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RESEARCH ARTICLE

Magnetic resonance elastography compared with rotational rheometry for in vitro brain tissue viscoelasticity measurement

Jonathan Vappou · Elodie Breton · Philippe Choquet · Christian Goetz · Rémy Willinger · André Constantinesco

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Abstract Magnetic resonance elastography (MRE) is an increasingly used method for non-invasive determination of tissue stiffness. MRE has shown its ability to measure in vivo elasticity or viscoelasticity depending on the chosen rheological model. However, few data exist on quantitative comparison of MRE with reference mechanical measurement techniques. MRE has only been validated on soft homogeneous gels under both Hookean elasticity and linear viscoelasticity assumptions, but comparison studies are lacking concerning viscoelastic properties of complex heterogeneous tissues. In this context, the present study aims at comparing an MRE-based method combined with a wave equation inversion algorithm to rotational rheometry. For this purpose, experiments are performed on in vitro porcine brain tissue. The dynamic behavior of shear storage (G') and loss (G'') moduli obtained by both rheometry and MRE at different frequency ranges is similar to that of linear viscoelastic properties of brain tissue found in other studies. This continuity between rheometry and MRE results consolidates the quantitative nature of values found by MRE in terms of viscoelastic parameters of soft heterogeneous tissues. Based on these results, the limits of MRE in terms of frequency range are also discussed.

Keywords Magnetic resonance elastography · Linear viscoelasticity · Phase encoding · Brain biomechanics

J. Vappou · R. Willinger
Institut de mécanique des fluides et des solides,
UMR 7507 CNRS-Université Louis Pasteur,
Strasbourg, France
e-mail: jvappou@imfs.u-strasbg.fr

E. Breton · P. Choquet · C. Goetz · A. Constantinesco (✉)
Service de biophysique et médecine nucléaire,
CHRU Hautepierre, Strasbourg, France
e-mail: andre.constantinesco@chru-strasbourg.fr

Introduction

Magnetic resonance elastography (MRE) is a fast growing research field as well as a technique that is being increasingly used to determine tissue stiffness. After the theoretical approach proposed by Lewa [1], MRE was originally described in 1995 [2] as a palpation-like diagnostic tool for detection of abnormal stiffness differences in soft tissues. Under an external mechanical harmonic excitation, and by means of a motion-synchronized encoding gradient included in the MRI sequence, it is possible to observe acoustic shear waves propagating inside the sample. The displacement map resulting from this wave propagation allows one to determine the rheological properties of the medium. For several years, and also in many recent studies, MRE has been based on the assumption of shear waves propagating in a purely Hookean elastic medium [2–7]. Despite this limiting assumption, MRE has been shown to be an efficient tool for diagnostic purposes where an estimation of a qualitative global stiffness value is usually sufficient [4–6].

More recently, inversion reconstruction techniques have been developed to determine quantitative viscoelastic parameters under assumption of linear viscoelasticity. This has led to the further development of this method, turning MRE into a powerful tool for the characterization of linear viscoelastic properties of soft tissues. In particular, such experiments have been performed on breast [8] and brain [9] tissue, providing a particularly novel in vivo distribution measurement of viscoelastic properties of the concerned organs.

However, few data exist in the literature that allow for a comparison between the results obtained by MRE and those obtained with conventional mechanical techniques. MRE has only been compared on soft homogeneous tissue-mimicking gels. Such comparisons have either been performed assuming Hookean elasticity (with compression–extension tests [2,10]

and with dynamic oscillatory tests [11]) or assuming linear viscoelasticity (with dynamic oscillatory measurements [12]). A comparison is missing between MRE and other mechanical techniques when investigating the viscoelastic properties of complex organs.

In this context, the present study offers to determine the dynamic viscoelastic properties of in vitro brain tissue by MRE in order to compare them with rotational rheometry performed on small brain samples.

Material and methods

Both rheometric and MR experiments were performed on normal porcine brains (aged from 6 to 8 months) obtained from a slaughterhouse and immediately refrigerated at 4°C. Total *post-mortem* time varied between 24 to 48 hours. Experiments were performed on eight brains, four for each method, under the same experimental conditions (*post-mortem* time range and conservation) until the beginning of the tests.

For rheometric experiments, cylindrical-shaped samples (20 mm in diameter, 4–5 mm high) were excised from white matter in the *corona radiata* region. Samples were placed in a parallel plate geometry and sand paper was glued to lower and upper plates of a rotational rheometer (AR2000, TA-instruments, DE, USA) in order to limit possible slippage between plates and sample. A moist chamber was used in order to prevent dehydration and experiments were performed at 25°C. A total of 12 samples were tested at $\varepsilon = 0.5\%$ strain in the 0.1–10 Hz frequency range. Raw phase was systematically checked in order to ensure appropriate inertia correction, and critical value of frequency limit ($f = 10$ Hz) was determined.

MR experiments were performed on a low-field 0.1 T resistive magnet (Bouhnik S.A.S., Velizy-Villacoublay, France) using a modified 2D spin-echo sequence. Two cycles of square-shaped motion encoding gradients (magnitude $\approx$ 15 mT/m) were included into the phase encoding direction. MRI and excitation devices are detailed in [12] and illustrated in Fig. 1. MR sequence used in this study is represented in Fig. 2. Typical MR parameters were TR = 800 ms, TE = 60 ms, field of view FOV = 90 × 90 mm, slice thickness 10 mm, NEX = 8, matrix size 128 × 96 (reconstructed 128×128), total acquisition time of 10 min for one image. Excitation frequency range was 80–140 Hz with 20 Hz steps and amplitude of harmonic motion was approximately of 10μm as measured by accelerometry prior to experiments. The porcine brains were placed in a cylindrical container and were plunged into echographic gel in order to increase RF coil loading [and therefore to enhance signal to noise ratio (S/N)], to settle mechanically the pig brain and to prevent its dehydration. A rectangular actuator (3 mm thick × 80 mm long × 30 mm wide) covered with sand paper was

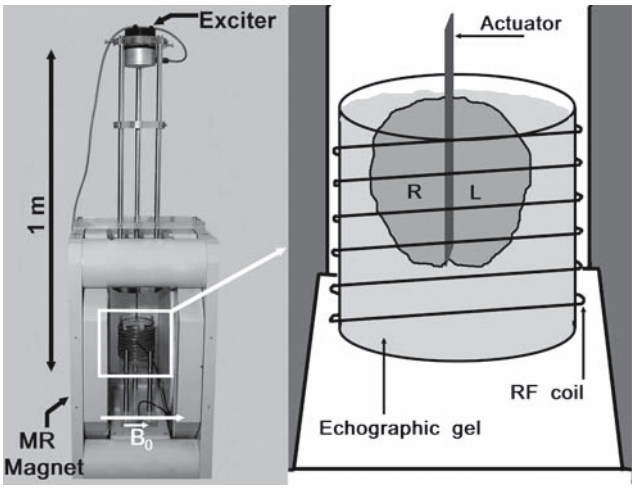

Fig. 1 Experimental device (*left*) showing magnet, exciter, and magnetic field B0 orientation. Schematic view (*right*) or location of actuator between *left* (*L*) and *right* (*R*) hemispheres of brain

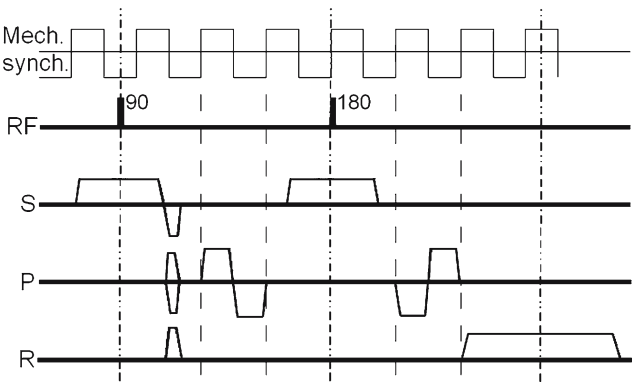

Fig. 2 MRI sequence pulse chronogram used in this study, showing synchronization between the motion-encoding gradient and the mechanical wave, the RF line, and the slice (*S*), phase (*P*), and read (*R*) encoding directions

placed between the two hemispheres of the brain, in mid sagittal plane. Experiments were realized at a temperature of 27°C ± 2°C.

An inverse wave equation inversion 2D-algorithm was used for determination of real and imaginary parts of complex wave number k from temporal Fourier transforms of displacement. Similar inverse approaches have been used by several authors for determination of viscoelastic properties by MRE [8,9,13]. For each frequency, eight phase offsets between motion and motion-sensitizing gradient were used, leading to a total acquisition time of 80 min. The component of wavefield used for reconstruction was the direction parallel to motion of the actuator (phase direction). Phase images were processed by application of a 2D Gaussian filter (5 × 5 convolution matrix and standard deviation of 2 pixels) as a low-pass frequency filter. Incompressibility of brain tissue was supposed, neglecting therefore the

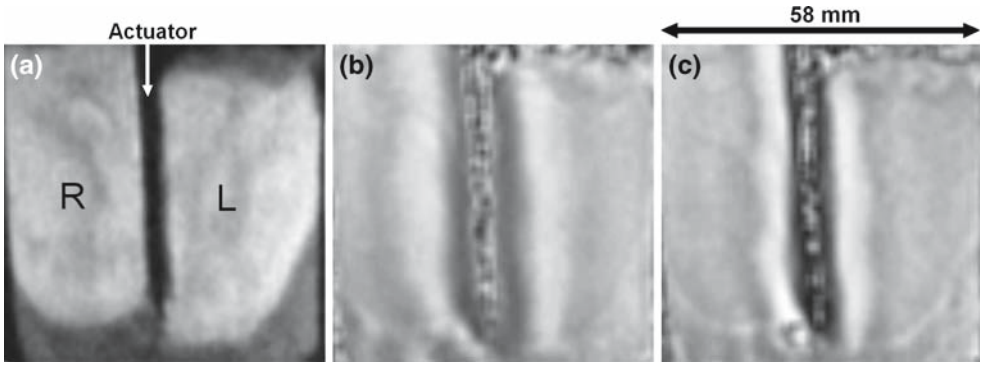

Fig. 3 Magnitude image (58 × 58 mm selection of original image) of a mid slice of brain (**a**) and phase images showing shear waves propagating through brain tissue at 80 Hz (**b**) and 120 Hz (**c**). Irregular shape of wavefront is due to heterogeneity of propagating medium. Shear waves are significantly attenuated, especially at high frequency

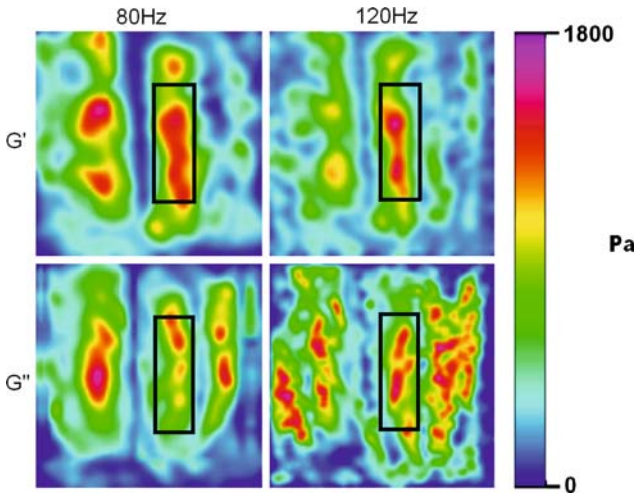

Fig. 4 Distribution map of G' (*first row*) and G'' (*second row*) at 80 and 120 Hz corresponding to Fig. 3 and example of selected ROI for calculation of shear moduli average. Due to heterogeneity of brain tissue, average value will depend on selected ROI

contribution of compression waves, and density was chosen to $\rho = 1,000\,\mathrm{kg\,m^{-3}}$. Storage and loss shear moduli were determined from resolution of complex equation $G = \rho\frac{\omega^2}{k^2}$ (see [14]), with ω being angular frequency and k the wave number. Resulting images were filtered by a third order median filter. Values of shear moduli were next averaged into a chosen region of interest (ROI). This ROI was settled as a rectangle located in close proximity to the actuator with dimensions of 10 × 30 mm in order to ensure predominant inclusion of tissue from the *corona radiata* region.

Results

Figure 3 shows wave propagation through brain tissue at 80 and 120 Hz, illustrating dependence of wavelength and attenuation on frequency. Corresponding distribution maps of G' and G'' with ROI used for average are shown in Fig. 4.

Figure 5 shows averaged values on all subjects of G' and G'' versus frequency for both methods, reported quantitatively in Table 1. Results are also represented in Fig. 6 for comparison with other data available in the literature concerning viscoelastic properties of brain tissue obtained by mechanical rheometric devices [15–20].

Discussion

In this study, an MRE-based method was used in vitro on whole porcine brains to calculate the values of shear storage and loss moduli. These values were compared with those obtained by rotational rheometry on excised samples of porcine brains. To our knowledge, this is the first comparison between MRE and conventional mechanical techniques in terms of viscoelastic properties of soft tissues. In spite of the particular complexity of brain tissue mechanical behavior that has led researchers to extend their studies to its non-linear properties [15–18,21,22], this study should be considered within the framework of current MRE research area and has therefore been restricted to linear viscoelasticity. Oscillatory rheometric tests have also been performed at a small strain value ($\varepsilon = 0.5\%$) included in brain tissue linear viscoelasticity range [15,18].

Values of shear moduli found by both methods are in the same order of magnitude as in several rheological studies performed on ex vivo mammalian brains [15,17,20] as shown in Fig. 6. Increasing behavior of G' and G'' with frequency was also found to be similar as in the previously mentioned studies. However, comparison with above-mentioned studies cannot be directly carried out because of the strong uncertainty related to differences in experimental protocols. In this study, major sources of uncertainty like donor species, origin and age as well as brain tissue storage conditions were limited, making it possible to compare rheometric and MRE results in similar experimental conditions.

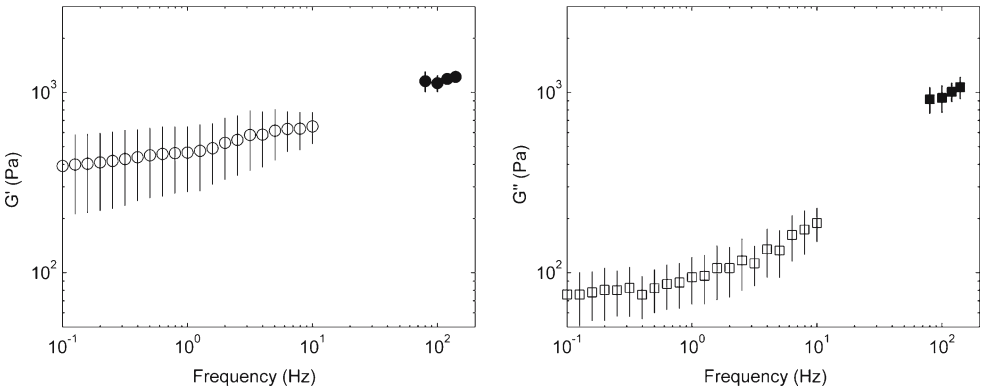

Fig. 5 Storage (*left*) and loss (*right*) shear moduli versus frequency for rotational rheometric data (*empty symbols*) and for MRI data (*full symbols*). For both methods, represented data are the average among examined subjects and standard deviation results from inter-subject variability

Table 1 Average values and standard deviation of storage (G') and loss (G'') shear moduli obtained by MRE (80, 100, 120, 140 Hz) and by rheometry at 0.1, 1, 10 Hz, as represented in Fig. 5

Frequency (Hz)	G' (Pa)	G''(Pa)
0.1	390 ± 180	75 ± 25
1	465 ± 180	94 ± 30
10	650 ± 130	190 ± 40
80	$1{,}150 \pm 150$	910 ± 155
100	$1{,}130 \pm 120$	935 ± 160
120	$1{,}190 \pm 80$	$1{,}010 \pm 120$
140	$1{,}220 \pm 85$	$1{,}070 \pm 155$

However, frequency range limitations of both methods did not allow direct comparison in a common frequency range. As a consequence, agreement between rheometric and MRE data was evaluated by calculating the correlation between presented data and results reported in other studies that cover larger frequency ranges [15,18]. Authors' combined data (rheometric+MRE) were found to have strong linear correlation with the results reported by Brands et al. ($R^2 = 0.99$ and $R^2 = 0.98$ for respectively, G' and G'') as well as with the results reported by Nicolle et al. ($R^2 = 0.91$ and $R^2 = 0.96$ for respectively, G' and G''). Such good correlation indicates that the frequency-dependent behavior described by combined results of rheometry+MRE is very similar to the one reported by Brands et al. [15] and Nicolle et al. [18]. Thus, if we assume such dynamic behavior based on the above-mentioned studies, MRE data are found to be a good extrapolation of rheometric data, showing strong agreement between results obtained by both methods. However, such agreement would be strengthened by performing rheometric tests at higher frequency values that would allow direct comparison in a common frequency range.

Possible sources of uncertainty are related to non-controlled experimental parameters specific to parallel-plate rheometry (uncertainty in boundary conditions, local pre-compression phenomena due to irregular sample shape, possible slipping etc.) and to limitations related to MRE as discussed below. Uncertainty also arises in relation to the area of brain that was considered for measurements. In order to reduce this source of error, measurements were done in the corona radiata region, chosen for its large size.

Values of shear moduli were averaged inside a ROI whose location and dimensions were chosen in order to ensure inclusion of *corona radiata* tissue as a majority. Due to brain tissue heterogeneity, it was observed that the resulting values of shear moduli were dependent on the choice of ROI. However, as an example, typical variation at 80 *Hz* was measured to be equal to $G' = 880 \pm 80$ Pa and $G'' = 780 \pm 95$ Pa for four different sizes and locations of ROI in the *corona*

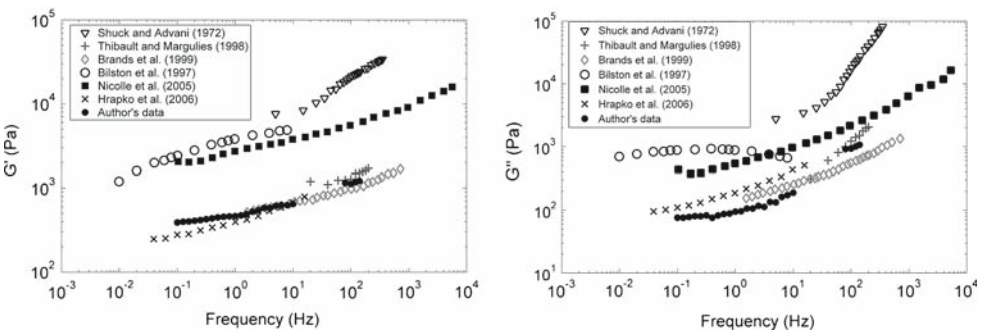

Fig. 6 Storage (*left*) and loss (*right*) shear moduli versus frequency compared with experimental data obtained by dynamic oscillatory tests on mammalian brain samples

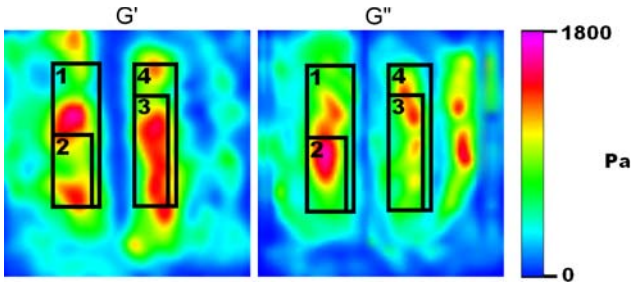

Fig. 7 Estimation of ROI's size and location influence on averaged results of G' (*left*) and G'' (*right*). Four ROI were chosen inside the corona radiata region. Corresponding results are reported in Table 2

Table 2 Dependence of G' and G'' on size and location of ROI as represented in Fig. 7

ROI	ROI Size (mm × mm)	G' (Pa)	G'' (Pa)
1	36×11	790 ± 270	795 ± 275
2	18×10	830 ± 180	905 ± 315
3	25×10	955 ± 210	740 ± 170
4	36×11	920 ± 220	690 ± 205

Standard deviation represents variability of shear moduli inside considered ROI

radiata region, showing that influence of choice of ROI is limited. Figure 7 and Table 2 illustrate different ROIs chosen for this example and corresponding values of shear moduli found by averaging.

An inversion-based method was used for determination of complex values of shear modulus. Despite its limitations concerning reconstruction of loss modulus, inversion method gives good results in high S/N regions where shear wave is not totally attenuated as discussed in [13]. Furthermore, it offers the possibility to obtain a frequency-dependent distribution map of both storage and loss moduli inside the brain.

The most significant limitation of this MRE method is its frequency range, which did not allow direct comparison with rotational rheometry in a common frequency range. This limitation is not only related to MRI device performances in terms of spatial resolution [12], but also to size and intrinsic rheological properties of analyzed objects. The increase of attenuation with frequency results in a decrease of typical decay length. As a consequence, the size of high S/N region where inversion algorithm is functional also decreases with frequency. Although reliability and quantitative nature of MRE were shown, and despite considerable advantages related to its non-invasive and non-destructive properties, MRE is unavoidably limited in terms of frequency range and its limitations are related to sample rheological properties and size. Irrespective of the MRI device and the inversion algorithm used, all soft tissues will have a critical frequency value above which shear waves will be immediately attenuated, making any measurement of viscoelastic properties impossible.

Conclusion

This study demonstrates the reliability of MRE as a tool for measurement of linear dynamic viscoelastic properties through comparison with a rheometric technique widely used for determination of soft tissue mechanical properties. This consolidates the quantitative nature of results obtained so far by MRE combined with linear viscoelasticity. It also demonstrates that such a method can now be used for biomechanical purposes as a reliable tool for non-destructive and non-invasive characterization of soft tissues viscoelasticity, keeping in mind its considerable limitations in terms of frequency range essentially related to shear wave attenuation.

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