MR Elastography at 7T to Measure Tissue Biomechanical Properties for Improved Registration of Histopathology and Radiation Therapy Images

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INTRODUCTION

The registration of multi-modality images (e.g. MR, CT, PET) improves tumor identification for targeted cancer radiation therapy (1). The biomechanical model based technique MORFEUS (1) has demonstrated superior performance in this registration task. Correlation with 3D histopathologic maps may be used to validate identification of tumor boundaries. However, fixation using formaldehyde solution during pathology tissue processing deforms the tissue and changes material properties non-uniformly. Using a biomechanical method such as MORFEUS to register histology to in-vivo images necessitates information on these changes. To measure the naturally occurring tissue property structure in fresh tissue and the extent and distribution of property changes in fixed tissue a quasi-static MR-elastography (2) method has been developed at high field (7 T), allowing rapid volumetric measures for whole organ resections, e.g. radical prostatectomy. An initial investigation has been performed using fresh ex-vivo and fixed porcine kidney samples, for which indentation testing was also used to measure the effect of fixation on tissue stiffness. The data obtained will be used to develop a 3-D finite element model solution (3) which maps the stiffness properties (Young's modulus, E) across fresh ex-vivo samples and the distribution of fixation effects across fixed samples. This will allow the calculation of population averages for fresh and fixed whole organs such as prostate, which will lead to more effective registration of in-vivo images with histopathology and hence improved assessment of treatment accuracy. Initial results demonstrate sensitivity to fresh tissue structure and the increase in stiffness of fixed tissue, which was supported by the results of indentation testing.

METHODS

Fresh porcine kidney was sliced into a cube of approximately 4 cm in each dimension. The tissue was selected to include a section of the medulla. The cube was placed in 10% neutral buffered formalin solution for 5 days after which it was embedded in a block (a cube of ~7 cm in each dimension) of 4% gelatin and 1.5% agarose gel (4) to provide stability during compression. A similar cube of fresh tissue was also embedded in gel. An elastography device built in Plexiglas (4) was used, consisting of a tissue sample holder (with a square base of 8×8 cm^2) in which a sample could be compressed by a square plate attached to a mechanical piston, connected via an eccentric disk to a non-magnetic ultrasonic piezo-electric motor (USR60-E3N, Shinsei, Japan). The motor provided compression at a rate of 1 Hz and the disk allowed a maximum compression amplitude of 1.5 mm. A tissue-gel block was placed in the holder and the device positioned in the bore of a 7-T pre-clinical MRI scanner (70/30 BioSpec, Bruker, Ettlingen, Germany), where a quadrature volume resonator (15.5 cm inner diameter) was used for transmission and reception. Moderate preloading was applied prior to compression. The compression motion was tracked via the scanner pre-clinical respiration monitor (SA Instruments Inc., New York), i.e. the respiratory bellows was mounted on a holder behind the piston, and the scanner sequence was triggered during the appropriate phase of the compression cycle using the respiratory triggering software. Phase accrual from static field inhomogeneities was minimized using the Bruker fastmap shimming routine prior to image acquisition. A Stimulated Echo (STEAM) sequence consisting of 3 consecutive 90° RF pulses (2) was used. The readout was timed to occur in the uncompressed state, while the displacement encoding gradients were applied in the compressed state. The gradient duration τ = 1 ms and the amplitude Gd = 40 mT/m implied a displacement sensitivity ϕ_d of 3.4π. The mixing time T_m between the 2nd and 3rd 90° pulses was 200 ms. An acquisition during motion was made of 9 coronal slices of 8 mm thickness, with 0.5 by 0.5 mm in-plane resolution (80×64 mm^2, 160×128 matrix, reconstructed to 256×256). The other imaging parameters were: TR = 1000 ms, TE = 12 ms and signal averages = 1. Two gradient directions were applied in succession: vertical (parallel to the direction of motion) and horizontal. Imaging time for a single gradient direction in 1 slice was approximately 2 mins. A reference acquisition in the uncompressed state and without motion was subsequently made for both diffusion directions, this time for a 160×32 imaging matrix, which reduced acquisition time by 4. Hence acquisition time for a whole volume was < 25 min (for 1 gradient direction), which was within an acceptable time frame for imaging fresh pathology specimens prior to fixation. Signal images were smoothed using a 5-point wide disk filter prior to processing to dampen noise. The during-motion acquisitions (S_{motion}) were corrected for phase changes not associated with motion using the reference static acquisition (S_{static}) (see eqn. 1). As differential phase was sufficient to calculate strain this was acquired by multiplying each voxel value by the conjugate of its neighbor in the direction of motion encoding, and this was scaled by ϕ_d to obtain differential displacement. Normal (ε11) and transverse (ε22) strain values could then be calculated via eqn. 2. The gel/tissue blocks were subsequently sliced into ~1 cm thick slices and divided into approximate 3×3 cm^2 sections of tissue or gel and Young's modulus was measured for the medulla, renal cortex and gel using a soft tissue elastometer (5).

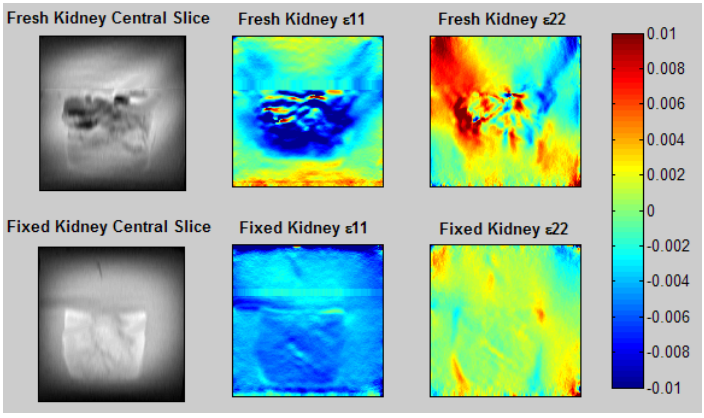
$$S_{cor}(\vec{r}) = \frac{S_{motion}(\vec{r}) S_{static}(\vec{r})^*}{|S_{static}(\vec{r})|} \approx |S_{motion}(\vec{r})| e^{i\phi(\vec{r})} \quad (1)$$

$$\varepsilon_{ij} = \frac{1}{2}\left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i}\right) \quad (2)$$

Table 1:	Mean (std) Young's Modulus (kPa)	
Tissue/Gel	*Fresh Sample*	*Fixed Sample*
Medulla	5.36 (1.4)	30.4 (18.5)
Renal Cortex	5.74 (1.11)	91.8 (26.6)
Gel	57.6 (22.2)	

RESULTS

The signal images and the corresponding vertical (ε11) and horizontal (ε22) strain images obtained for a central slice of the fresh and fixed samples are shown in the figure. (The direction of compression was upwards from the base of the images). A central slice was chosen for display to illustrate features from the medulla. Firstly, the fresh tissue slice shows greater (absolute) strain values for the tissue than the surrounding gel, whereas the fixed tissue strain images indicate more similar strain values to the gel. Also, features that are visible in the signal images have apparently given rise to strain patterns in the fresh and fixed images. Finally the indentation results (see table 1) confirmed that the stiffness increased by 15 fold in the renal cortex and 6 fold in the medulla from fresh to fixed tissue and the gel stiffness was approximately the average of the fixed tissue values. (Note: the band visible across the upper end of the ε11 images resulted from a reconstruction artefact.)



DISCUSSION AND CONCLUSION

Quasi-static MR elastography at 7 T is feasible for pathology samples and this time-optimized protocol gives rise to images that are sensitive to the gross effects of formalin fixation and also fine structural detail within both fresh and fixed tissue. The imaging times required are acceptable within pathology tissue processing time-frames and the time required per slice could be reduced still further by, for example, using echo planar imaging (EPI), which alternatively would allow for higher resolution both in-plane and through-plane, and some initial experiments with EPI have demonstrated this. Another approach towards achieving finer detail would be by making the volume of the sample holder smaller, which would allow the use of more sensitive volume resonators. A gradient of fixation effects from the surface to the centre of the fixed block is not readily observable from these strain images, however it is possible that the sample was uniformly fixed after 5 days. Future work will hence explore the gradual effects of fixation over shorter periods, e.g. 24 hrs. This data will be used in a finite element modelling based algorithm to reconstruct the Young's Modulus values for the 3-D volume via iterative calculation of stress values (3). The 3-D distributions obtained will be used to form population averages of fresh and fixed whole ex-vivo organs such as prostate.

REFERENCES 1. Brock KK et al, *Med Phys* 2005,32:1647-1659; 2. Chenevert TL et. *Magn Reson Med* 1998,39:482-490; 3. Samani A et al, *IEEE Trans Med Imag* 2001,20:877-885; 4. Samani A et al, *Phys Med Biol* 2003,48:2183-2198; 5. Egorov V et al., *Med Engin Physics* 2008, 30:206-212.