

# Comparing hepatic 2D and 3D magnetic resonance elastography methods in a clinical setting – Initial experiences

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## Abstract

**Purpose:** Continuous monitoring of liver fibrosis progression in patients is not feasible with the current diagnostic golden standard (needle biopsy). Recently, magnetic resonance elastography (MRE) has emerged as a promising method for such continuous monitoring. Since there are different MRE methods that could be used in a clinical setting there is a need to investigate whether measurements produced by these MRE methods are comparable. Hence, the purpose of this pilot study was to evaluate whether the measurements of the viscoelastic properties produced by 2D (stiffness) and 3D (elasticity and ‘ $G_{\text{abs,Elastic}}$ ’) MRE are comparable.

**Materials and methods:** Seven patients with diffuse or suspect diffuse liver disease were examined in the same day with the two MRE methods. 2D MRE was performed using an acoustic passive transducer, with a 1.5 T GE 450 W MR system. 3D MRE was performed using an electromagnetic active transducer, with a 1.5 T Philips Achieva MR system. Finally, mean viscoelastic values were extracted from the same anatomical region for both methods by an experienced radiologist.

**Results:** Stiffness correlated well with the elasticity,  $R^2 = 0.96$  ( $P < 0.001$ ; slope = 1.08, intercept = 0.61 kPa), as well as with ‘ $G_{\text{abs,Elastic}}$ ’  $R^2 = 0.96$  ( $P < 0.001$ ; slope = 0.95, intercept = 0.28 kPa).

**Conclusion:** This pilot study shows that different MRE methods can produce comparable measurements of the viscoelastic properties of the liver. The existence of such comparable measurements is important, both from a clinical as well as a research perspective, since it allows for equipment-independent monitoring of disease progression.

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**Keywords:** Liver; Rheology; Elastography; Fibrosis; MRE; MRI

## 1. Introduction

The long-term prognosis of chronic liver diseases, caused, for example, by alcohol, viral hepatitis, non-alcoholic fatty liver disease (NAFLD), and autoimmune or metabolic disorders, depends principally on the extent and progression of liver

fibrosis. Histopathological examination of a liver biopsy, conventionally considered to be the gold standard for evaluating hepatic fibrosis, has several drawbacks. These include the risk of complications, inter- and intra-observer variability, inaccurate staging due to spatial sampling errors and the fact that heterogeneous distribution and rate of fibrosis progression, which is commonly not constant over time, may not be reflected in a single biopsy [1–7].

Animal models as well as data on human liver disease have demonstrated that fibrosis, and even cirrhosis, may be reversible. These observations have stimulated efforts to find non-invasive

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alternatives allowing a close monitoring of patients and facilitating clinical decision-making [8,9].

Serum biomarkers, ultrasound elastography and a number of magnetic resonance (MR) applications have been proposed to replace liver biopsy, either as single methods, or in various combinations. Among the MR techniques, magnetic resonance elastography (MRE) appears to be reliable in identifying significant fibrosis (stage  $\geq$  F2) and AUROC values  $>0.90$  have been reported [10–12].

MRE is a phase-contrast-based MRI imaging technique. In principle it consists of three key steps: (i) mechanical motion (or shear waves) is applied to the tissue, either from an external or an internal source such as heart motion. (ii) The tissue response to the stress of this motion is imaged using phase-contrast MRI with motion encoding gradients. (iii) The image data are processed to obtain information about viscoelastic properties of the liver [13,14].

In hepatic MRE, various types of external drivers have been used to induce the mechanical waves; acoustic, piezoelectric or pneumatic [14]. In this study, two such designs are used, acoustic and electromagnetic. For the imaging techniques both 2D and 3D methods have been proposed and the presently available commercial system uses the 2D MRE data sampling technique. The use of either 2D or 3D affects the ability to use more or less complex post-processing algorithms to derive the mechanical properties of the tissue. The 3D sampling technique, which presently is not commercially available, allows for separation of the complex shear modulus into two basic components, elasticity and viscosity, whereas the commercially available 2D MRE presents the shear stiffness. Furthermore by using a 2D acquisition technique there is also an implicit assumption that the shear waves induced by the driver only propagate in the selected imaging slice, which is not the case in the 3D technique, where the algorithm solves the wave propagation in all three dimensions [13].

Since there are different MRE methods that could be used in a clinical setting there is a need to investigate if the measurements of the viscoelastic properties of the liver produced by these different MRE methods are comparable. Thus, the purpose of this pilot study was to compare 2D and 3D MRE, using a commercially available 2D MRE system and a 3D MRE research system, with respect to liver stiffness and elasticity in patients with diffuse or suspected diffuse liver disease.

## 2. Materials and methods

### 2.1. Patients

In this study, seven patients were examined in the course of one day (2012). The patients were separately recruited from an on-going study [15]. These patients were selected due to their elevated serum alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) levels. Physical examination and laboratory tests revealed no signs of liver cirrhosis. The biopsy and the histopathological grading of these patients were gained from the records of the previously mentioned on-going study [15]. Table 1 presents basic descriptive parameters as well as the time between the initial biopsy and the MRE examinations ("Biopsy age" in Table 1). The time between each MRE acquisition (2D and 3D MRE) was dependent on how long it took for the patient to move between the two MR systems within the hospital (typically less than 10 min).

All participants gave their informed consent before the start of the study. The study was approved by the regional ethics committee (Reference No. M72-07, T92-08).

### 2.2. Data acquisition and image analysis

#### 2.2.1. 2D MRE

The 2D MRE (MR-Touch, GE Medical Systems, Milwaukee, US) was performed by transmitting mechanical waves at 60 Hz into the right side of the liver by a passive transducer (acoustic) placed on the anterior chest wall to the right of the xiphoid process of the patient, who was lying in a supine position. A 1.5 T GE 450 W MR system (GE Healthcare, Milwaukee, US) was used, along with a phased array body coil (HD8 Torso, using all 8 coil elements). The quantitative shear stiffness maps were generated by processing the acquired images with a previously described local frequency estimation inversion algorithm [16].

#### 2.2.2. 3D MRE

The principle of the 3D MRE method used has been described previously [17,18]. In short, mechanical waves of 56 Hz were transmitted into the right side of the liver by an active transducer (electromagnetic) that was placed on the anterior chest wall to the right of the xiphoid process of the patient, who

Table 1  
Demographic variables, fibrosis staging and diagnosis.

Patient	Gender	Age <sup>a</sup> (year)	BMI (kg/m <sup>2</sup> )	Biopsy age <sup>b</sup> (year)	Biopsy localization <sup>c</sup>	Fibrosis stage <sup>d</sup>	Diagnosis <sup>e</sup>
1	F	80	22.9	2.4	Right	2	PSC
2	M	33	22.8	3.4	Left	3	PSC
3	M	69	27.8	4.6	Left	4	NAFLD
4	F	41	20.7	0.9	Left	3	AIH
5	F	75	19.6	3.3	Right	2	AIH, PBC
6	F	44	25.6	1.3	Right	2	AIH
7	F	51	27.9	1.9	Left	1	AIH

<sup>a</sup> Age refers to the patient's age when the MRE examinations were performed.

<sup>b</sup> Biopsy age refers to the time in-between the initial biopsy and when the MRE examinations were performed.

<sup>c</sup> Biopsy localization refers to either the left or the right liver lobe.

<sup>d</sup> Fibrosis stage according to Batts–Ludwig fibrosis scoring; 1 = portal fibrosis, 2 = periportal fibrosis, 3 = septal fibrosis, 4 = cirrhosis.

<sup>e</sup> Diagnosis; PSC = primary sclerosing cholangitis, NAFLD = non-alcoholic fatty liver disease, AIH = autoimmune hepatitis, PBC = primary biliary cirrhosis.

Table 2  
Summary of the MR protocols.

	2D MRE, GRE	3D MRE, GRE
MR system	GE 450 W, 1.5 T	Philips Achieva, 1.5 T
Field of view	440 mm × 440 mm	320 mm × 256 mm
Matrix	256 × 64	80 × 38
Slice thickness	10 mm	4 mm
# Slices	4	9
Flip angle	30°	15°
TR	50 ms	112 ms
TE	21.7 ms	9.21 ms
Acceleration	ASSET=2	SENSE=2
# Breath-hold	4	4

was lying in a supine position. A 1.5 T Philips Achieva MR system (Philips HealthCare, Best, The Netherlands) was used, along with a phased array body coil (Sense TorsoXL, using all 16 coil elements). The shear waves were obtained by applying the curl operator and using the Voigt rheological model to obtain shear elasticity maps. Details of the elasticity/viscosity map calculations can be found elsewhere [17,18].

Relevant protocol parameters are summarized in Table 2.

### 2.2.3. Image analysis of the viscoelastic maps

For each patient, a region of interest (ROI) was placed manually by a radiologist (with more than 20 years' experience in abdominal radiology; BN) in an appropriate single 10 mm slice acquired using 2D MRE. The shape and size of the ROI were limited by the uncertainty mesh calculated by the 2D MRE system. Thereafter a corresponding ROI for the 3D MRE was placed manually over three slices such that it covered the same anatomical region as with the 2D MRE measurement (each 3D MRE slice had a thickness of 4 mm). This yielded a total cranio-caudal coverage of the ROIs equal to 10 mm (for the 2D MRE) and 12 mm (for the 3D MRE). Subsequently, the mean and standard deviations (unit kPa) of the stiffness (2D MRE), elasticity (3D MRE) and ' $G_{\text{abs,Elastic}}$ ' (3D MRE) both in units of kPa were calculated for each ROI and patient. ' $G_{\text{abs,Elastic}}$ ' is the absolute value of the shear modulus, which in principle is equivalent to the viscoelastic property shear stiffness.

### 2.3. Statistics and computer software

Statistical analyses included a linear regression with a 95% confidence interval on the fitted regression parameters;  $R^2$  was used as a measure of model fit and data correlation. The statistical analyses were performed using Mathematica (9.0.1.0, Wolfram Research Inc., Champaign, IL, U.S.), the ROI drawing and elastogram quantification for the data from the 2D MRE was performed on a PACS-system (PACS IDS7, 15.1.10.8, Sectra AB, Linköping, Sweden), and for the 3D MRE the ROIs were placed and analysed using a custom software package implemented in ROOT (5.30/01, CERN, Geneva, Switzerland) generously provided by R. Sinkus (Kings College, London, UK).

## 3. Results

The measured values for all patients are presented in Table 3. An example of a ROI placement in the viscoelastic maps is shown in Fig. 1. Both the elasticity and the ' $G_{\text{abs,Elastic}}$ ' correlated well with the stiffness measurement carried out on the 2D MRE system (Fig. 2a and b), as was shown by the elasticity and stiffness correlation  $R^2=0.96$  ( $P<0.001$ ), slope=1.08 ( $P<0.001$ , 95% CI={0.83;1.33}), intercept=0.61 kPa ( $P=0.08$ , 95% CI={-0.12;1.34}), ' $G_{\text{abs,Elastic}}$ ' and stiffness correlation  $R^2=0.96$  ( $P<0.001$ ), slope=0.95 ( $P<0.001$ , 95% CI={0.72;1.18}), intercept=0.28 kPa ( $P=0.43$ , 95% CI={-0.56;1.12}).

## 4. Discussion

The main result was that there was a very good correlation between the elastograms obtained from the two different MRE methods, one using a passive acoustic transducer and 2D acquisition and one using an active electromagnetic transducer and 3D acquisition; in both comparisons (i.e., elasticity and ' $G_{\text{abs,Elastic}}$ ' vs. stiffness) the linear factor in the regression was close to one. If these observations hold true in larger studies, the existence of robust and reliable absolute quantification tools from different manufacturers producing directly comparable data is encouraging, both from a patient as well as a research perspective. However, care should be taken when comparing the elasticity and stiffness measures, since they have slightly different physical interpretations, and a standardized way of representing/processing MRE would be very beneficial. In recent publications the authors have argued that the use of multi-frequency MRE (MMRE) could allow for such a robust standardization of MRE [19,20] – this would be a promising enhancement for the diagnosis and monitoring of disease progression in a clinical setting. An added value of the MMRE approach is that it potentially also allows for assessment and differentiation of the inflammatory processes in the liver parenchyma from fibrosis [19–21]. This possibility to also assess the inflammatory component in diffuse liver disease would be an important step forward towards the creation of a comprehensive non-invasive MR-toolset for measuring and monitoring various histopathological parameters.

Table 3  
Measured viscoelastic properties.

Patient	Fibrosis stage <sup>a</sup>	3D MRE <sup>b</sup>		2D MRE <sup>b</sup>
		Elasticity (kPa)	$G_{\text{abs,Elastic}}$ (kPa)	Stiffness (kPa)
1	2	1.96 ± 0.37	2.34 ± 0.41	3.03 ± 0.55
2	3	0.77 ± 0.67	1.76 ± 0.36	1.63 ± 0.25
3	4	5.72 ± 2.58	7.03 ± 2.45	7.06 ± 1.62
4	3	2.18 ± 0.29	2.50 ± 0.44	2.56 ± 0.55
5	2	1.96 ± 0.02	2.49 ± 0.54	3.18 ± 0.62
6	2	1.99 ± 0.26	2.54 ± 0.41	2.88 ± 0.54
7	1	3.13 ± 0.64	3.86 ± 0.86	3.44 ± 0.80

<sup>a</sup> Fibrosis stage based on histopathological examination (see Table 1).

<sup>b</sup> Viscoelastic data presented as mean ± one standard deviation.

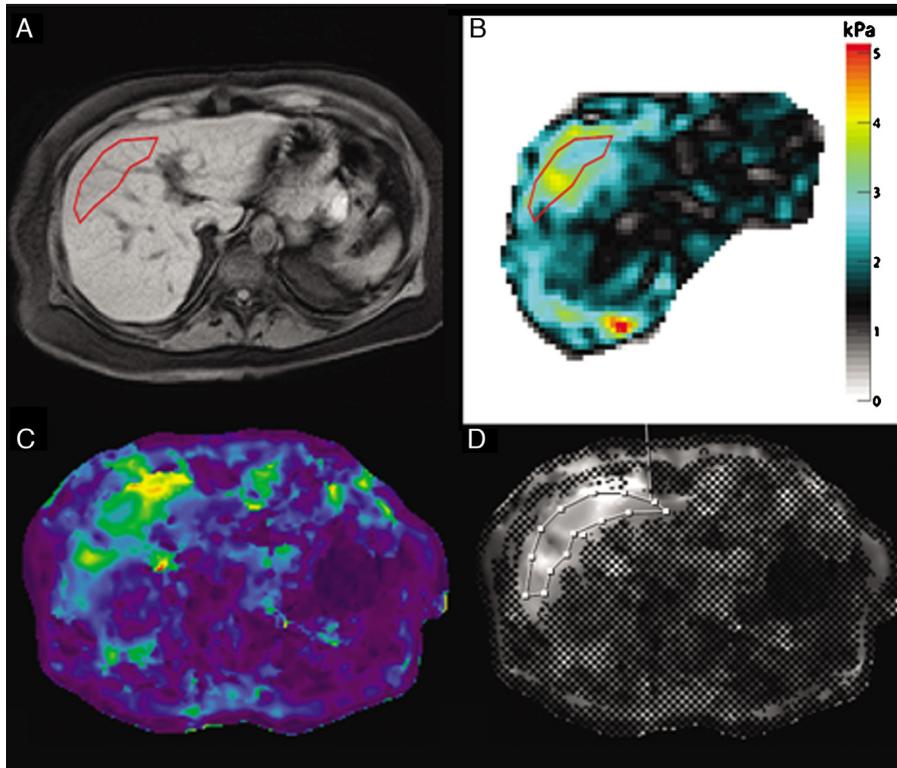


Fig. 1. Viscoelastic maps and ROI positions for patient 7. (A) A conventional THRIVE image, acquired prior to the 3D MRE. The 3D MRE elasticity map is shown in false colour in (B), with the ROI marked by a red outline (also shown overlaid on the THRIVE image in (A)). (C) The 2D MRE stiffness map in false colour, and in (D) the confidence mesh is shown overlaid on the 2D MRE stiffness map (regions excluded from the mesh correspond to regions with high confidence in the calculations), as well as the ROI marked by a white outline. As can be seen in (A) and (D) the ROIs are placed in the same anatomical region of the liver for both 2D and 3D MRE.

There are a few potential limitations when interpreting the results of the present study: (i) A relatively small sample size was used. (ii) The biopsies were in some cases performed up to 4 years prior to the MRE. Importantly, the biopsies were included in this work to show the spread of the fibrosis stages in the patient cohort, and not to gauge the diagnostic power of the MRE methods. (iii) The biopsies were not spatially correlated with the MRE ROIs. (iv) The patients were not required to fast prior to the examination, and the postprandial effect has been shown to affect the absolute stiffness/elasticity values [22]. However, this postprandial effect

probably had very little effect on the comparisons between the two systems since the patient examinations were obtained as close in time as was possible. (v) The driver frequencies were not identical (although very close) and this could also have influenced the observed absolute values [23]. Despite these limitations, we believe that this is an important addition to the body of knowledge on using MRE in a clinical setting with different MRE methods. A central aspect of this small patient group is that the spread in the fibrosis stages is presumably representative for patients with suspected diffuse liver disease in need of diagnostic workup. Also, the aetiology in

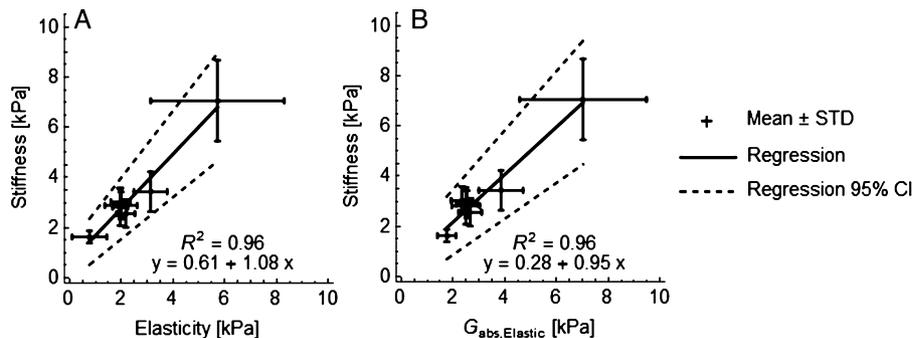


Fig. 2. Correlation analysis of the viscoelastic properties. In both panels the data are presented as the mean value of the viscoelastic properties, the error bars correspond to one standard deviation, and the dashed lines correspond to the 95% confidence interval (CI) of the linear regression. (A) The correlation of elasticity and stiffness, and (B) the correlation of ' $G_{abs,Elastic}$ ' and stiffness. In both comparisons  $R^2$  was equal to 0.96, and only the slope of the linear regression was significant ( $P < 0.001$ ).

this patient group is heterogeneous, which is a typical clinical situation.

In summary, this pilot study shows that different MRE methods can produce comparable measurements of the viscoelastic properties of the liver. The existence of such comparable measurements is important, both from a clinical as well as a research perspective, since it allows for equipment-independent monitoring of disease progression.

### Conflict of interest

None declared.

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