The Effects of Interstitial Tissue Pressure on the Elastic Shear Modulus in MR Elastography

J. B. Weaver[1], P. R. Perrinez[2], J. A. Bergeron[3], F. E. Kennedy[2], M. M. Doyley[1], P. J. Hoopes[3], K. D. Paulsen[2]

[1]Department of Radiology, Dartmouth-Hitchcock Medical Center, Lebanon, NH, United States, [2]Thayer School of Engineering, Dartmouth College, Hanover, NH, United States, [3]Department of Surgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH, United States

Introduction: MR Elastography (MRE) has been used primarily to identify breast cancer which is known empirically to be stiffer than normal breast tissue; between 40% and 60% of all breast cancer is first identified by physical examination. Elastography, a quantitative physical examination, has long been expected to enhance cancer diagnoses in the breast and other organs. Other applications of MRE have also emerged in the brain, liver, and diabetic feet. However, the biologic mechanisms which make cancer and other pathology stiffer than normal tissue are unknown. Several characteristics are likely to contribute: the two most likely are an increased level of fibrous stroma [1] and increased tissue pressure (TP) [2-4]. We are reporting the first evidence of TP affecting the shear modulus (μ) of tissue which opens the possibility of MRE identifying and monitoring treatment of a wide array of pathologic conditions associated with increased TP's and edema and with decreased TP's: e.g., cancer [2-4], diabetes, stroke, transplant rejection [5] and ischemia.

Interstitial fluid pressures are normally slightly below atmospheric pressure except in rigidly enclosed tissues such as the brain in the skull and the kidney in its stiff capsule [6]. In rigidly enclosed organs such as the brain, the TP is comparable to that in edematous or cancerous tissue, ~15 to 20 mm Hg [2,3]. TP in brain tissue following death will revert to atmospheric pressure which is similar to that in normal breast tissue.

Methods: An MRE sequence was acquired on the pre-mortem brain of farm-strain Yorkshire swine, two months of age, under gas anesthesia, and another MRE subsequently post-mortem. The shaker used to produce vibrations in the porcine brain, shown in Figs. 1,2, also held the head rigidly in place for both sequences. A 3D phase contrast pulse sequence (TR=20.4ms, TE=15.6ms, 10 ms motion encoding gradients) was used to record the harmonic motion (98 Hz, 6 to 10 μm amplitudes) [7]. An iterative, finite element based reconstruction of the Navier equations for linear elastic behavior was used to reconstruct the images of the shear modulus (μ) and Lame's constant, λ, [8]. Tissue pressure measurements were made using a Wave-Wire© (Volcano Therapeutics) guide-wire developed for intravascular blood pressure measurements. It was inserted in the brain through a 22 gauge needle.

Results & Discussion: TP measurements in the live, anethesized porcine brain were ~19 mm-Hg which is comparable to the values of interstitial fluid pressure in several cancers [2,3]. The μ was averaged over the top half of the brain, avoiding the bottom of the skull where blood pooling occurs post-mortem. The quadrant where the needle was inserted to obtain pressure measurements was also not included in the average; swelling or bleeding around the needle was observed in one animal.

Animal	Dead TP	Δ TP	Live Temp.	Dead Temp.	Live μ	Dead μ	$\Delta\mu$	$\Delta\mu$ / Δ TP
1	6 mm-Hg	13 mm-Hg	97.2 °F	94.5 °F	8.6 kPa	5.3 kPa	3.3 kPa	0.24 kPa/mm-Hg
2	10 mm-Hg	9 mm-Hg	96.2 °F	91.0 °F	7.3 kPa	5.9 kPa	1.4 kPa	0.16 kPa/mm-Hg

The pre-mortem μ was an average factor of 1.43 greater than the post-portem values. Repeated MRE measurements have good precision with a standard deviation of 3.5% [9] so the average change in μ of 12 standard deviations has very high significance. The change in μ was significant in both animals. The changes in μ were not spatially uniform but were not noticeably correlated with grey and white matter in either animal. Experiments to isolate all the effects occurring at death are needed; e.g., the post-mortem temperature drop increased the μ which reduced the change in μ observed and was a larger effect in the second animal where the change in μ was smaller. In addition, post-mortem TP changes are non-uniform because blood drainage is non-uniform. The mechanical behavior as a function of pressure is probably best described by a bi-phasic (porous elasticity) model and will depend on several factors including the tissue matrix, but the effect can also be described using a linear elastic model at each pressure as we have done here. The μ observed are consistent with a nonlinear change with pressure as might be expected from a bi-phasic model.

Conclusions: The significant reduction in μ in the post-mortem brain is likely due primarily to decreased TP and has many implications. The μ of excised tissue samples from enclosed organs, including cancers with fibrous capsules, will be significantly less than the μ measured in vivo because of TP changes. Another significant implication is that the increased TP observed in cancer contributes significantly to the increased μ in cancer but does not account for all of the increase observed.

More generally, the results show that MRE might be used to noninvasively detect and monitor a wide array of pathology associated with edema and increased TP's, decreased TP's, increased oncotic pressures, and ischemia including cancer, diabetes, stroke, transplant rejection and ischemic disease. For example, increased TP is thought to inhibit some cancer treatments [1,10], so MRE might play an important role in non-invasively monitoring treatment. The methods should also enable better characterization of the mechanical behavior of tissue as a function of TP using bi-phasic models.

References:

1) Netti et al.: Cancer Research 60, 2497–2503, 2000.
2) Gutmann et al.: Cancer Research 52:1993-5, 1992.
3) Nathanson and Nelson: Annals of Surgical Oncology 1(4):333-8, 1994.
4) Stohrer, et al., Cancer Research 60: 4251–4255, 2000.
5) Johnsson C. et. al., Transplantation. 70(11):1575-80, 2000.
6) Guyton: "Textbook of Medical Physiology", (W.B. Saunders, Philidelphia, PA, 1986), p 355.
7) Weaver, et. al., Med. Phys., 28(8):1620-1628, 2001.
8) Van Houten, et al., Mag. Reson. in Med. 45(5):827-837, 2001.
9) Weaver et. al., Clinical Biomechanics, In Press.
10) Curnis, et al., J. of Clinical Investigation, 110(4):475-482, 2002.

Supported by R01-DK-063013, R01-NS-33900. and P01-CA-80139.

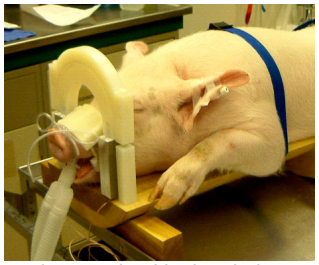

Fig. 1: Animal in the shaker

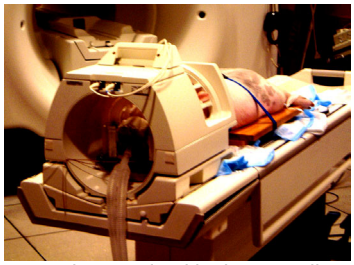

Fig. 2: Animal in the RF coil.