Transient MR elastography (t-MRE) using ultrasound radiation force: theory, safety, and initial experiments in vitro.

Rémi Souchon, Rares Salomir, Olivier Beuf, Laurent Milot, Denis Grenier, Denis Lyonnet, Jean-Yves Chapelon, Olivier Rouvière

Transient MR Elastography (t-MRE) using ultrasound radiation force: theory, safety, and initial experiments in vitro

Rémi Souchon[1,2], Rares Salomir[1,2], Olivier Beuf[4], Laurent Milot[4], Denis Grenier[4], Denis Lyonnet[3], Jean-Yves Chapelon[1,2], Olivier Rouvière[1,3]

[1] Inserm, U556, Lyon, F-69003, France; [2] Université de Lyon, Lyon, F-69003, France; [3] Hospices Civils de Lyon, Hôpital Edouard Herriot, Lyon, F-69003, France; [4] CREATIS-LRMN CNRS UMR 5220, Inserm U630, Université de Lyon, University Lyon 1, INSA–Lyon, Lyon, France

Corresponding author: Rémi Souchon, INSERM U556, 151 cours Albert Thomas, 69424 Lyon cedex 03, France. Email: Remi.Souchon@inserm.fr

Total word count: 5792

Abstract

The purpose of our study was to assess the feasibility of using ultrasound radiation force as a safe vibration source for transient MR elastography (t-MRE). We present a theoretical framework to predict the phase shift of the complex MRE signal, the temperature elevation due to ultrasound, and safety indicators (I_{SPPA}, I_{SPTA}, MI). Next, we report wave images acquired in porcine liver samples in vitro. MR thermometry was used to estimate the temperature elevation induced by ultrasound. Finally, we discuss the implications of our results with regard to the feasibility of using radiation force for t-MRE in a clinical setting, and a specific EPI MRE sequence is proposed.

Keywords: Magnetic resonance elastography, shear wave, radiation force, transient, ultrasound

Running title: Transient MR Elastography

Introduction

MR elastography is based on the measurement of the velocity of shear waves in biological tissues (21, 29, 19). A MR elastography sequence is typically derived from an RF spoiled gradient-recalled sequence, modified to include a motion-encoding gradient pulse (MEG). The MEG converts the local displacement of the tissues into a phase shift in the complex MR signal. The relation between the phase shift (φ) of the MR signal at the position $\vec{r}$, the gradient strength (G), the gradient duration T_G, the displacement ($\vec{u}$), and the gyromagnetic ratio (γ) is given by:

$$\varphi(\vec{r}) = \gamma \int_0^{T_G} \vec{G}(t) \bullet \vec{u}\,(\vec{r},t)\,dt \qquad [1]$$

The shear waves are usually induced by positioning an external vibrator in contact with the patient, and by driving the device so as to generate a continuous vibration. The shear elastic modulus (μ) is derived from the shear wave velocity (c_s) and from the density of the medium (ρ), usually assuming a linear homogeneous elastic medium:

$$\mu = \rho c_s^2 \qquad [2]$$

MR elastography has already proven to be a valuable tool in the assessment of hepatic fibrosis (27). It is also expected to provide significant improvement in the detection and characterization of breast masses (32) and of prostate cancer (16).

However, depending on the target organ, producing high quality MRE images can be challenging. The penetration of the shear waves is limited by significant attenuation, and by wave reflections at interfaces between tissues that exhibit a significant stiffness contrast (e.g. interfaces between muscle and fat). Furthermore, the estimation of wave velocity can be made difficult by wave reflections and standing wave patterns. In most applications reported to date, wave images were acquired in a single plane, under the assumption that the shear waves propagate in-plane. This assumption may be challenged by wave refraction: whenever the shear waves propagate from one medium to another that possesses a different stiffness (e.g. from soft normal liver tissue to stiff hepatocarcinoma), the wave front can be distorted and the wave may start propagating with oblique incidence out of the imaging plane. Such scenario would typically result in an erroneous estimate of shear wave velocity, hence of elasticity.

The concept of using ultrasound radiation force instead of an external vibrator for elasticity imaging – either ultrasound-based or MR-based – is not new (33, 12, 29, 36, 22, 5, 30). Radiation force is caused by the change of momentum of the ultrasound waves as they propagate, either because of wave absorption or of wave reflection (35, 7, 6, 34, 9, 8). The radiation force is localized and highly directional, its main axis being in the direction of propagation of the ultrasound beam. The force components in the other directions are at least an order of magnitude smaller (29). In the case of a focused transducer, the radiation force is usually negligible outside of the focal zone. The volumic force F (expressed in N/m^3) induced by an ultrasound beam in a homogeneous absorbing medium depends on the amplitude absorption coefficient of the pressure wave α (in Np/m), on the acoustic intensity I (in W/m^2), and on the velocity c of the pressure wave (34): $F = 2\alpha I / c$ [3]

This force initiates a wave that propagates, both in longitudinal (compressional) mode and in transverse (shear) mode (fig. 1). Vibro-acoustography (12) uses the magnitude of the compressional wave to provide an image related to tissue elasticity. Most other elasticity imaging techniques, including MRE, rely on shear wave propagation to estimate elasticity.

The use of radiation force is expected to provide several advantages in MRE. First, it is possible to generate shear wave directly inside the tissue of interest by positioning the focus of the transducer at the desired location. Second, the desired penetration can be achieved by the choice of an appropriate central frequency of the ultrasonic waves (typically in the low MHz range). Third, penetration is further facilitated because most energy of ultrasonic compressional waves propagate through interfaces between layers of different shear stiffness (such as muscle and fat), whereas shear waves undergo significant reflections at these interfaces. Fourth, the directionality of the force is known *a priori*, facilitating the choice of the direction of the motion sensitizing gradients.

However, the use of radiation force as a vibration source has two main limitations. First, an « acoustic path » is needed for the ultrasound beam to reach the target organ. This may preclude the use of radiation force in organs located behind bone and/or air. Second, ultrasound is associated with tissue heating and possible cavitation. These effects must be carefully evaluated to ensure patient safety (1, 14, 23, 2, 11).

By applying a short ultrasound burst, it is possible to induce a transient shear wave. Compared to continuous excitation (36, 30), the short bursts can drastically reduce tissue heating. Furthermore, the use of transient displacements eliminates problems due to standing waves (10, 20).

Therefore, the purpose of our study was to assess the feasibility of using radiation force as a safe vibration source for t-MRE. In the next section, we present a model that estimates both the phase shift of the MR signal and temperature elevation as a function of acoustic parameters, MR parameters, and of the properties of the tissues. In the subsequent section, we present wave (phase shift) images acquired in porcine liver samples in vitro. MR thermometry was used to estimate the temperature elevation. Finally, we discuss the implications of our results with regard to the feasibility of using radiation force for t-MRE in a clinical setting, and a specific EPI MRE sequence is proposed.

Theory

Acoustic radiation force and heat deposition depend on acoustic intensity. At the focus of a spherically focused transducer, the spatial-peak acoustic intensity I – averaged over one cycle of the ultrasonic signal – is given by:

$$I(t) = \frac{2\pi}{c^2}\frac{d}{R} f^2 P_a(t) \exp(-2\beta f x) \qquad [4]$$

The variable t denotes time, c is the speed of sound, d is the depth of the concave transducer and R is its focal distance, f is the frequency of the ultrasound wave, $P_a(t)$ is the output acoustic power of the transducer (averaged over one cycle of the ultrasound signal), $\beta = \alpha / f$ denotes the ultrasonic attenuation (in Np/m/MHz), and x denotes the depth at which the focus is located. Equation [4] is fundamental for all subsequent calculations, and details of its derivation are given in Appendix A. Incorporating [4] into [3] gives the radiation force at the focus:

$$F(t) = \frac{4\pi\beta}{c^3}\frac{d}{R} f^3 P_a(t) \exp(-2\beta f x) \qquad [5]$$

Of course, the displacement $u(t)$ at the focus depends not only on the radiation force at the focus, but on its spatial distribution as well. The relationship of motion with the duration of the ultrasound pulse and the spatial distribution of the force was investigated in detail by several authors (3, 29, 8). For the sake of simplicity, we chose an overdamped response to model the transient displacement $u(t)$ at the focus (i.e. we assumed that the medium does not oscillate). The choice of this model was based on the transient displacement waveforms reported in (2) and (8).

$$u(t) = 0 \qquad ; t \leq 0 \qquad [6a]$$

$$u(t) = \frac{F}{k}\left(1 - \exp(-t/\tau)\right) \qquad ; 0 \leq t \leq T \qquad [6b]$$

$$u(t) = u(T)\exp(-t/\tau) \qquad ; T < t \qquad [6c]$$

Here k is a proportionality constant relating force and displacement, and τ is the time constant of the transient response. k and τ depend on the visco-elastic properties of the tissues, and on the spatial distribution of radiation force. The time constant τ depends on tissue density as well. The parameters k and τ are usually unknown. The ratio F/k is the asymptotic (quasi-static) displacement that would ultimately be achieved if the burst duration was infinite.

This simple displacement model is useful to derive a closed-form solution for the phase shift of the MRE signal. Let us consider the case of a MEG with duration T_G and constant magnitude G. Incorporating [6] into [1], and assuming that $T_G > T$, the phase shift of the MRE signal is given by:

$$\varphi = \gamma G T \frac{F}{k}\left(1 - \frac{\tau}{T} e^{-\frac{T_G - T}{\tau}}\left(1 - e^{-\frac{T}{\tau}}\right)\right) \qquad [7]$$

Equation [7] gives the maximum phase shift, which occurs whenever the MEG is synchronous with the start of the transient vibration. Equations [6] and [7] assume constant acoustic power P_a (hence constant force F) over the duration of the acoustic burst, and F is given by [5].

It is interesting to note that the term between the parentheses is always less than 1, and converges to 1 when $T \to +\infty$. For $T \ll \tau$, this term behaves approximately like $1-\exp(-T_G/\tau)$. The practical consequences are that, when both T and T_G are small compared to τ, (transient regime), the phase shift is approximately proportional to the product $T.T_G$, and for $T \gg \tau$, (static regime) the phase shift becomes proportional to T:

$$\varphi \approx \gamma G T \frac{T_G}{\tau}\frac{F}{k}\text{; Transient regime} \qquad [8a]$$

$$\varphi \approx \gamma G T \frac{F}{k}\text{; Static regime} \qquad [8b]$$

The temperature elevation at the focus is given by the bio-heat transfer equation (BHTE), which accounts for heat conduction, blood perfusion, and volumetric heat rate (24). For the sake of simplification, we assumed that both perfusion and heat conduction are negligible. This assumption is a worst-case, conservative, scenario because the neglected effects contribute to heat evacuation. Under this assumption, the BHTE reduces to:

$$\rho c_\theta \frac{\partial \theta}{\partial t} = 2\beta f I(t) \quad [9]$$

In [9], c_θ is the specific heat of the tissue (J/kg/m^3), θ is the temperature elevation due to the ultrasound beam (°C), and intensity I is given by [4]. Hence, for N short ultrasound bursts, each having constant acoustic power P_a and duration T, the temperature elevation $\Delta\theta$ is given by:

$$\Delta\theta = \frac{4\pi\beta}{\rho c^2 c_\theta}\frac{d}{R} NTf^3 P_a \exp(-2\beta fx) \quad [10]$$

Other indicators related to the safety of ultrasound can be derived from acoustic intensity. Namely, these are the spatial-peak pulse average intensity I_{SPPA}, the spatial-peak time-average intensity I_{SPTA}, and the mechanical index MI (13, 2). For an ultrasound burst with constant acoustic power, these indicators are given by:

$$I_{SPPA} = \frac{2\pi}{c^2}\frac{d}{R} f^2 P_a \exp(-2\beta fx) \quad [11]$$

$$I_{SPTA} = I_{SPPA} T / TR \quad [12]$$

$$MI = 10^{-3} \exp(-\beta fx)\sqrt{\frac{4\pi\rho}{c}\frac{d}{R} fP_a} \quad [13]$$

TR is the delay between two consecutive ultrasound bursts. In our application, it is equal to the repetition time of the MRE sequence. Detailed derivation of these indicators is given in Appendix A. We do not provide equations for the thermal index (TI) because TI does not account for exposure duration, and may therefore not be a relevant indicator in our application. Instead we used [10], which provided a direct, yet conservative, estimate of temperature elevation.

Methods

MRE sequence

The MRE sequence was programmed on a 1.5 T Symphony MR system (Siemens Medical Solutions, Erlangen, Germany) using the Integrated Development Environment for Application from Siemens. A conventional FLASH phase-contrast MRI sequence was modified to include an additional Motion-

Encoding Gradient that can be switched on and off along any desired direction. This sequence was originally designed for "conventional" MRE using a monochromatic vibration. The MEG was bipolar, with lobes of equal amplitude switched in polarity. As a consequence, the transient shear wave appeared twice in each image. Each line was acquired using two consecutive RF pulses and MEG having opposite polarity (fig. 2). The phase subtraction between the two polarity-reversed acquisitions removed systematic phase errors or phase shifts due to magnetic field inhomogeneities, and doubled the sensitivity to displacement. The MEG and the acoustic pulses were synchronized together using a trigger pulse generated by the MR system for each TR at the beginning of the sequence.

The acquisition parameters were: 33.5 ms TR, 256x256 matrix size, 10 mm slice thickness, 0.78x0.78 mm^2 voxel size, FOV 20x20 cm^2, 17 s acquisition duration, MEG amplitude G=18 mT/m. TE was between 14 and 25 ms, depending on MEG duration. A large slice thickness was used to increase the SNR. The voxel size matched the dimensions of the -3 dB focal region of the transducer (0.8x0.8x9 mm) so that, in coronal views (perpendicular to the beam axis), tissue displacement was approximately uniform within the voxel (because of the cylindrical shape of the wave front).

Shear wave generation

A piezoceramic transducer in the shape of a spherical cap (diameter $2a$=70 mm, focus R=90 mm, depth d=7.1 mm, efficiency η=80%) was operated at frequency f=2.4 MHz. A pulse generator (HP 8112A, Hewlett-Packard) was used to set the delay between the MEG and the emission of the acoustic pulse. The pulse generator triggered a first function generator (HP 33120A, Agilent) that was in charge of delivering a modulating signal $M(t)$. A second function generator (HP 8116A, Hewlett Packard) was in charge of providing the modulated signal, with central frequency f. Finally, the transducer was driven by a broadband amplifier (fig. 3). In order to minimize interferences between the amplifier and the MR scanner, a LC rejector filter – with resonant frequency matched to the Larmor frequency – was placed in series with the transducer. Additionally, a λ/4 coaxial cable having minimal reflection coefficient at the Larmor frequency was placed in parallel with the transducer.

Experimental protocol for t-MRE

Five porcine liver samples were acquired from the local butcher shop (the time after death was 2-4 days, and the samples had been preserved at + 4°C). The samples were immersed in an isotonic saline solution and degassed. Then the samples were inserted inside a thin polyurethane balloon. The ultrasound transducer was positioned at the bottom of a tank filled with degassed water, and the samples were held above the transducer as shown in fig. 3. The water and the samples were at room temperature.

The voltage applied to the transducer was modulated by a low frequency signal $M(t)=1-\cos(2\pi t/T)$, with period matched to the gradient duration ($T=T_G$). Figure 2 shows the temporal waveform of the power applied to the transducer (that also represents the temporal profile of the force), and the MEG, for the acquisition of a single line in k-space. This pattern was repeated N_{lines}=256 times, resulting in 512 ultrasonic bursts per image.

We varied the acoustic power P_{max} (4, 8, 12, 16, 32 and 48 W), the burst duration T (5.6, 8.3 and 16.7 ms), and the depth of the focus x (30 and 40 mm). The configurations tested corresponded to $I_{SPPA.7}$ varying between 40 W/cm^2 and 680 W/cm^2, $I_{SPTA.7}$ varying between 20 and 110 W/cm^2, and $MI_{.7}$ between 1.1 and 4.8 (details in Appendix B).

We acquired MR images in a coronal plane perpendicular to the ultrasound beam. The center of the slice was positioned 5 mm below the focus (dashed line in fig. 4a). In order to image the wave propagation, eight wave (phase shift) images were acquired, varying the delay between the start of the ultrasound burst and the start of the MEG by steps of ΔT~4.2 ms.

MR thermometry sequence

MR thermometry (28) was performed on a Philips Achieva 1.5 T scanner using a single-slice, RF-spoiled, segmented gradient-echo echo-planar imaging (EPI) sequence with an EPI factor of 5 k-space lines per TR, and the following parameters: TR 100.5 ms, TE 12 ms, matrix size 128x128, voxel size 0.9x0.9x4.9 mm^3, and flip angle 35°. A receive-only surface coil (96 mm inner diameter) was placed on top of the sample. Two saturation slab stacks of 80 mm thickness (one at each side of the FOV in the phase encoding direction) were used to avoid image foldover and to suppress possible motion artifact due to acoustic streaming in water. The temporal resolution for consecutive images was 2 seconds. Lipid MR signal is a source of errors for MR thermometry, since the lipid proton resonance frequency (PRF) is independent of temperature. Lipid signal was suppressed using spectral selective binomial '11' excitation RF pulses.

Experimental protocol for MR thermometry

The ultrasonic firing sequences were the identical to those used in the transient shear wave imaging protocol. 8x512 ultrasound bursts (corresponding to 8 MRE frames with 256 lines per frame and 2 bursts per line) were emitted with repetition period 33.5 ms, resulting in a total acquisition duration of 136 s. Doing so, our aim was to set up a « best case » scenario as far as acquisition duration is concerned – all MRE frames would be acquired with no wait period in between, thus reducing the total acquisition duration –, but that happens to be a worst-case scenario as far as thermal effects are concerned (because no time for cooling is allowed between two consecutive MRE frames). Temperature images were acquired continuously every 2 seconds.

For the imaging plane perpendicular to the ultrasound beam, the voxel size matched the –3 dB focal region of the transducer ($0.8 \times 0.8 \times 9$ mm^3), and the temperature measurements were considered to be representative of the average temperature at the focus. In the other imaging planes, the temperature elevation was apodized (hence underestimated) because the slice thickness was larger than the ultrasound beam width.

Results

Transient shear waves

Figure 4a shows a MR image of the setup. Fig. 4b shows the corresponding phase shift image. The displacement due to ultrasonic radiation force is shown by solid arrows. Note that acoustic streaming (water flow) due to the acoustic beam was also visible (dashed arrows).

Figures 5-7 show typical series of wave (phase shift) images for the three values of burst duration T. In all the images, each tick corresponds to a distance of 1 cm, and the gray scale ranges from $-\pi/4$ radians (black) to $+\pi/4$ radians (white). Figure 5a shows the initial motion at the focus of the transducer. In subsequent images (5b-5h), the propagation of the shear wave is clearly visible. The same phenomenon is visible in figures 6-7, with lower contrast due to T being shorter.

Figure 8 shows the measured phase shift as a function of distance from the focus, for the images presented in figure 6 (T=8.3 ms, P_{max}=32 W, x=30 mm). The error bars show the standard deviation of the phase shift, measurement over 20 voxels positioned with regular spacing around the focus. The dotted lines indicate the phase envelope, which was measured from the upper and lower values of the phase shift over the eight frames. The progression of the wave is clearly visible over a distance of approximately 15 mm. In this sample, the speed of the shear wave (estimated by manually finding the location of the peak negative phase shift in the data shown in fig. 8) was approximately 1.1 m/s. This corresponds to a shear modulus of 1.2 kPa (assuming density ρ = 1000 kg/m^3).

In the subsequent figures, we use phase envelopes – represented in dotted lines in fig. 8 – to compare various configurations. Figure 9 shows the effect of varying the acoustic power. As expected, the phase shift is proportional to the acoustic power. Figure 10 shows the influence of the burst duration T for P_{max}=16 W and x=30 mm. The phase envelope (averaged over 5 independent realizations) is shown for various burst durations. The phase shift at the focus was approximately proportional to T^2. Noting that in our experiments $T^2 = T.T_G$ (because T=T_G), this observation was consistent with [8a], and suggests that

the burst durations were shorter than the time constant τ. The rapid increase in phase shift with T^2 is of considerable interest, because temperature only increases with T.
Using the phase shift measurements at the focus (shown at radial distance r=0 in fig. 10), we tried to determine the numerical values of the unknowns (F/k and τ) in [7]. The values were obtained by solving [7] for two different values of T. Over a total of 21 available cases, 5 cases gave consistent results, with a time constant τ between 6 and 8 ms, and an asymptotic displacement F/k between 70 and 90 µm for $P_{\max}$=16 W, x=40 mm. In 6 cases the phase shift varied almost as T^2 ($\varphi \propto T^b$ with b between 1.89 and 2.15) and the system allowed an infinity of solutions. In the remaining cases the phase shift varied more rapidly than T^2 (φ was proportional to T^b with b between 2.11 and 3.45) and equation 7 allowed no solution. A possible source of discrepancy between the model and the experimental data lies in the fact that our simple model does not account for the modulation of the burst.

An important consequence of the rapid variation of phase shift with T^2 (fig. 10) is that, for a given heat deposition (i.e. for a constant product $T.P_{\max}$), the phase shift can be increased by the use of low acoustic power and long burst duration. Figure 11 illustrates this phenomenon, by showing the phase envelopes obtained with three different configurations having the same heat deposition. Each plot represents an average over five samples. Equation [8a] suggests that the underlying reason for this beneficial behavior was the concurrent increase in gradient duration T_G (as T_G=T in our experiments). However, equation [8b] predicts that, for burst durations longer than the time constant τ, this phase enhancement no longer occurs.

MR thermometry

Figure 12 shows the temperature increase at time t=17 s, i.e. immediately after 512 ultrasound bursts (corresponding to the acquisition of a single wave image). Specific parameters for this acquisition were $P_{\max}$=32 W, T=8.3 ms, x=30 mm (same as for fig. 6). The standard deviation of the temperature measurements was $\sigma_\theta \approx$ 0.7 °C.

As expected, other configurations having the same time-average acoustic intensity (namely, the configurations that were compared in fig. 11: P_{max}=16 W, T=16.7 ms, and $P_{\max}$=48 W, T=5.6 ms) showed similar temperature profiles. Additionally, temperature increased quasi-linearly with acoustic power $P_{\max}$. The relations between temperature rise and acoustic parameters being relatively well known, we do not present data for all acquisitions.

In the subsequent figures, we focus on the data shown in figure 12, and highlight some interesting features. Figure 13 shows the spatial extent of the heated region. The temperature elevation profile is plotted (a) along axes y and z that are perpendicular to the ultrasound beam, and (b) along the acoustic axis x. Temperature elevation is shown in °C, and the horizontal axes are in mm. The peak temperature increase was +6 °C (fig. 13a). In figure 13b, temperature was measured using an imaging plane that contains the acoustic axis, hence peak temperature is underestimated (+5 °C). The full width at half maximum (FWHM) dimensions of the heated region was 3.4 x 3.4 x 17.3 mm^3.

Figure 14 shows the temporal profile of the temperature variation, measured at the focus of the transducer, for 8 consecutive wave images (8x512 ultrasonic bursts), and P_{max}=32W, T=8.3 ms, x=30 mm. The temperature elevation is in °C, and the horizontal axis (time) is in seconds. The temperature initially rose with a slope of $\Delta\theta/\Delta t$ = 0.52 °C/s, and reached a maximum of +10°C. At time t=136 s, ultrasound was turned off, and cooling is visible for t>136 s.

The initial slope of the temperature variation is of particular interest. In the first seconds of the experiment, heat diffusion can be neglected, and temperature increased linearly with the number of ultrasound bursts (i.e. with time), as predicted by [10]. The slope of 0.52 °C/s was obtained for a repetition time TR=33.5 ms, i.e. N=30 bursts per second. Hence each burst induced a temperature variation $\theta_0 = \Delta\theta/\Delta t/N$ = 0.017 °C (in this particular tissue, and for this particular set of parameters). If we decide on a maximum acceptable temperature rise θ_{max}, then we can determine the maximum number of bursts $N_{max} = \theta_{max} / \theta_0$. [14]

If we arbitrarily set θ_{max} = 1 °C (equivalent to a Thermal Index TI=1 in sonography), then the maximum allowable number of bursts is N_{max}=58. In our current implementation of the technique (512 bursts per image), the number of bursts must therefore be reduced by a factor of 9. Note that this maximum number of bursts is only applicable to our specific setup, in porcine liver samples, with specific experimental conditions P_{max}=32 W, T=8.3 ms, z=30 mm. For other organs, implementations and/or parameters, the same process may be repeated to determine the maximum number of bursts.

Discussion

A rise of +6°C (equivalent to a Thermal Index of 6.0) is currently the upper limit for the approval of diagnostic ultrasound equipment by the Food and Drug Administration (13). The temperature elevations observed in our samples for the acquisition of a single image (+6 °C) was within the FDA limits. However, the safety threshold was exceeded when multiple images were acquired consecutively. As a comparison, ARFI was reported to induce temperature changes of less than 2 °C (23), and Supersonic Shear Imaging operates within the FDA limits (5). Our results are nevertheless encouraging, because we expect lower temperature elevations in vivo (because of perfusion). For example, Hynynen et al. (15) investigated the role of perfusion in hyperthermia, and reported that the temperature achieved with full flow in the kidney was five times lower than in the case with no flow.

To further reduce heat deposition, the burst power, the burst duration, or the number of bursts, must be reduced. Our initial results showed that an acoustic power as low as 4 W was sufficient to detect the shear wave, albeit over a short distance only (~5 mm) (data shown in fig. 9 for P_{max}=4 W, T=16.7 ms, x=30 mm). The use of long bursts with low acoustic power seems a promising solution, because of the significant gain in phase shift that was observed (fig. 11), but this solution implies a loss in MR signal due to an increased TE, and possibly an increased sensitivity to undesirable motion. Finally, the number of bursts can be reduced at the expense of resolution and/or of the field of view, by decreasing the number of lines. For example, 1-D MRE is an extreme case of line reduction (37).

Our results suggest that an EPI MRE sequence would be particularly well suited for t-MRE using ultrasound radiation force. An EPI sequence with n lines readout per TR would divide the number of ultrasound bursts by n. The small loss in SNR that would be incurred (because of T_2^* weighting of the echo train) could be compensated by an increase in TR and in flip angle. An EPI sequence would have the additional benefit of being extremely rapid, making it possible to acquire MRE images during a breathhold. Based on our experimental data, an EPI factor of $n \geq 9$ would allow the acquisition of a wave image similar to those shown in figures 5-7, in approximately 2 seconds, for a temperature increase of +1 °C. Common EPI factors being in the range 5 to 11, an EPI factor n=9 is easily achievable.

Even if heat deposition is reduced to an acceptable level for a single image, the possibility of a thermal buildup (due to multiple acquisitions during an examination) must be acknowledged and accounted for. Therefore, in future studies, we recommend that MRE acquisitions that use ultrasound radiation force be systematically associated with temperature monitoring.

We observed waves travelling over a distances between 5 mm (data shown in fig. 9 for P_{max}=4 W, T=16.7 ms, x=30 mm) and 20 mm (figs. 5-7). In a clinical application, the distance over which the wave will be detectable is application-dependent. It ultimately depends on two factors, namely the magnitude of the phase shift that can be achieved under acceptable safety condition, and the noise in the phase shift estimates ($\Delta\varphi$). In the future, a gain in the magnitude of the phase shift may by obtained by optimizing the transducer geometry, frequency, and/or the ultrasound signal waveform. For example, the displacement may be increased by changing the ultrasound beam width (3), by the use of wave profiles that contain shock fronts (25), by multiple consecutive bursts designed to create a Mach cone (5), and/or using multiple foci. The noise in the phase shift image is directly related to the signal-to-noise ratio (SNR) in the magnitude image (28): $\Delta\varphi = 1/SNR$ (radians). Hence, any gain in SNR directly induces a gain in penetration. To that purpose, the injection of a contrast agent, such as gadolinium, may be of interest.

Finally, it is worth noting that the use of transient shear waves, which intrinsically span over a large range of frequencies, may provide new opportunities for measuring wave dispersion (i.e. wave speed and tissue elasticity as a function of frequency). McCracken et al. proposed two methods that measure the group velocity of the transient wave (20). It is probably possible to adapt these methods to account for the broadband nature of the transient pulse. However the development of these new methods is beyond the scope of this article.

Conclusion

This study showed that MRE is capable of imaging transient shear waves generated by ultrasonic radiation force in biological tissues ex vivo. The measured phase shifts were as high as π radians at the focus; hence the waves were easily detectable.

Because this technique required high acoustic power and a large number of ultrasound bursts, safety issues were addressed. First, we developed a model that can be used to predict the peak phase shift, the temperature elevation at the focus, and other important safety indicators (I_{SPPA}, I_{SPTA}, MI). Second, experimental temperature measurements are reported. The temperature elevation measured at the focus was on the order of +6 °C for the acquisition of a single wave image, and reached up to +10 °C for 8 consecutive wave images. We expect to measure lower temperatures in vivo, especially in highly perfused organs such as the kidney (15). However, because of the possibility of thermal buildup when consecutive images are acquired, we believe that heat deposition must be further reduced before the technique can be used in vivo, and that concurrent temperature monitoring, for example via MR thermometry, will be necessary to ensure patient safety.

One of the most interesting observations was that the phase shift varied with the product $P_a.T^2$, whereas temperature increased with $P_a.T$. Hence, for a given temperature elevation, long bursts induced a larger phase shift than short bursts (fig. 11). The use of long bursts with low acoustic power is therefore expected to provide a safe and effective way to generate wave images, maximizing phase shift, while minimizing heat deposition and the mechanical index.

Finally, our experimental results suggest that an EPI MRE sequence would be particularly well suited for t-MRE using ultrasound radiation force. We estimated that an EPI factor of $n \geq 9$ would allow the acquisition of a wave image similar to those shown in figures 5-7, in approximately 2 seconds, for a temperature increase of +1 °C (per image). The EPI sequence would have the additional benefit of being extremely rapid, making it possible to acquire MRE images during a breath hold. An EPI version of the sequence reported by Le et al. (18), which performs simultaneous temperature and stiffness measurement, would provide an elegant solution to ensure safety while performing t-MRE with ultrasound.

References

1. Abbott JG. Rationale and derivation of MI and TI - A review. Ultrasound Med Biol 1999;25(3):431-441
2. AIUM/NEMA. Standard for real-time display of thermal and mechanical acoustic output indices on diagnostic ultrasound equipment, Revision 2. National Electrical Manufacturers Association (NEMA) Standards Publication UD 3-2004, 2004.
3. Andreev VG, Dmitriev VN, Pishchalnikov YA, Rudenko OV, Sapozhnikov OA, Sarvazyan AP. Observation of shear waves excited by focused ultrasound in a rubber-like medium. Acoustical Physics 1997; 43:123-128
4. Arditi M, Stuart Foster F, Hunt JW. Transient fields of concave annular arrays. Ultrasonic Imaging 1981;3:37-61
5. Bercoff J, Tanter M, Fink M. Supersonic shear imaging: a new technique for soft tissue elasticity mapping. IEEE Trans Ultrason Ferroelectrics Freq Contr 2004;51(4):396-409
6. Beyer RT. Radiation pressure-the history of a mislabeled tensor. J Acoust Soc Am 1978;63(4):1025-1030
7. Borgnis FE. Acoustic radiation pressure of plane compressional waves. Reviews of Modern Physics 1953;25(3):653-664
8. Callé S, Rémenieras JP, Bou Matar O, Elkateb Hachemi M, Patat F. Temporal analysis of tissue displacement induced by a transient ultrasound radiation force. J Acoust Soc Am 2005;118(5):2829-2840
9. Callé S. Application de la force de radiation ultrasonore à l'imagerie d'élasticité des tissus biologiques. PhD Thesis, Univ. François Rabelais, Tours, France, 2003 (in French)
10. Catheline S, Wu F, Fink M. A solution to diffraction biases in sonoelasticity: the acoustic impulse technique. J Acoust Soc Am 1999;105(5):2941-2950
11. Duck FA. Medical and non-medical protection standards for ultrasound and infrasound. Progr Biophys Mol Biol 2007;93(1-3):176-191
12. Fatemi M, Greenleaf JF. Ultrasound-stimulated vibro-acoustic spectrography. Science 1998;280:82-85
13. FDA. Information for manufacturers seeking marketing clearance of diagnostic ultrasound systems and transducers. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health, 1997
14. Herman BA, Harris GR. Models and regulatory considerations for transient temperature rise during diagnostic ultrasound pulses. Ultrasound Med Biol 2002;28(9):1217-1224
15. Hynynen K, De Young D, Kundrat M, Moros E. The effect of blood perfusion rate on the temperature distributions induced by multiple, scanned and focused ultrasonic beams in dog’s kidney in vivo. Int J Hyperthermia 1989;5(4):485-498

16. Kemper J, Sinkus R, Lorenzen J, Nolte-Ernsting C, Stork A, Adam G. MR elastography of the prostate: initial in vivo application. Fortschr Röntgenstr 2004;176:1094-1099
17. Khokhlova VA, Souchon R, Tavakkoli J, Sapozhnikov OA, Cathignol D. Numerical modeling of finite-amplitude sound beams: Shock formation in the near field of a cw plane piston source. J Acoust Soc Am 2001;110(1):95-108
18. Le Y, Glaser K, Rouvière O, Ehman R, Felmlee JP. Feasibility of simultaneous temperature and tissue stiffness detection by MRE. Magn Reson Med 2006;55(3):700-705
19. Manduca A, Oliphant TE, Dresner MA, Mahowald JL, Kruse SA, Amromin E, Felmlee JP, Greenleaf JP, Ehman RL. Magnetic resonance elastography: non-invasive mapping of tissue elasticity. Med Image Anal 2001;5(4):237-254
20. McCracken PJ, Manduca A, Felmlee J, Ehman R. Mechanical transient-based magnetic resonance elastography. Magn Reson Med 2005;53(3):628-639
21. Muthupillai R, Lomas DJ, Rossman PJ, Greenleaf JF, Manduca A, Ehman RL. Magnetic resonance elastography by direct visualization of propagating acoustic strain waves. Science 1995;269:1854-1857
22. Nightingale K, McAleavey S, Trahey G. Shear-wave generation using acoustic radiation force - In vivo and ex vivo results. Ultrasound Med Biol 2003;29(12):1715-1723
23. Palmeri ML, Frinkley KD, Nightingale KR. Experimental studies of the thermal effects associated with radiation force imaging of soft tissues. Ultrasonic Imaging 2004;26:100-114
24. Pennes HH. Analysis of tissue and arterial blood temperatures in resting forearm. J Appl Physiol 1948;1:93–122
25. Pishchalnikov YA, Sapozhnikov OA, Sinilo TV. Increase in the efficiency of the shear wave generation in gelatin due to the nonlinear absorption of a focused ultrasonic beam. Acoustical Physics 2002;48(2):214-219
26. Ribault M, Chapelon JY, Cathignol D, Gelet AL. Differential attenuation imaging for the characterization of high intensity focused ultrasound lesions. Ultrasonic Imaging 1998;20:160-177
27. Rouviere O, Yin M, Dresner MA, Rossman PJ, Burgart LJ, Fidler JL, Ehman RL. MR elastography of the liver: preliminary results. Radiology 2006;240(2):440-448
28. Salomir R, Palussière J, Vimeux FC, de Zwart JA, Quesson B, Gauchet M, Lelong P, Pergrale J, Grenier N, Moonen CTW. Local hyperthermia with MR-guided focused ultrasound: Spiral trajectory of the focal point optimized for temperature uniformity in the target region. J Magn Reson Imag 2000;12:571-583
29. Sarvazyan AP, Rudenko OV, Swanson SD, Fowlkes JB, Emelianov SY. Shear wave elasticity imaging: a new ultrasonic technology of medical diagnostics. Ultrasound Med Biol 1998;24(9):1419-1435
30. Segal LA, O'Brien WD Jr. Frequency dependent ultrasonic attenuation coefficient assessment in fresh tissue. Proc IEEE Ultrasonics Symp, 797-799, 1983
31. Siegler P, Jenne JW, Divkovic G, Schad LR. Temperature effect in high intensity focused ultrasound therapy control using dynamic MR elastography. Proc Intl Soc Mag Reson Med 2005;13:2363-2363

32. Sinkus R, Tanter M, Xydeas T, Catheline S, Bercoff J, Fink M. Viscoelastic shear properties of in vivo breast lesions measured by MR elastography. Magn Reson Imaging 2005;23(2):159-165
33. Sugimoto T, Ueha S, Itoh K. Tissue hardness measurement using the radiation force of focused ultrasound. Proc IEEE Ultrasonics Symp 1990:1377-1380
34. Torr GR. The acoustic radiation force. Am J Phys 1984;52(5):402-408
35. Westervelt PJ. The theory of steady forces caused by sound waves. J Acoust Soc Am 1951;23(4):312-315
36. Wu T, Felmlee JP, Greenleaf JF, Riederer SJ, Ehman RL. MR imaging of shear waves generated by focused ultrasound. Magn Reson Med 2000;43(1):111-115
37. Yuan L, Glaser KJ, Rouviere O, Gorny KR, Chen S, Manduca A, Ehman RL, Felmlee JP. Preliminary assessment of one-dimensional MR elastography for use in monitoring focused ultrasound therapy. Phys Med Biol 2007;52(19):5909-5919

Appendix A – Derivation of I_{SPPA}, I_{SPTA} and *MI*

The mechanical index *MI* is an indicator of possible cavitation effects, while the temporal-average acoustic intensity I_{SPTA} provides an indication of possible thermal effects. These indices are defined by the AIUM standards (13, 2). Details of the calculations of these indicators are given in this appendix, for ultrasonic bursts having constant acoustic power P_a, duration T, and repetition time TR. The pressure p at the focus of a concave spherical transducer is given by:

$$p(t) = -\frac{d}{c}\frac{\partial p_0}{\partial t}\left(t - \frac{R}{c}\right) \qquad [A_1]$$

where t is the time, d is the depth of the concave source, c is the speed of sound, p_0 is the pressure at the surface of the source, and R is the focal distance. Equation A_1 was derived from (4), with the additional assumption that, at the surface of the transducer, pressure (p_0), density of the propagating medium (ρ) and normal particle velocity (v_0) are related by $p_0(t) = \rho c v_0(t)$ $[A_2]$

In the case of a continuous wave with pulsation $\omega=2\pi f$, the acoustic intensity at the focus is given by:

$$I(t) = \frac{p^2(t)}{\rho c} = \frac{\omega^2 d^2}{c^2} I_0(t) \qquad [A_3]$$

where $I_0=P_a/S$ is the acoustic intensity at the surface of the transducer, P_a is the acoustic power at the surface of the transducer, and $S=2\pi Rd$ is the surface of the transducer. Combining equations A_1-A_3 and including the effect of attenuation, the spatial-peak intensity at the focus – averaged over one cycle of the ultrasonic signal – is given by:

$$I_{SP}(t) = \frac{2\pi}{c^2}\frac{d}{R} f^2 P_a(t) e^{-2\beta f x} \qquad [A_4]$$

β denotes frequency-dependent attenuation (in Np/m/MHz), and x denotes the depth at which the focus is located. For a pulse having constant acoustic power P_a, the spatial-peak pulse-average intensity I_{SPPA} is simply:

$$I_{\mathrm{SPPA}} = \frac{2\pi}{c^2}\frac{d}{R} f^2 P_{\mathrm{a}}\, e^{-2\beta f x} \qquad [A_5]$$

The spatial-peak temporal-average intensity I_{SPTA} is the temporal average of intensity over one or more pulse repetition periods. In our application, the pulse repetition period is TR, and:

$$I_{\mathrm{SPTA}} = I_{\mathrm{SPPA}} . T / TR \qquad [A_6]$$

The mechanical index MI is equal to the spatial peak value of the peak rarefactional pressure p_{r} (expressed in MPa) divided by the square root of the center frequency f (expressed in MHz). Hence using SI units, $MI = 10^{-3} p_{\mathrm{r}} / \sqrt{f}$ [A_7]

For the sake of simplicity, we assumed linear wave propagation. Under this assumption, and noting that the ultrasonic period ($1/f$) is much smaller than the pulse duration T, the pressure waveform is approximately sinusoidal. The acoustic intensity I_{SP} – averaged over one cycle of the ultrasonic signal – is related to peak pressure $p_{\max}$ by:

$$I_{\mathrm{SP}} = p_{\max}^2 / (2\rho c) \qquad [A_8]$$

Combining equations A_4, A_7 and A_8, gives [13]. Evaluating precisely the mechanical index will require specific investigation, because ultrasound propagation is probably nonlinear, at least for the highest intensities we used. Nonlinear propagation can drastically alter the temporal profile of the pressure wave, making it difficult to predict the value of the peak negative pressure. In the simulations reported in (17), nonlinear wave propagation had a tendency to attenuate the peak rarefactional pressure. This would indicate that [13] over-estimates MI.

In our experiments, the acoustic power was:

$$P_{\mathrm{a}}(t) = (1 - \cos(2\pi t / T))^2 P_{\max} / 4 \qquad [A_9]$$

Here $P_{\max}$ denotes the maximum acoustic power (fig. 2), and $0 \le t \le T$. The spatial-peak pulse-average intensity I_{SPPA} is the ratio of the pulse intensity integral to the pulse duration T (13). It is given by:

$$I_{\mathrm{SPPA}} = \frac{3\pi}{4c^2}\frac{d}{R} f^2 P_{\max} e^{-2\beta f z} \qquad [A_{10}]$$

Appendix B – I_{SPPA}, I_{SPTA} and MI estimates

Tables 1 and 2 show the values for $I_{SPPA.7}$, $I_{SPTA.7}$, and $MI_{.7}$ for all configurations tested in this study. The subscript ".7" denotes that the indicators were derated to account for ultrasonic attenuation using $\beta = 0.7$

dB/cm/MHZ in degassed porcine liver samples (26, 30). This definition differs from that of the AIUM/NEMA (2), which assumes an average attenuation of 0.3 dB/cm/MHz (denoted by subscript ".3"). Our purpose differs somewhat from that of the AIUM/NEMA document, in that we want to report an estimate of the *actual intensity*, whereas the AIUIM/NEMA standards were designed to provide an *indicator* of the likeliness of thermal and/or mechanical effects. Hence our choice to report values derated by an attenuation of 0.7 dB/cm/MHz, which are representative of our experimental conditions.

	Depth x=30 mm		Depth x=40 mm	
P_{max} (W)	$I_{SPPA.7}$ (W/cm^2)	$MI_{.7}$	$I_{SPPA.7}$ (W/cm^2)	$MI_{.7}$
4	57	1.4	38	1.1
8	113	2.0	77	1.6
12	170	2.4	115	2.0
16	226	2.8	154	2.3
32	453	3.9	307	3.2
48	679	4.8	461	4.0

Table 1. $I_{SPPA.7}$ and $MI_{.7}$

	Depth *x*=30 mm			**Depth *x*=40 mm**		
P_{max} (W)	***T*= 16.7 ms**	***T*= 8.3 ms**	***T*= 5.6 ms**	***T*= 16.7 ms**	***T*= 8.3 ms**	***T*= 5.6 ms**
4	28			19		
8	56	28		38	19	
12	84	42	28	57	29	19
16	113	56	38	77	38	26
32		113	75		77	51
48			113			77

Table 2. $I_{SPTA.7}$ (W/cm²). The combinations corresponding to shaded areas were not used in our experiments.

Figure captions

Figure 1. Illustration of transient shear waves generated by ultrasound radiation force.

Figure 2. MRE sequence timings, showing the RF pulses, the MEG, and the power applied to the transducer, for the acquisition of a single line in the MR image. A variable delay (corresponding to the time of flight of the transient shear wave) separates the ultrasonic burst from the MEG.

Figure 3. Experimental setup

Figure 4: (a) MR image of the setup (transverse plane). The transducer is visible in black at the bottom. The liver sample (oval shaped, at the top) is positioned on a horizontal sample holder (black) pierced with a hole in its centre. The acoustic axis (arrow) is vertical, and the coronal plane used in figures 5-7 in shown (dashed line). The image size is 12x12 cm^2. (b) Phase shift image showing motion induced by radiation force (solid arrows). The gray scale spans from $-\pi/4$ radians (black) to $+\pi/4$ radians (white).

Figure 5. Typical series of 8 consecutive wave (phase shift) images, for T=16.7 ms, P_{max}=16 W, x=30 mm. The imaging plane is perpendicular to the acoustic axis. Each image is 8x8 cm^2. The images are separated by a time interval $\Delta T \sim 4.2$ ms.

Figure 6. Typical series of 8 consecutive wave images for T=8.3 ms, P_{max}=32 W, x=30 mm. Each image is approximately 8x8 cm^2. The images are separated by a time interval $\Delta T \sim 4.2$ ms.

Figure 7: Typical series of 8 consecutive wave images for T=5.6 ms, P_{max}=48 W, x=30 mm. Each image is approximately 8x8 cm^2. The images are separated by a time interval $\Delta T \sim 4.2$ ms.

Figure 8: Phase shift (radians) vs. radial distance (mm), for the images shown in fig. 6 (T=8.3 ms, P_{max}=32 W, x=30 mm). The error bars show the standard deviation of the phase shift measurements. The dotted lines indicate the phase envelope (upper and lower values of the phase shift). The arrows indicate the approximate location of the peak negative phase shift.

Figure 9, Effect of acoustic power on the phase shift: Phase envelope (rad) vs. radial distance (mm) for T=16.7 ms, x=30 mm, and various acoustic powers P_{max}. Each plot represents an average over five independent realizations. The phase shift was proportional to P_{max}.

Figure 10, Effet of burst duration / gradient duration on the phase shift: Phase envelope (rad) vs. radial distance (mm) for P_{max}=16 W and x=30 mm.

Figure 11: Phase envelope (rad) vs. radial distance (mm), for three configurations having the same heat deposition. (for x=40 mm). The phase shift increased linearly with burst duration T.

Figure 12: Temperature elevation after 512 ultrasonic bursts (i.e. immediately after the acquisition of one wave image) for P_{max}=32W, T=8.3 ms, x=30 mm. The gray scale ranges from 0°C (black) to +10°C (white). The images are 40x40 mm^2 in size. (a) Coronal plane, perpendicular to the acoustic axis, and (b) transverse plane that contains the acoustic axis (arrow).

Figure 13: Spatial extent of the heated region, after 512 ultrasonic bursts (i.e. immediately after the acquisition of one wave image), for P_{max}=32W, T=8.3 ms, x=30 mm. The temperature profiles (°C) are shown vs. distance from the focus (mm): (a) along axes perpendicular to the acoutic beam and (b) along the acoustic beam (x-axis).

Figure 14. Temperature elevation (°C) vs. time (s) at the focus of the transducer, for 8 consecutive wave images (8x512 ultrasonic bursts) and P_{max}=32W, T=8.3 ms, x=30 mm.