sessions. **(d)** ROI placement in axial sections, avoiding liver margins and large vessels. **(e)** Wave image shows that waves penetrate well throughout entire ROI. **(f)** Elastogram of liver. Voxels are color-coded from 0 to 3.5 kPa. The mean elasticity value within this selected ROI was 2.10 kPa.

parameter α (in mm^{-1}), and propagation parameter β (in mm^{-1}) values were measured inside the ROI and used for reproducibility analysis (Fig 1f).

Voxel-Wise Reproducibility Analysis

To study the influence of spatial resolution on voxel-wise reproducibility, we spatially convolved all voxels within each ROI. To achieve this, a Gaussian filter with a kernel size of 80 × 80 voxels and increasing full width at half maximum (FWHM) was applied to the data. This procedure effectively averages each voxel with an increasing number of neighboring voxels, thereby decreasing the spatial resolution. Boundary effects were corrected for, preventing contamination from voxels outside the ROI. For each spatial resolution, every baseline voxel was paired with its corresponding voxel of the repeated image. For each participant, mean reproducibility was calculated for all voxel pairs for all four MR elastography parameters. From this analysis, the optimal trade-off between spatial resolution and reproducibility was determined.

Statistical Analysis

Reproducibility was quantitatively assessed by using a modified Bland-Altman analysis (14,15). First, the percentage difference between repeated measurements (rm) was calculated for each individual, as follows: difference (rm1, rm2)/mean (rm1, rm2) × 100%. Then, the standard deviation of the percentage difference (SD%) was calculated for all individuals per (sub)group. Finally, the repeatability index (RI) was calculated as follows: 1.96 × SD%.

The RI defines the threshold values below which the percentage difference between repeated measurements is expected to lie for 95% of pairs of repeated measurements. RIs were calculated instead of the more widely used coefficient of repeatability (14) to enable comparison of the reproducibility of elasticity, viscosity, attenuation parameter α, and propagation parameter β.

Baseline characteristics were compared with the Mann-Whitney *U* test. Means ± 95% confidence intervals were obtained. Variances of percentage differences were compared with the Levene test. $P < .05$ was considered indicative of a statistically significant difference. Power analysis was performed by using software (PASS 2008; NSCC Statistical Software, Kaysville, Utah). For statistical analysis and graphical representation of data, Matlab R2011a (MathWorks), GraphPad Prism 5 (GraphPad Software, La Jolla, Calif), and IBM SPSS 19.0 (IBM SPSS Statistics, Armonk, NY) were used.

Results

Participants and Study Procedures

Two patients were excluded from analysis: One patient was excluded because of technical problems with the MR unit, and the other patient withdrew from the study before all procedures were completed. Therefore, results of 30 participants were analyzed (16 healthy volunteers and 14 patients). Anthropometric data are presented in Table 1. Overall, women were significantly younger than men (P = .034). There were no significant differences with respect to body mass index. The median interval between the baseline and between-weeks session was 15.5 days (range, 3–30 days).

All patients had histologic proof of liver fibrosis. Liver fibrosis was scored according to the Metavir score from stage F0 (no fibrosis) to stage F4 (cirrhosis) (16). Six patients had mild fibrosis (stage F1), one patient had moderate fibrosis (stage F2), six patients had severe fibrosis (stage F3), and one patient had cirrhosis (stage F4).

MR Imaging

The data obtained with MR elastography are shown in Table 2. The selected liver ROIs comprised a mean (±standard deviation) of 187 voxels ± 53, with a voxel size of $4 \times 4 \times 12$ mm^3.

The anatomic MR series were read by a radiologist for focal lesions. One patient had a known hemangioma. Another patient had a benign cyst in the right kidney. No other focal lesions were observed.

Reproducibility Analysis

Patients vs volunteers.—There were no significant differences in reproducibility results between patients and volunteers with regard to elasticity, viscosity, or attenuation parameter α (Table 3). For propagation parameter β, reproducibility results of patients and volunteers differed significantly for the intraimage session only (P = .037). In all further analyses, results of patients and volunteers are combined.

Table 1

Anthropometric Data of Participants

Parameter	All Subjects (n = 30)	Patients (n = 14)	Volunteers (n = 16)
Sex			
M	18	11	7
F	12	3	9
Age (y)*			
All subjects	30.4 (18.9–58.6)	45.1 (30.8–58.6)	24.8 (18.9–31.5)
M	37.0 (24.1–58.6)†	45.8 (30.8–58.6)	27.5 (24.1–31.5)
F	26.2 (18.9–52.1)†	44.5 (43.3–52.1)	23.6 (18.9–30.0)
BMI (kg/m^2)*			
All subjects	24.7 (19.0–29.0)	26.2 (19.1–29.0)	23.0 (19.0–27.6)
M	25.7 (21.6–26.8)	26.0 (22.7–26.8)	23.1 (21.6–25.7)
F	23.3 (19.0–29.0)	26.6 (19.1–29.0)	22.9 (19.0–27.6)
Liver disease			
Hepatitis B	9	9 (8 M, 1 F)	0
Hepatitis C	5	5 (3 M, 2 F)	0

Note.—Except where indicated, data are numbers of subjects. BMI = body mass index.

* Data are medians. Numbers in parentheses are ranges.

† Statistically significant difference; P = .034.

Table 2

Results of MR Elastography

Parameter	All Subjects (n = 30)	Patients (n = 14)	Volunteers (n = 16)
Elasticity (kPa)			
Baseline (image 1)	1.83 ± 0.22	2.14 ± 0.42	1.57 ± 0.09
Intraimage analysis (image 2)	1.82 ± 0.22	2.13 ± 0.42	1.55 ± 0.08
Within-day analysis (image 3)	1.81 ± 0.23	2.15 ± 0.44	1.52 ± 0.07
Between-weeks analysis (image 4)	1.82 ± 0.18	2.09 ± 0.33	1.57 ± 0.10
Viscosity (Pa·sec)			
Baseline (image 1)	2.19 ± 0.26	2.58 ± 0.48	1.84 ± 0.12
Intraimage analysis (image 2)	2.15 ± 0.26	2.55 ± 0.50	1.81 ± 0.09
Within-day analysis (image 3)	2.19 ± 0.27	2.62 ± 0.52	1.81 ± 0.07
Between-weeks analysis (image 4)	2.21 ± 0.24	2.57 ± 0.44	1.89 ± 0.13
Attenuation parameter α (mm^{-1})			
Baseline (image 1)	0.041 ± 0.0027	0.039 ± 0.0041	0.043 ± 0.0036
Intraimage analysis (image 2)	0.041 ± 0.0024	0.039 ± 0.0043	0.043 ± 0.0026
Within-day analysis (image 3)	0.042 ± 0.0023	0.039 ± 0.0037	0.044 ± 0.0024
Between-weeks analysis (image 4)	0.042 ± 0.0023	0.040 ± 0.0043	0.044 ± 0.0022
Propagation parameter β (mm^{-1})			
Baseline (image 1)	0.228 ± 0.0099	0.213 ± 0.018	0.241 ± 0.006
Intraimage analysis (image 2)	0.229 ± 0.0100	0.214 ± 0.018	0.243 ± 0.005
Within-day analysis (image 3)	0.230 ± 0.0103	0.213 ± 0.019	0.245 ± 0.005
Between-weeks analysis (image 4)	0.228 ± 0.0093	0.212 ± 0.016	0.240 ± 0.007

Note.—Data are means ± 95% confidence intervals.

Intraimage, within-day, and between-weeks sessions.—The whole-ROI reproducibility results for intraimage, within-day, and between-weeks sessions are summarized in Table 4 and illustrated in Figure 2. Over-time changes (between-weeks RI) of more than 22.2% for elasticity, 26.3% for viscosity, 26.8% for the attenuation parameter α, and 10.1% for the

Table 3

Reproducibility: Patients versus Volunteers

Parameter	Intraimage Analysis				Within-Day Analysis				Between-Weeks Analysis			
	RI Patients (%)*	RI Volunteers (%)*	LS	*P* Value	RI Patients (%)*	RI Volunteers (%)*	LS	*P* Value	RI Patients (%)*	RI Volunteers (%)*	LS	*P* Value
Elasticity	5.4 ± 2.8	8.3 ± 3.9	3.48	.073	15.9 ± 8.1	17.3 ± 8.1	0.20	.662	21.8 ± 11.1	23.2 ± 10.9	0.02	.886
Viscosity	11.2 ± 5.7	20.6 ± 9.7	1.93	.176	24.0 ± 12.3	19.0 ± 8.9	0.85	.365	17.9 ± 9.1	32.4 ± 15.3	2.86	.102
Attenuation parameter α	13.4 ± 6.8	13.4 ± 6.3	0.01	.911	16.3 ± 8.3	21.6 ± 10.2	0.52	.477	27.5 ± 14.0	27.1 ± 12.7	0.53	.474
Propagation parameter β	2.7 ± 1.4	5.0 ± 2.3	4.81	.037	8.0 ± 4.1	8.5 ± 4.0	0.07	.801	8.9 ± 4.5	11.3 ± 5.3	0.11	.738

Note.—LS = Levene statistic.

* Data are mean RIs ± 95% confidence intervals.

Table 4

Results of Reproducibility Analysis for All Subjects

Parameter	Intraimage Analysis	Within-Day Analysis	Between-Weeks Analysis
Elasticity	7.0 ± 2.3	16.8 ± 5.5	22.2 ± 7.3
Viscosity	16.6 ± 5.5	21.2 ± 7.0	26.3 ± 8.7
Attenuation parameter α	10.9 ± 3.6	19.3 ± 6.4	26.8 ± 8.8
Propagation parameter β	4.1 ± 1.3	8.3 ± 2.7	10.1 ± 3.3

Note.—Data are mean RIs (as percentages)± 95% confidence intervals.

Figure 2

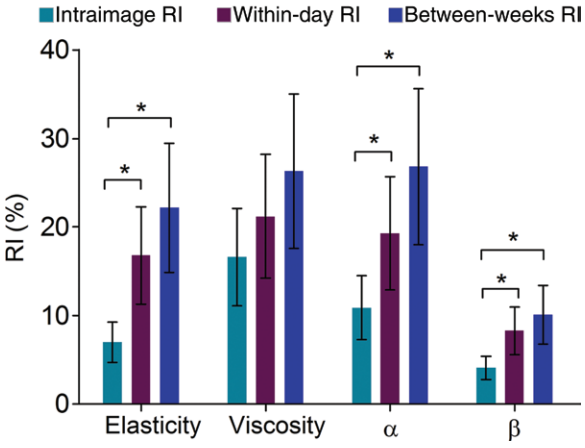

Figure 2: Whole-ROI reproducibility results for each MR elastography parameter. Bar chart shows RI of elasticity, viscosity, attenuation parameter α, and propagation parameter β for all 30 participants. Error bars represent 95% confidence intervals. * = statistically significant difference ($P < .05$).

propagation parameter β were statistically significant.

For each MR elastography parameter except viscosity, the RI increased for each consecutive reproducibility session (intraimage < within-day < between-weeks). For elasticity, attenuation parameter α, and propagation parameter β, within-day and between-weeks reproducibility results were significantly lower than intraimage reproducibility results ($P \leq .018$ for all). Within-day results were not significantly different from between-weeks results (Table 5). These results suggest that, in this population, patient repositioning had a significant effect on reproducibility but day-to-day physiologic changes did not. Reproducibility results of viscosity did not correspond to this pattern; no reproducibility session was significantly different from the other.

Voxel-Wise Reproducibility Analysis

The effect of decreasing the spatial resolution of MR elastography is illustrated in Figure 3. At the lowest resolution of 120-mm FWHM, each voxel within the selected ROI approximated the mean value of the entire ROI. Improvement of reproducibility at decreasing spatial resolution is shown in Figure 4. We defined the optimal trade-off between spatial resolution and reproducibility as 1.25 times the between-weeks RI at the lowest resolution. This optimal trade-off point was found at different resolutions for each parameter and was at 8-mm FWHM (two voxels) for elasticity, 16-mm FWHM (four voxels) for viscosity, 16-mm FWHM (four voxels) for attenuation parameter α, and 8-mm FWHM (two voxels) for propagation parameter β. Mean RIs at these resolutions were 27.8% for elasticity, 32.9% for viscosity, 33.5% for attenuation parameter α, and 12.6% for propagation parameter β. These results reflect the resolution from which MR elastography can reproduce viscoelastic changes.

Discussion

With this study, we demonstrated that the difference between repeated MR elastography examinations of the liver for the same individual on different

Table 5

Reproducibility: Intraimage versus Within-Day versus Between-Weeks Analyses

	Elasticity		Viscosity		α		β	
Parameter	LS	*P* Value	LS	*P* Value	LS	*P* Value	LS	*P* Value
Intraimage vs within-day analysis	11.69	.001	1.91	.172	5.97	.018	11.94	.001
Intraimage vs between-weeks analysis	16.97	.0001	3.68	.060	13.68	.0005	10.66	.002
Within-day vs between-weeks analysis	1.48	.229	0.53	.468	2.65	.109	0.28	.598

Note.—Statistical analysis was performed on RI values shown in Table 4. LS = Levene statistic.

Figure 3

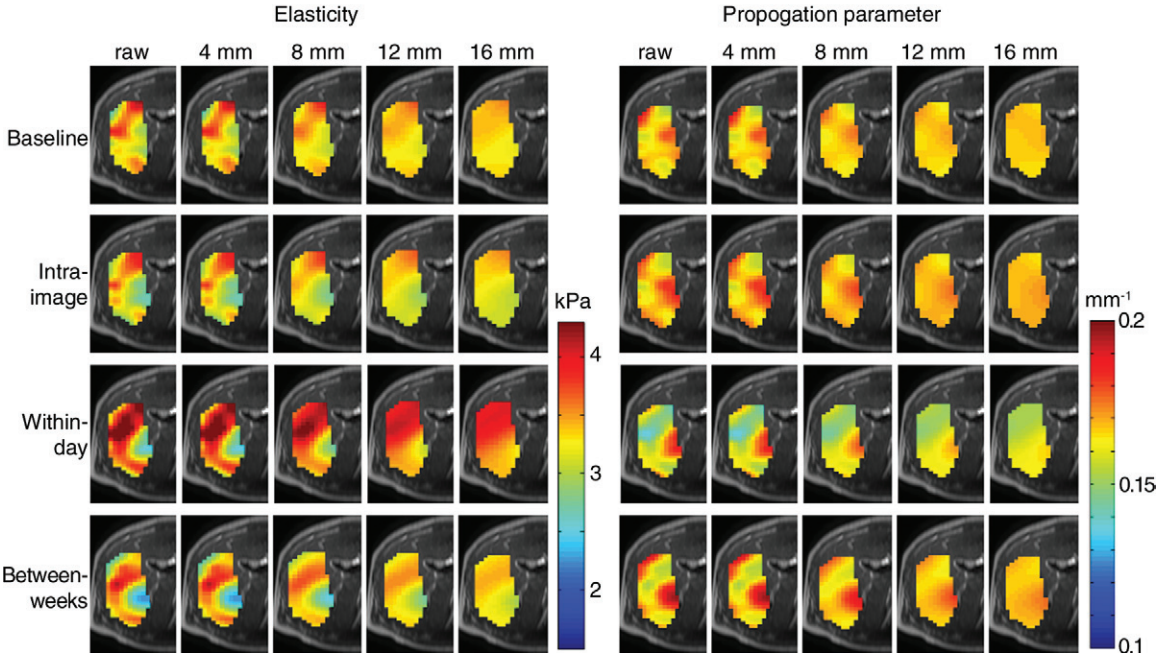

Figure 3: MR elastography as a function of spatial resolution. Axial images obtained in 51-year-old woman with liver cirrhosis demonstrate, left, elasticity and, right, propagation parameter β. Images show how image resolution is decreased by applying a Gaussian filter with increasing FWHM of 4, 8, 12, and 16 mm. Images were obtained at baseline, intraimage session, within-day session, and between-weeks session. For elasticity, mean MR elastography values were 3.3, 3.2, 3.7, and 3.3 kPa, respectively. For β, mean values were 0.167, 0.169, 0.159, and 0.169 mm^{-1}, respectively. Pattern at intraimage session closely resembles that at baseline. For within-day and between-weeks sessions, patterns correspond, but to a lesser extent. Mean value of within-day image differs markedly from that of other three images.

days (between-weeks RI) did not exceed 22.2% for elasticity and 26.3% for viscosity when using a spin-echo echo-planar sequence at 3.0-T MR imaging. This means that, over time, changes beyond these thresholds indicate a significant change. Because both elasticity and viscosity are derived from attenuation parameter α and propagation parameter β, we also investigated their respective reproducibility. We found propagation parameter β to be a surprisingly reproducible parameter, with a between-weeks RI not exceeding 10.1%. Attenuation parameter α, conversely, was the least reproducible parameter, with a between-weeks RI of 26.8%. In addition, we found that reproducibility was significantly affected by patient repositioning but not by day-to-day physiologic changes in the patient.

In addition, we evaluated the reproducibility of MR elastography on a voxel-based level. We showed that the optimal trade-off between spatial resolution and reproducibility was different for each of the MR elastography parameters analyzed. Elasticity and propagation parameter β performed best, with an optimal point at 8-mm FWHM (two voxels). Results of viscosity and attenuation parameter α were not as good, with an optimal resolution of 16-mm FWHM. This means that viscoelasticity in areas of this size can be reproduced

Figure 4

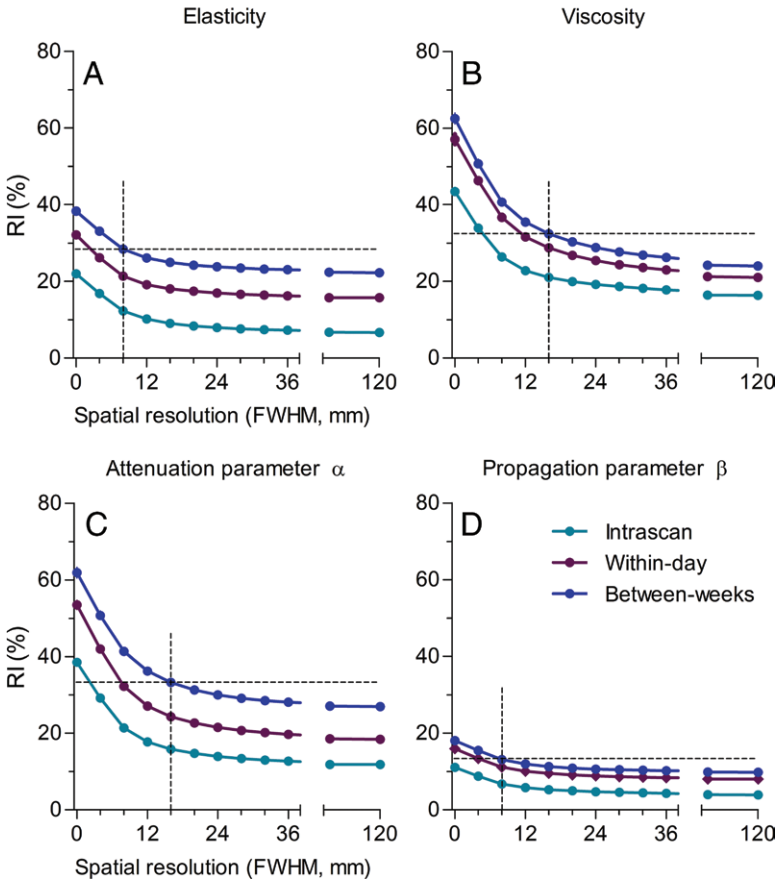

Figure 4: Voxel-wise reproducibility in relation to spatial resolution for each MR elastography parameter. Graphs represent voxel-wise results from all 30 participants (5594 paired voxels). Data points represent mean RIs. Spatial resolution was decreased by using Gaussian filter with FWHM. For each parameter, optimal trade-off point between spatial resolution and reproducibility for between-weeks reproducibility is shown where dotted lines meet (at 1.25 times the RI at 120-mm FWHM). This optimal trade-off point is found at 8-mm FWHM for elasticity and propagation parameter β (*A, D*) and at 16-mm FWHM for viscosity and attenuation parameter α (*B, C*).

with a precision that is 25% lower than the larger whole-liver ROIs. In line therewith, these results—theoretically—reflect the size that would be required for focal liver lesions to be reproducible with MR elastography.

Other studies have investigated the reproducibility of MR elastography of the liver. Hines et al (17) repeated MR elastography of the liver in 20 healthy volunteers and 10 patients with chronic liver disease on the same day. MR elastography was repeated 7–14 days later in the healthy subjects. Longitudinal stiffness changes greater than 37% were significant, which is higher than any of our between-weeks thresholds. Shire et al (18) conducted a repeatability study in five healthy volunteers and four patients with hepatitis C virus. MR elastography was repeated on the same day and then once more after 1–14 days. The within-subjects coefficients of variation (wCV) ranged from 6.1% to 10.8%. Because RI = 2.77 × wCV, these results correspond to RIs ranging from 16.9% to 29.9% (19). These results were comparable to our results, not only with respect to the reproducibility but also with respect to the fact that their between-weeks results were not significantly higher than their within-day results. Both of these studies were carried out with a 1.5-T MR system with use of different MR elastography acquisition and postprocessing technique. One study with acquisition and postprocessing methods comparable to ours investigated the reproducibility of elasticity and viscosity in five healthy volunteers (20). The within-subject coefficients of variation was 9% for elasticity (RI: 24.9%) and 7% for viscosity (RI: 19.4%). Again, these results are comparable to our results.

MR elastographic examinations in this study were not standardized with respect to time of day or prandial state. This is a limitation to our study, because prandial state has been shown to influence MR elastography results in patients with liver fibrosis—especially when cirrhosis is present (21). No significant differences with respect to prandial state were observed in the literature in healthy individuals (21,22). We mostly performed MR elastography early in the morning and asked participants not to eat breakfast. Unfortunately, this was not always achieved. We do, however, believe that this limitation did not influence our results much because the differences between within-day and between-weeks reproducibility were not significant for any MR elastography parameter. Furthermore, our data reflect daily clinical practice in which patients are scheduled for MR imaging throughout the day.

Another limitation of this study is the fact that our MR elastography acquisition technique consisted of six consecutive breath holds on expiration. We practiced the breath holding with our participants before imaging and asked them to try and hold their breaths in the same fashion each time. Still, this could have caused variations in the exact anatomic location of MR elastography measurement. In addition, repositioning the participants during the within-day and between-weeks sessions might not always have been optimal even though we put a lot of effort into careful repositioning. Therefore, we registered all repeated images onto their baseline images by using an automated registration algorithm.

This study gives an extensive overview of the reproducibility of liver MR elastography at 3.0-T MR imaging. Sources that create variation of the MR elastography measurement are related to the acquisition of the data (averaging over several breath holds, the MR sequence that was used), to the reconstruction algorithm (sensitivity to noise), and to the patient (anatomic location of measurement, physiologic variation, disease change). With respect to the acquisition technique, a more robust new MR elastography sequence with a higher signal-to-noise ratio is already being developed, making use of short echo times and fractional encoding (fast field echo) (23). With respect to the reconstruction algorithm, this study shows that the postprocessing algorithm of MR elastography can be further improved by making the reconstruction of attenuation parameter α more robust. We found propagation parameter β to be very stable, but whether the diagnostic accuracy of propagation parameter β is comparable or even better than that of elasticity in the assessment of liver fibrosis remains to be investigated. Last, with respect to the patient, future studies should investigate the applicability of the defined thresholds in longitudinal studies in which patients with liver fibrosis are being treated and results of liver biopsy are available. It would be of value to compare the defined thresholds with the relative difference in MR elastography results per histopathologic fibrosis stage and to see whether there is any overlap.

In conclusion, when MR elastography of the liver is performed with a spin-echo echo-planar sequence at 3.0 T, propagation parameter β is the most reliable parameter, with an over-time threshold for significant change of 10.1% and the ability to reproduce viscoelasticity from a resolution of 8-mm FWHM.

Disclosures of Conflicts of Interest: A.E.B. No relevant conflicts of interest to disclose. **P.G.** No relevant conflicts of interest to disclose. **A.D.N.** No relevant conflicts of interest to disclose. **P.F.C.G.** No relevant conflicts of interest to disclose. **R.S.** No relevant conflicts of interest to disclose. **J.S.** No relevant conflicts of interest to disclose. **A.J.N.** No relevant conflicts of interest to disclose.

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