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IN VIVO IMAGING OF DYNAMIC SHEAR MODULUS OF RODENT MAMMARY TUMORS USING ULTRASOUND

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INTRODUCTION

Biomechanical properties of living tissue are very important in maintaining normal tissue function, cellular and extracellular structural integrity. Therefore, the quantitative determination of biomechanical properties of breast tissue, especially in vivo, serves an important role in clinical diagnosis.

Fibroadenoma and carcinoma are common benign and malignant tumor types among breast patients. They are both characterized as tissue stiffening (2~10 times stiffer in shear modulus). [1] Dynamic shear-wave imaging technique was developed to study the mechanical properties in many laboratories during the past decade. Although the information from those studies is reproducible and consistent, the relation between tissue structure and mechanical parameters is still unknown. In order to make mechanical property a more effective indicator in breast tumor diagnosis, study on the contrast mechanism of shear-wave imaging is necessary.

We chose two types of tumors with different microstructure to study: spontaneous rat fiber-rich fibroadenoma and cell-rich mouse 4T1 syngeneic xenograft modeled cancer. Histology and ECM protein analysis aided in identifying tumor type and its cellular and extracellular structure which helped us build the connection of mechanical measurements and clinical findings.

MATERIALS AND METHODS

Doppler ultrasound shear-wave imaging technique was used which generates shear wave energy through an axially vibrating needle at frequencies between 50 and 450 Hz to estimate complex shear modulus of mammary tumors. Experiments were conducted on the SonixRP ultrasonic system (Ultrasonix Medical Corporation, Richmond, BC) using a BW-14/60 linear array probe. Shear waves were generated by a harmonically actuated fine needle which was inserted into the center of the tumor. Pulsed Doppler techniques were applied to record the particle velocity field. Shear-wave speeds estimated from spatial-phase gradients of each excitation frequency generated shear-wave speed dispersion curves which were then fitted to Kelvin-Voigt rheological model to find spatially averaged estimation of the complex shear modulus: $\mu(\omega)=\mu 1-i\omega\eta$, where $\mu 1$ is the elastic shear modulus and η is the dynamic viscous coefficient. Details of the acquisition, modeling, and signal processing are described elsewhere [2].

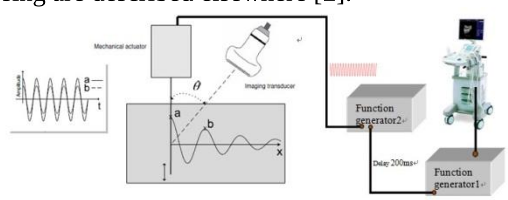

Figure 1. Diagram of ultrasonic shear-wave imaging setup.

Mammary tumors in five Sprague-Dawley rats and four BALB/c mice (Harlan, Indianapolis) have been studied. Immediately after tumor imaging, the tumor was excised and cut into three cylindrical samples for standard testing on AR-G2 rheometer (TA Instruments, New Castle, USA).

RESULTS

Quantitative shear modulus measurements in tumors

Figure 2 is the shear-wave speed dispersions of both types of tumors. Different tumors exhibit similar frequency-dependent behaviors except Rat 5 with a hyperplasia tumor. Estimated viscoelastic modulus from K-V model is summarized in Table 1 & 2. A positive correlation exists between elasticity and viscosity parameters of tissue. Noticeably, in rat fibroadenomas, the stages of tumors correlate with the modulus increase.

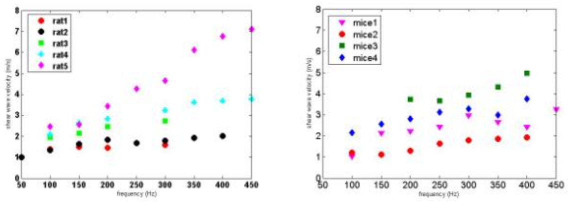

Figure 2. Shear-wave speeds versus frequency for rat tumors (left) and mouse tumors (right). Rat 1-4 tumors were diagnosed as fibroadenoma. Rat 5 tumor was diagnosed as lobular hyperplasia. All mouse tumors were anaplastic carcinoma. Missing frequencies were because raw dataset is jeopardized where true values of shear-wave speed cannot be estimated.

Table 1: Summary of rat shear wave imaging and rheometry results

	Tumor type (stage)	Estimated Modulus		RHEOMETER 5% STRAIN	
		μ[Pa]	η[Pa·s]	μ[Pa]	η[Pa·s]
Rat 1	Fibroadenoma (1)	1832.2	0.9	N/A	
Rat 2	Fibroadenoma (1)	1485.6	1.16	230.9	2.38
Rat 3	Fibroadenoma (2)	2728.6	3.46	N/A	
Rat 4	Fibroadenoma (2)	4420.4	3.54	864.6	3.64
Rat 5	Expanded lobular hyperplasia	2841.8	8.26	398.8	7.01

Table 2: Summary of mice shear wave imaging result

	Tumor type	Estimated Modulus	
		μ[Pa]	η[Pa·s]
Mouse1	Carcinoma	4844.7	1.7
Mouse2		943.9	0.99
Mouse3		8423.8	5.7
Mouse 4		4718.8	3.4

Comparison of rat fibroadenoma and mouse carcinoma

Non-parametric statistical testing (Permutation test) was performed for both VE parameters where we accepted the null hypothesis that data from the two groups are really just one population, despite vast difference in microstructure and collagen content. (Figure 3 shows the comparison of two tumor types) Attenuation curves show different behavior between 150~300Hz indicating that attenuation might be an important supplement to shear-wave speed in elasticity imaging diagnosis.

DISCUSSION

This study demonstrates that measurement of mechanical properties using ultrasound is feasible. The measurements from rodent animals are comparable to human patients study results from other labs. [3]For rat fibroadenoma tumors, the measured elastic and viscous coefficients agree well with standard rheometry in trend. The difference between our estimated modulus and rheometry results can be originated from nonlinear properties of shear modulus at different frequency and strain ranges, which often exists in biological tissue where nonlinearity and interstitial fluid flow take effect.

The disagreement between fibroadenoma and carcinoma might exist in higher frequency or in attenuation dispersion behaviors which are investigated using other excitation methods. Rat 5 with a lobular hyperplasia tumor exhibited high viscosity resulting from the adhesive nature of benign cells.

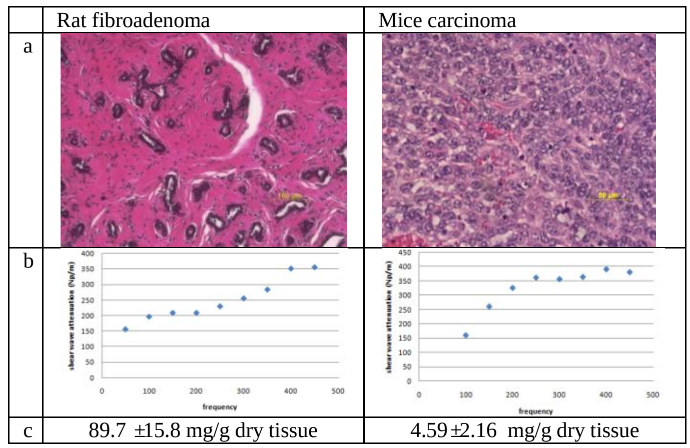

Figure 3. (a) Optical microscope images of H&E stained tumors. (b) Attenuation dispersion curve of each tumor type. (c) Average collagen content in each tumor type.

CONCLUSION

A novel, dynamic shear wave imaging system has been developed for quantitatively mapping breast tissue biomechanical properties in vivo. Inter-animal consistency is achieved among limited numbers of data sets. Viscoelastic properties are correlated with fibrosis grade. Shear wave velocity dispersion curves could not distinguish between tumors types; however, the addition of frequency-dependent attenuation enables separation. Viscoelastic properties are important in quantification of tissue microenvironment which can aid in the tumor detection and classification. More detailed knowledge of mammary tumors mechanobiology on the scale of a millimeter is expected to help illuminate the role of elasticity imaging in cancer diagnosis.

REFERENCE

[1] R. Sinkus, et,al, "Viscoelastic shear properties of in vivo breast lesions measured by MR elastography," *Mag. Res. Imaging*, 23:159-65, 2005

[2] M. Orescanin, M. F. Insana, "Shear Modulus Estimation With Vibrating Needle Stimulation," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*,57(6):1358-67, 2010

[3] Alexia L. McKnight , et al, "MR Elastography of Breast Cancer: Preliminary Results", *AJR*, 178(6):1411-17, 2002