Liver MR-Elastography

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Chronic liver diseases typically lead to liver fibrosis. Recent investigations demonstrate that liver fibrosis is reversible using effective treatment during the early phase of disease progression [1-4]. In this context, the stage of liver fibrosis plays a major role: it determines firstly the treatment options and secondly also the prognosis. The current gold standard for determining the stage of liver fibrosis is the biopsy. As an invasive procedure it is for instance not well suited for treatment follow-up studies, which is however mandatory in order to separate in the early phase responders from non-responders. Moreover, needle biopsy is probing only a tiny quasi 1-D volume of the entire liver and is thus prone to sampling variability and inter-observer variation in the interpretation of the semi-quantitative scoring systems [5-8].
Thus, there is a need for non-invasive alternatives to liver biopsy which should at least be capable to reliably differentiate between three stages of fibrosis: none/early, intermediate and advanced/cirrhotic. An identification of the intermediate stage is necessary since patients with hepatitis B, C and non-alcoholic liver disease should be treated [2,4]. Late stage patients require for instance follow-up studies regarding potential hepatocellular carcinomas [9-11].
Various non-invasive methods technique have been proposed to assess the stage of liver fibrosis. These methods include liver imaging methods via MRI or Ultrasound and biochemical scores [12-16]. The most common score is the so-called ”aspartate to platelets ratio index” (APRI). Although those techniques certainly carry diagnostic value, their accuracy for staging intermediate fibrosis remains debated [2].
From clinical experience it is well known that liver stiffness changes with the degree of fibrosis. Here, MR-elastography (MRE) as a novel non-invasive method for measuring the visco-elastic properties of the liver, may play an important role. Preliminary reports [17-19] suggest that MR elastography is a feasible method to stage liver fibrosis. More recent clinical results clear demonstrate that MRE can separate those three stages of liver fibrosis [20].
None of the commonly used non-invasive imaging techniques (ultrasound, CT and MRI) are directly sensitive to the physical parameters elasticity or viscosity. Therefore, those properties can only be obtained indirectly. There is actually a close physical link between the propagation of mechanical waves in a viscoelastic medium and its viscoelastic properties. Thus, the general concept of elastography is

- to somehow generate mechanical waves within the medium,
- to measure those waves via a non-invasive imaging technique, and finally
- reconstruct maps of the viscoelastic properties from the measured wave fields.

The last step, i.e. converting the measured wave fields into maps of elasticity and viscosity, necessitates utilization of rheology, i.e. the theory explaining the relationship between stress and strain [21].

In the following, the general theoretical concept of elasticity imaging will be reviewed. Afterwards, the MR-acquisition technique will be discussed and finally clinical results are reported.

Theory of Mechanical Wave Propagation in Viscoelastic Media

Two kinds of waves are generated when pushing on a viscoelastic medium: compressional waves and transversal waves. In tissue, which is quasi-incompressible, this leads to an enormous imbalance between the speeds of the individual waves: the compressional wave travels at about 1550 m/s while the transversal (or shear) wave travels at 1-10 m/s. This difference in order of magnitude is found back in the according material parameters, i.e. the 2nd Lamé coefficient λ (describing the effect of compression) and the shear modulus μ (handling the effect of shearing the material) differ by 6 orders of magnitude! The corresponding equation of motion is

$$\rho \partial_t^2 \vec{u}(\vec{x},t) = \mu \nabla^2 \vec{u}(\vec{x},t) + (\lambda + \mu) \nabla (\nabla \vec{u}(\vec{x},t)) \quad , \tag{1}$$

with ρ the density of the material and $\vec{u}(\vec{x},t)$ the displacement vector at position $\vec{x}$ and time τ (assuming local homogeneity). Due to the almost incompressible nature of tissue the value of $\nabla \vec{u}(\vec{x},t)$ is so small that it is not feasible to evaluate this term given normal values of SNR (~10%) and finite spatial resolution (~1-2mm). The small magnitude of this term is minutely balanced by the large magnitude of the 2nd Lamé coefficient λ. [22]. Thus, it is meaningful to rewrite Eq.1 by introducing the pressure $p = (\lambda + \mu) \nabla \vec{u}(\vec{x},t)$, i.e.

$$\rho \partial_t^2 \vec{u}(\vec{x},t) = \mu \nabla^2 \vec{u}(\vec{x},t) + \nabla p \quad , \tag{2}$$

which resembles Eq.1 in case of local homogeneity. Otherwise, it is the correct extension for the pressure term in case of local heterogeneity. The pressure *p* represents the part originating from the compressional wave field and must not be neglected. Since elastography operates in the near field of the vibrational source, it is not evident that the contributions of the term ∇p can simply be eliminated by low-pass filters, which is motivated by the large wavelength of the compressional wave. An unbiased method is the application of the curl-operator because the rotation of the gradient of a scalar field is identical to zero (certainly introducing more noise due to the application of an additional derivative). This yields a Helmholz equation which simplifies in case of mono-chromatic excitation (i.e. $\vec{u}(\vec{x},t) = \vec{u}(\vec{x}) \exp(i\omega t)$) to

$$-\rho \omega^2 \vec{q}(\vec{x}) = G^*(\omega) \nabla^2 \vec{q}(\vec{x}) \quad , \quad \vec{q}(\vec{x}) = \nabla \times \vec{u}(\vec{x}) \in \mathbb{R}^3 \quad . \tag{3}$$

Here, the shear modulus $G^*(\omega) = G_d(\omega) + iG_l(\omega)$ is introduced whose complex-valued extension shall account for loss effects. This ad-hoc method of introducing viscose effects can certainly not resemble true nature and it is now necessary to link G_d and G_l to a particular rheological model in order to interpret these values in terms of spring constants μ and dashpot constants η. However, when working at one single frequency G_d and G_l are independent of any rheological model and we will in the following denote G_d as the elasticity (i.e. resembling the stiffness of the material) and G_l as the viscosity (i.e. resembling the absorbing properties of the material). It is important to realize, that Eq.3 provides at most one complex number (i.e. $G^*(\omega)$) although there are three equations! This is due to the assumption of isotropy. It is certainly feasible to go beyond isotropy and assume for instance locally a transverse anisotropic material [23,24].

MR-Elastography Sequence

The concept of the MRE sequence is similar to the classical MR diffusion sequence. The different components of the mechanical wave can be measured in case of a mono-chromatic excitation using a modified spin-echo pulse-sequence (Fig. 1a). A sinusoidal flow-encoding gradient (FEG) is placed prior and after the π-pulse with its shape equal to the pulse shape of the mechanical excitation [25]. The gradient channel to which the FEG is added determines which component of $\vec{u}(\vec{x},t)$ is measured. Thereby, the phase of the final MR-image is directly proportional to the value of the corresponding wave-component at a given phase of the oscillatory cycle [26]. Possible wraps within the MR-phase-images obstruct this straightforward relationship and necessitate utilization of unwrapping algorithm. The repetition time TR is chosen such that the sequence is phase-locked to the mechanical excitation frequency ν i.e., $TR = N \cdot T$, with $T = 1000/\nu\,[\mathrm{ms}]$ the basic interval and N an integer number. The same holds for the time separation between the beginning of the first FEG and the end of the last FEG, i.e., $TF = M \cdot T/2$ with M an integer number. An additional time delay TD allows to shift the phase between the onset of the mechanical excitation and the beginning of the imaging sequence. Thereby, snap-shots of the moving wave can be measured at different times during the oscillatory cycle. Alternatively, motion-sensitized gradient echo sequences can be used. Usually, this necessitates to measure each displacement field twice (with reversed motion encoding gradients) and subtract the images afterwards. Thereby, systematic phase errors are eliminated and the sensitivity to small displacements is doubled [26]. Similar sequences are possible for the assessment of quasi-static motion in case of ν→0 [27,28]. Recently, balanced steady-state free precession (b-SSFP) sequences have been proposed for mono-chromatic MRE in order to significantly accelerate data acquisition [29]. The sequence demonstrates very high sensitivity to small cyclic motion due to a subtle interplay between the dynamic equilibrium state to alternating spin de-phasing. However, the amplification factor depends upon T2, which makes a straightforward inversion of Eq.3 not possible. Thus, when utilizing such kind of sequence for a heterogeneous material, it is necessary to acquire a detailed T2 map.

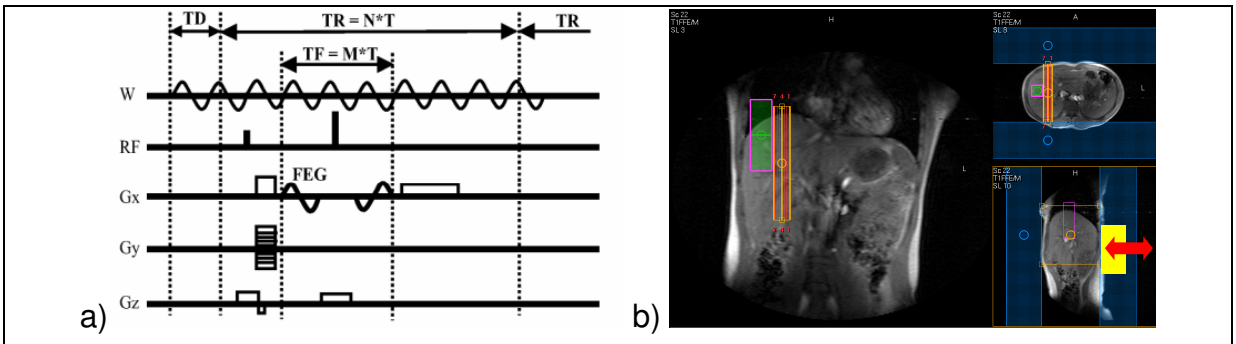

Fig.1: a) MR-sequence for the MRE experiment. A common spin-echo sequence is extended by sinusoidal flow-encoding gradients (FEG) located to both sides of the π-pulse. The timing of the sequence is tailored to be phase-locked to the mechanical stimulation (W). b) Plan-scan of the MRE-sequence. The stack of adjacent slices is orientated here sagitally. The NAV (green area) is located next to the image stack. The mechanical transducer is located at the back of the patient pushing in A-P direction (yellow rectangle).

Typically, the patient is in supine position with the mechanical transducer placed on the back pushing upwards in A-P direction using relatively low (~50Hz) mechanical frequencies (Fig.1b). Respiratory motion is compensated either via multiple breath-holds or by an interleaved MR-navigator (NAV), which measures the position of the diaphragm and enables acceptance/rejection of “wrong” respiratory motion states in real-time.

Clinical Results for Liver Fibrosis

Selected MRE results for patients with fibrosis grade F2 and F4 are shown in Fig.2. Image orientation is sagital (Fig.2a,e). It is obvious from Figs.2b,f that the shear wavelength increases dramatically for the F4 case when compared to the F2 case indicating an significantly increased stiffness of the liver. This is also visible in the corresponding images of the elasticity (Fig.2c,g) and viscosity (Fig.2d,h). Both, elasticity and viscosity increase in case of F4.
The compilation of our recent study is presented in Fig.3 [20]. The increase of elasticity (stiffness) as a function of degree of fibrosis is clearly visible (Fig.3a). When objectively analysing the results in terms of ROC-curves, very high specificities and sensitivities are found using elasticity as indicator to discriminate among F0-F1 and F2-F4 (Fig.3b). In the present study, the elasticity measurements allowed to clearly separate the intermediate fibrosis stages and more precisely F2 from F0 - F1. With an optimised cut-off value of 2.5 kPa for F≥2, the sensitivity of using elasticity as indicator was 0.98 at a specificity of 1.00. This high accuracy is clinically important because, according to the American Association for the Study of Liver Diseases, patients with hepatitis C genotype-1 infection should be treated only when substantial fibrosis (≥ F2) is observed [4,30]. Advanced fibrosis and cirrhosis were also diagnosed accurately. The cut-off value of 3.1 kPa for F ≥ 3 had a sensitivity of 0.95 and a specificity of 1.00. This high accuracy in the diagnosis of advanced fibrosis is also important because patients with advanced fibrosis should be screened for portal hypertension and hepatocellular carcinoma [9-11]. The viscosity measurements were less accurate than the elasticity measurements to stage liver fibrosis (Fig.3b). This does not mean that a simple elastic model should be used to measure the liver stiffness instead of the visco-elastic model used in the present study. Indeed, living tissues have both elastic and viscous properties. Ignoring this viscous component would artificially increase the results of elasticity [17].

In conclusion, the current clinical results indicate that MR elastography is an accurate method to stage liver fibrosis and that it is superior to APRI. This non-invasive staging method has a potential role in the determination of the treatment and the prognosis in patients with chronic liver disease because substantial and advanced fibrosis is readily diagnosed.

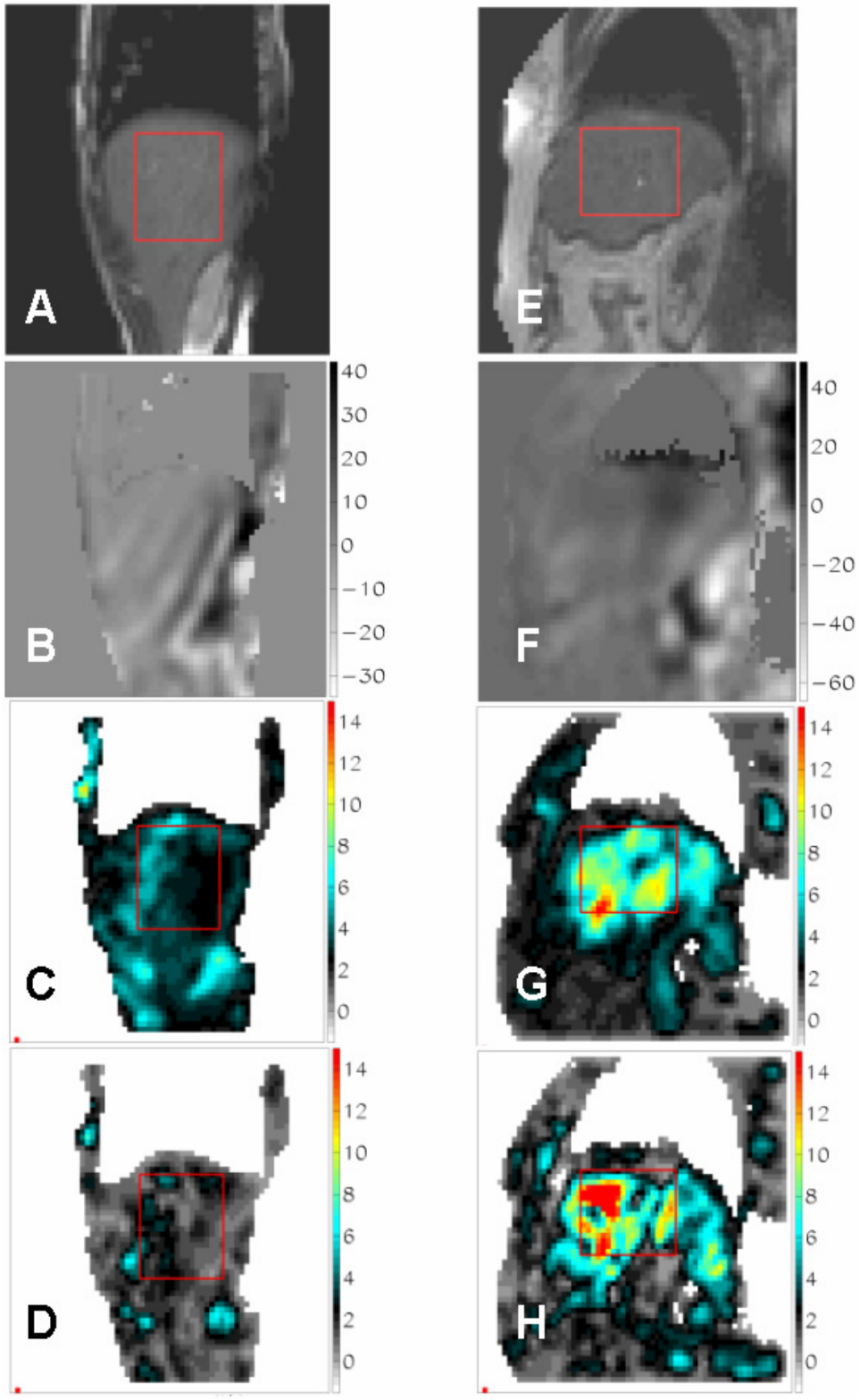

Fig 2: Reconstructed images of the central slice of a patient with F2 METAVIR score (A-D) and patient with F4 (E-H). Magnitude images (A, E) show the largest rectangular region of interest within the liver. Corresponding images of the wave in slice selection direction (B, F in units of µm) showing good penetration of the waves within the liver. Clearly, the wavelength in case of F4 has dramatically increased. The elasticity (C) and viscosity (D) maps of the patient with F2 are relatively homogeneous. The mean elasticity and viscosity measured within the region of interest on these sections are respectively 2.89±0.68 kPa and 0.9±0.6 kPa. The elasticity (G) and viscosity (H) maps of the patient with F4 are heterogeneous. The corresponding elasticity and viscosity measurements are 6.78±2.44 kPa and 2.86±1.68 kPa.

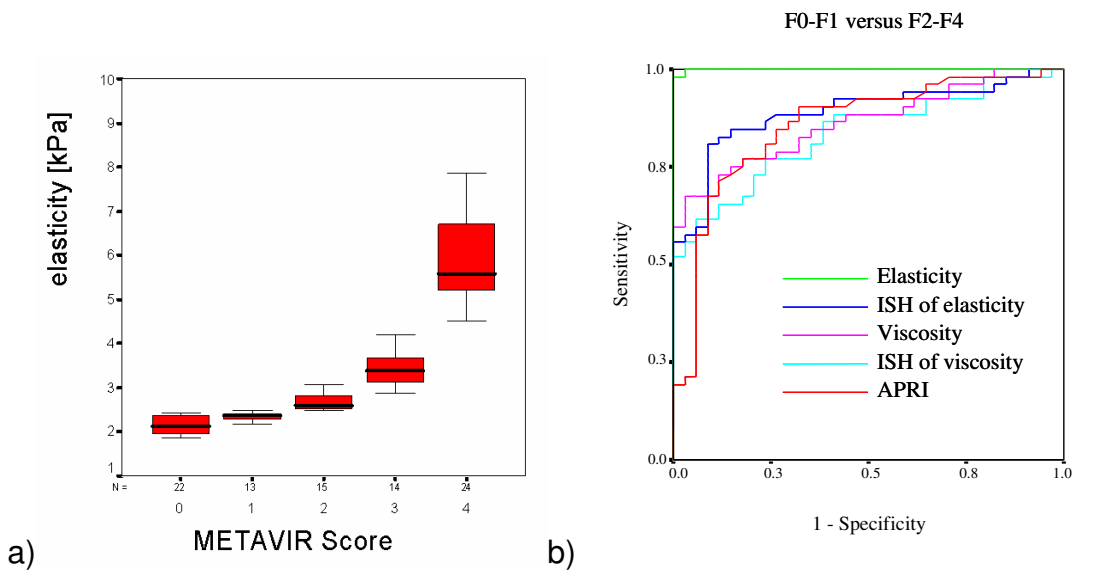

Fig.3: a) Box plots of elasticity for each METAVIR fibrosis stage. Boundary of boxes closest to zero indicates 25th percentile, line within boxes shows median and boundary of boxes furthest from zero indicates 75th percentile. Error bars indicate 10th and 90th percentiles. b) ROC curves for elasticity, intra-subject heterogeneity (ISH) of elasticity, viscosity, intra-subject heterogeneity of viscosity, and APRI for F ≥ 2 threshold.

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