Proceedings of 20th International Congress on Acoustics, ICA 2010

23-27 August 2010, Sydney, Australia

Combined Vibro-acoustography (VA) imaging and Shearwave Dispersion Ultrasonic Vibrometry (SDUV) for measuring prostate viscoelastic material properties – An in vitro feasibility study

F.G. Mitri, M.W. Urban, M. Fatemi, and J.F. Greenleaf

College of Medicine, Mayo Clinic, Department of Physiology and Biomedical Engineering, Rochester MN 55905, USA
Emails: mitri@ieee.org; mitri.farid@mayo.edu

PACS: 43.80.EV, 43.80.VJ

ABSTRACT

Improved methods for prostate guided-biopsy are required to effectively guide needle biopsy to the suspected site. In addition, tissue stiffness measurement would help identifying a suspected site to perform biopsy because stiffness has been shown to correlate with pathology. More importantly, early detection of prostate cancer may guide therapy and eliminate invasive procedures. Vibro-acoustography (VA) is sensitive to tissue stiffness and may allow locating an appropriate side for biopsy. Furthermore, Shearwave Dispersion Ultrasound Vibrometry (SDUV) can provide quantitative information about tissue viscoelasticity. For prostate applications, the SDUV technique should be guided by an imaging modality leading to a better biopsy and reduction of the sampling error. The purpose of this study is to evaluate the feasibility of combining VA and SDUV to perform "virtual biopsy" at a specific location. Shear elasticity and viscosity measurements of an excised human prostate are obtained and discussed.

INTRODUCTION

From studies evaluating prostate cancer, it is known that a significant number of cancers were missed on initial biopsy [1]. Although investigators have reported the successful real-time monitoring of prostate imaging and needle biopsy guiding with conventional transrectal ultrasound (TRUS) as well as Power Doppler transrectal ultrasound imaging that had been suggested to improve the prostate cancer detection rate [2, 3], there are drawbacks to this technique.

Ultrasound imaging inherently produces speckle, which is the snowy pattern that results from random interference of echoes from the tissue scatter. This artifact reduces image contrast, degrades its quality, and hampers accurate imaging of lesions. Moreover, TRUS is not capable of distinguishing the variation of stiffness and consequently, quantitative estimation of the elastic parameters is lacking. Thus far, the evaluation of elastic parameters by conventional imaging modalities has been limited.

Recent breakthroughs in imaging have catalyzed the development of novel techniques, such as "elasticity imaging methods" that are sensitive to the elastic properties of tissue [4-12]. Although these tools are valuable in detecting abnormal prostate lesions, they are however inapplicable when abnormalities are not confined to a local region and there is no normal background tissue to provide contrast. In addition, estimation of elastic parameters largely depends on the boundary conditions. Such circumstances require quantitative methods, where tissue elasticity is inversely solved in unit of Pascal. Considerable efforts have been therefore directed to developing quantitative methods in recent years. Several investigators have proposed the use of shear wave propagation speed for quantifying tissue stiffness [13-16]. However, tissue viscosity is neglected in these methods, and this omission may cause bias in the estimation of tissue elasticity. In addition, important information about tissue state may be lost due to the neglect of viscosity because recent studies suggest that viscosity is another useful index of tissue health [17, 18]. Supersonic shear imaging has the potential to solve quantitatively both tissue elasticity and viscosity [19]. However, this technique requires super fast imaging (with a frame rate up to 5000 frames per second), which is not compatible with current commercial ultrasound scanners.

In various medical imaging applications, Vibro-acoustography (VA) [20, 21] has been successfully used for imaging small particles such as microcalcifications in breast tissue [22], calcifications in arteries [23], excised human cancerous liver tissue [24], standard brachytherapy seeds [25] in gel phantoms [26] and in an excised prostate in vitro [27] and monitoring prostate cryotherapy [28]. On the other hand, a newly emerging method called Shearwave Dispersion Ultrasound Vibrometry (SDUV) [29], that quantifies both elasticity and viscosity by evaluating dispersion of shear wave propagation speed, has been successfully used to characterize bovine striated muscle and swine liver tissue [29] both *in vitro* and *in vivo*, and may potentially improve evaluation of prostate mechanical parameters and guide needle biopsy to the appropriate suspected site.

The purpose of this study is therefore directed toward evaluating the feasibility of using VA imaging to locate a suitable site for SDUV measurements of elasticity and viscosity in an excised human prostate in vitro.

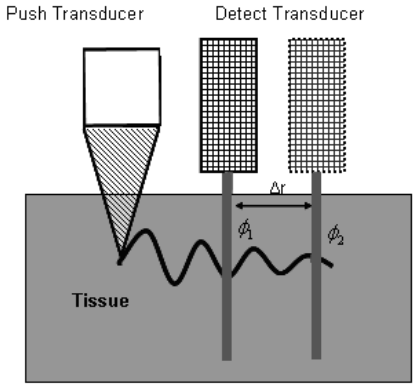

Figure 1. SDUV applies a localized force generated by a 'Push Transducer' coupled to the tissue, transmitting repeated ultrasound tone bursts of ultrasound. A separated transducer acts as the detector ('Detect Transducer').

METHODS

Principle of SDUV

In Shearwave Dispersion Ultrasound Vibrometry (SDUV) [29], an external localized force is applied to generate harmonic shear waves that propagate outward from the vibration center.

For a homogenous Voigt model the shear wave speed c_s depends on its angular frequency ω_s:

$$c_s(\omega_s) = \sqrt{2\left(\mu_1^2 + \omega_s^2\mu_2^2\right) \Big/ \rho\left(\mu_1 + \sqrt{\mu_1^2 + \omega_s^2\mu_2^2}\right)}, \quad (1)$$

where ρ, μ_1 and μ_2 are the density, shear elasticity and shear viscosity of the medium, respectively. The external localized force is generated by a "Push Transducer" (Fig. 1) that transmits repeated tone bursts of ultrasound. Typically, a push sequence consists of 10 tonebursts that exert a force of constant amplitude every 10 ms.

A shear wave propagating outwards from the vibration center can be monitored by a "detect" transducer operating in pulse-echo mode at two locations along the propagation path. The propagation speed of a shear wave is estimated by tracking its phase change over the distance it has propagated. The phase velocity of the shear wave is characterized at a number of selected frequencies to assess the dispersion of its wave velocity.

The shear wave speed is calculated using the formula [29]:

$$c_s(\omega_s) = \omega_s \Delta r / \Delta\phi_s, \quad (2)$$

where $\Delta\phi_s = \phi_1 - \phi_2$ is the phase change over the traveled distance Δr. The variation of c_s versus frequency is then fit by (1) to inversely solve for elasticity and viscosity.

Here, the envisioned operation of SDUV on the prostate is as follows: initially an image of the prostate is taken using VA to locate a site for SDUV. Then, a location of interest is selected within the VA image and the ultrasound "push" transducer temporarily switches to SDUV mode to measure prostate elasticity and viscosity at the specified location.

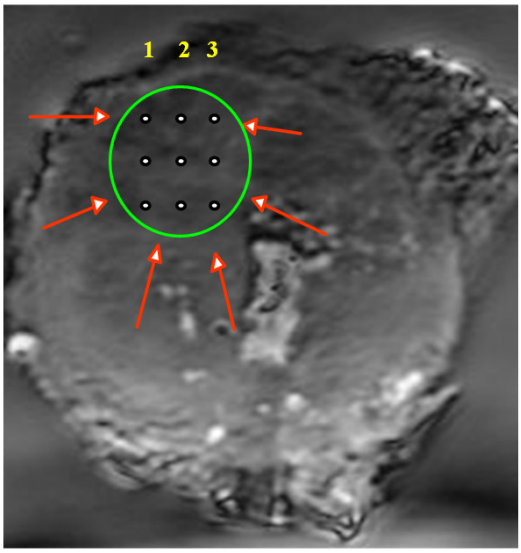

Figure 2. VA image of the excised prostate at Δf = 50 kHz. The arrows point to the selected region within the green circle. SDUV excitation points are denoted by the numbers 1, 2, 3 … and shown as white dots on the figure. The image size is 100 x 100 mm^2.

Experiment

A freshly excised human prostate from a cadaver was fixed in formaldehyde for 1 hour and then embedded in a gel phantom. The gel block was placed in a water tank and scanned by VA at f_1=3MHz, f_2=3MHz + Δf, where Δf = 50 kHz. Then a prostatic region was selected from the VA image (green circle in Fig. 2) in which propagation of shear waves was performed at 9 different locations (labeled 1, 2, 3 etc…) corresponding to 8 measurements, 10 mm apart, at 50 Hz and its higher harmonics (100 to 400 Hz). The phase of shear waves at frequencies 50-400 Hz was estimated from these vibration-time records by performing a fast Fourier transform and extracting the phase at frequencies of interest. Eq.(2) was used to estimate the shear wave speed.

An *in vitro* experiment was conducted in an excised human prostate to test the feasibility of SDUV measurements in human tissue. Two separate transducers were used in this experiment as shown in Fig. 1. The pulse sequence was decomposed into two groups: the push pulses and the detect pulses. The push pulses drove a push transducer to generate the push beams in the tissue, while the detect pulses drove a separate detect transducer (positioned beside the push transducer) to generate the detect beams. The experiment conformed to the policy of the Institutional Review Board.

VA imaging was performed to find suitable locations (far from calcifications) for SDUV measurements. SDUV measurements were then performed with one "push" transducer and one "detect" transducer as shown in Fig. 1. These two transducers operated at a pulse repetition frequency (PRF_p) equal to 100 Hz and PRF_d equal to 1.6 kHz, respectively (the subscripts "p" and "d" refer to "push" and "detect"). Each push beam had an ultrasound frequency of 3 MHz and a duration of 0.3 ms. The detect beam had a center frequency of 5 MHz and echoes were recorded at 100 MHz sampling rate. The typical duration for a single measurement is in the order of 60-100 ms.

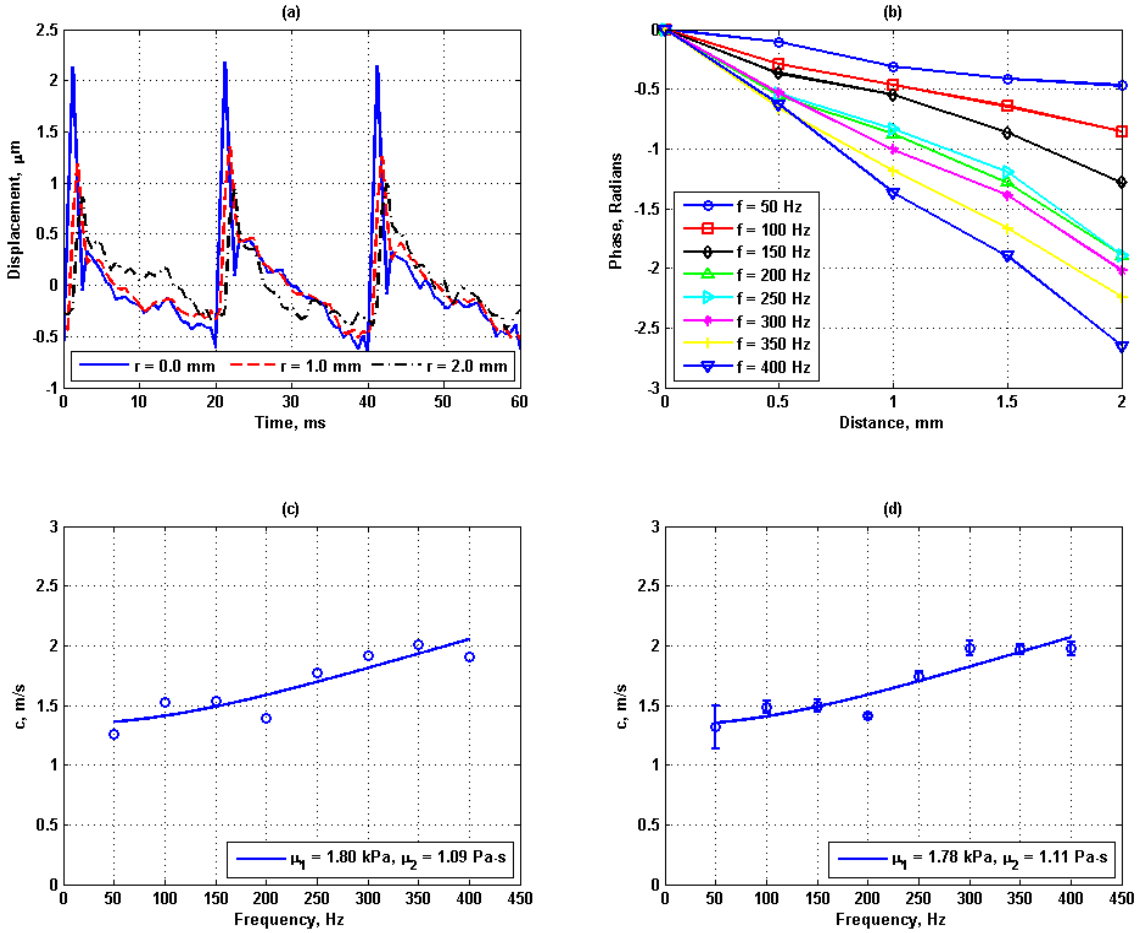

Fig. 3. SDUV measurement for the excised human prostate. (a) & (b): amplitude of displacement and phase of vibration records at 3 locations 1 mm apart. (c): shear wave speed vs. frequency. The stiffness and viscosity were μ_1 = 1.80 kPa and μ_2 = 1.09 Pa.s, respectively (d): Shear wave speeds calculated from 5 acquisitions to check the repeatability of (c). The mean stiffness and viscosity were μ_1 = 1.78 kPa and μ_2 = 1.11 Pa.s, respectively.

RESULTS AND DISCUSSION

Figure 2 shows the VA image at Δf = 50 kHz, in which the prostate tissue boundary is clearly noticeable. In addition, intraprostatic calcifications appear as bright spots in the image. The prostatic region (green circle) was selected from the VA image over which SDUV measurements were performed. The VA scan shows a clear image of the prostatic tissue, the gland's border, the urethra, and the surrounding tissue with remarkable details. It is interesting to note the contrast and texture difference between the central and peripheral prostatic zones in the VA image, indicating the potential of VA in differentiating tissues with different biological structures. A few calcifications can also be seen in the image.

Figure 3-(a) shows the propagating shear waves at three different locations, 1 mm apart. One can clearly see shear waves of the fundamental frequency (50 Hz) as well as its higher harmonics (100 to 400 Hz). The phase of shear waves at frequencies 50-400 Hz was estimated from these vibration-time records by the Kalman filter and shown in Figure 3-(b), which demonstrates that the shear wave phase changes linearly (as assumed with Eq.(2)) with propagation distance for all frequencies studied. The shear wave speed, shown as circles in Fig. 3-(c), is calculated using the phase information in Fig. 3-(b). The solid line is the fit by Eq.(1) to the measured shear wave speeds which gives μ_1 = 1.80 kPa and μ_2 = 1.09 Pa·s. The means and standard deviations of prostate shear wave speeds obtained from 5 separate SDUV measurements are shown in Fig. 3-(d) that shows good repeatability of wave speeds and close values to those is Fig. 3-(c). We have also performed measurements at 9 different locations within the prostate. The fit with the Voigt model of the measured shear wave speeds gives a mean and standard deviation (over the 9 locations) values for both the elastic modulus μ_1 = 5.20 ± 0.65 kPa and viscosity μ_2 = 2.53 ± 0.26 Pa·s.

We are aware of a previous literature report on measuring the prostate elasticity of 7 healthy volunteers *in vivo* using MRE [30]. The elasticity values obtained with MRE [30] in the central and peripheral prostatic portion were μ_1 = 2.2 ± 0.3 kPa and μ_1 = 3.3 ± 0.5 kPa, respectively. The SDUV results showed approximately two times higher elasticity values from *in vivo* magnetic resonance elastography [30]. This may be attributed to several factors: in MRE, measurement of the elastic modulus was done at a fixed excitation frequency, 65 Hz. At this frequency, the effect of viscosity may be largely ignored as shown by Eq.(1). Thus the shear wave speed in this limit is given from Eq.(1) as

$$c_s(\omega_s \to 0) \approx \sqrt{\mu_1/\rho}. \qquad (3)$$

Our SDUV measurement at 50 – 100 Hz gives a mean shear wave speed of $c_s \approx 1.75$ *m/s* (Fig. 3-(c),(d)), and assuming that the density for tissue approximates water ($\rho \approx 1000$ kg/m^3), the value of the stiffness is therefore $\mu_1 \approx 3.06$ kPa, a value that is very close to the result obtained with MRE. The higher values for the stiffness may also be attributed to the fact that it was an excised prostate without blood perfusion and slightly fixed with formaldehyde. In addition, the choice of the fitting model is of particular importance since it determines the estimation process of elasticity and viscosity.

CONCLUSION

This study showed the feasibility of using VA imaging to locate a specific region within an excised human prostate *in vitro*. SDUV measurement of prostate elasticity and viscosity are generally in agreement with preliminary values reported previously in the literature. Future work is directed toward *in vivo* measurements in a clinical setting.

REFERENCES

[1] M. Norberg, L. Egevad, L. Holmberg, P. Sparen, B. J. Norlen, and C. Busch, "The sextant protocol for ultrasound-guided core biopsies of the prostate underestimates the presence of cancer," *Urology*, vol. 50, no. 4, pp. 562-566, 1997.

[2] E. F. Donnelly, L. Geng, W. E. Wojcicki, A. C. Fleischer, and D. E. Hallahan, "Quantified power Doppler US of tumor blood flow correlates with microscopic quantification of tumor blood vessels," *Radiology*, vol. 219, no. 1, pp. 166-170, 2001.

[3] M. Remzi, M. Dobrovits, A. Reissigl, V. Ravery, M. Waldert, C. Wiunig, Y. K. Fong, and B. Djavan, "Can power Doppler enhanced transrectal ultrasound guided biopsy improve prostate cancer detection on first and repeat prostate biopsy?," *European Urology*, vol. 46, no. 4, pp. 451-456, 2004.

[4] J. Lorenzen, R. Sinkus, and G. Adam, "Elastography: Quantitative imaging modality of the elastic tissue properties," *Rofo-Fortschritte Auf Dem Gebiet Der Rontgenstrahlen Und Der Bildgebenden Verfahren*, vol. 175, no. 5, pp. 623-630, 2003.

[5] D. J. Rubens, M. A. Hadley, S. K. Alam, L. Gao, R. D. Mayer, and K. J. Parker, "Sonoelasticity Imaging of Prostate-Cancer - in-Vitro Results," *Radiology*, vol. 195, no. 2, pp. 379-383, 1995.

[6] D. L. Cochlin, R. H. Ganatra, and D. F. R. Griffiths, "Elastography in the detection of prostatic cancer," *Clinical Radiology*, vol. 57, no. 11, pp. 1014-1020, 2002.

[7] R. Souchon, O. Rouviere, A. Gelet, V. Detti, S. Srinivasan, J. Ophir, and J. Y. Chapelon, "Visualisation of hifu lesions using elastography of the human prostate in vivo: Preliminary results," *Ultrasound in Medicine and Biology*, vol. 29, no. 7, pp. 1007-1015, 2003.

[8] L. Curiel, R. Souchon, O. Rouviere, A. Gelet, and J. Y. Chapelon, "Elastography for the follow-up of high-intensity focused ultrasound prostate cancer treatment: Initial comparison with MRI," *Ultrasound in Medicine and Biology*, vol. 31, no. 11, pp. 1461-1468, 2005.

[9] K. Konig, U. Scheipers, A. Pesavento, A. Lorenz, H. Ermert, and T. Senge, "Initial experiences with real-time elastography guided biopsies of the prostate," *Journal of Urology*, vol. 174, no. 1, pp. 115-117, 2005.

[10] V. Egorov, S. Ayrapetyan, and A. P. Sarvazyan, "Prostate mechanical imaging: 3-D image composition and feature calculations," *IEEE Transactions on Medical Imaging*, vol. 25, no. 10, pp. 1329-1340, 2006.

[11] R. E. Weiss, V. Egorov, S. Ayrapetyan, N. Sarvazyan, and A. Sarvazyan, "Prostate mechanical imaging: A new method for prostate assessment," *Urology*, vol. 71, no. 3, pp. 425-429, 2008.

[12] M. Zhang, P. Nigwekar, B. Castaneda, K. Hoyt, J. V. Joseph, A. D. Agnese, E. M. Messing, J. G. Strang, D. J. Rubens, and K. J. Parker, "Quantitative characterization of viscoelastic properties of human prostate correlated with histology," *Ultrasound in Medicine and Biology*, vol. 34, no. 7, pp. 1033-1042, 2008.

[13] A. P. Sarvazyan, O. V. Rudenko, S. D. Swanson, J. B. Fowlkes, and S. Y. Emelianov, "Shear wave elasticity imaging: A new ultrasonic technology of medical diagnostics," *Ultrasound in Medicine and Biology*, vol. 24, no. 9, pp. 1419-1435, 1998.

[14] L. Sandrin, M. Tanter, S. Catheline, and M. Fink, "Shear modulus imaging with 2-D transient elastography," *IEEE Transactions on Ultrasonics Ferroelectrics and Frequency Control*, vol. 49, no. 4, pp. 426-435, 2002.

[15] K. Nightingale, S. McAleavey, and G. Trahey, "Shear-wave generation using acoustic radiation force: In vivo and ex vivo results," *Ultrasound in Medicine and Biology*, vol. 29, no. 12, pp. 1715-1723, 2003.

[16] Z. Wu, L. S. Taylor, D. J. Rubens, and K. J. Parker, "Sonoelastographic imaging of interference patterns for estimation of the shear velocity of homogeneous biomaterials," *Physics in Medicine and Biology*, vol. 49, no. 6, pp. 911-922, 2004.

[17] L. Huwart, F. Peeters, R. Sinkus, L. Annet, N. Salameh, L. C. ter Beek, Y. Horsmans, and B. E. Van Beers, "Liver fibrosis: non-invasive assessment with MR elastography," *NMR in Biomedicine*, vol. 19, no. 2, pp. 173-179, 2006.

[18] N. Salameh, F. Peeters, R. Sinkus, J. Abarca-Quinones, L. Annet, L. C. ter Beek, I. Leclercq, and B. E. Van Beers, "Hepatic viscoelastic parameters measured with MR elastography: Correlations with quantitative analysis of liver fibrosis in the rat," *Journal of Magnetic Resonance Imaging*, vol. 26, no. 4, pp. 956-962, 2007.

[19] J. Bercoff, M. Tanter, and M. Fink, "Supersonic shear imaging: A new technique for soft tissue elasticity mapping," *IEEE Transactions on Ultrasonics Ferroelectrics and Frequency Control*, vol. 51, no. 4, pp. 396-409, 2004.

[20] M. Fatemi and J. F. Greenleaf, "Vibro-acoustography: An imaging modality based on ultrasound-stimulated acoustic emission," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 12, pp. 6603-6608, 1999.

[21] M. Fatemi and J. F. Greenleaf, "Ultrasound-stimulated vibro-acoustic spectrography," *Science*, vol. 280, no. 5360, pp. 82-85, 1998.

[22] M. Fatemi, L. E. Wold, A. Alizad, and J. F. Greenleaf, "Vibro-acoustic tissue mammography," *IEEE Transactions on Medical Imaging*, vol. 21, no. 1, pp. 1-8, 2002.

[23] M. Fatemi, A. Manduca, and J. F. Greenleaf, "Imaging elastic properties of biological tissues by low-frequency harmonic vibration," *Proc. IEEE*, vol. 91, no. 10, pp. 1503-1519, 2003.

[24] A. Alizad, L. E. Wold, J. F. Greenleaf, and M. Fatemi, "Imaging mass lesions by vibro-acoustography: Modeling and experiments," *IEEE Transactions on Medical Imaging*, vol. 23, no. 9, pp. 1087-1093, 2004.

[25] F. G. Mitri, B. J. Davis, J. F. Greenleaf, and M. Fatemi, "In vitro comparative study of vibro-acoustography versus pulse-echo ultrasound in imaging permanent prostate brachytherapy seeds," *Ultrasonics*, vol. 49, no. 1, pp. 31-38, 2009.

[26] F. G. Mitri, P. Trompette, and J. Y. Chapelon, "Improving the use of vibro-acoustography for brachytherapy metal seed imaging: A feasibility study," *IEEE Transactions on Medical Imaging*, vol. 23, no. 1, pp. 1-6, 2004.

[27] F. G. Mitri, B. J. Davis, M. W. Urban, A. Alizad, J. F. Greenleaf, G. H. Lischer, T. M. Wilson, and M. Fatemi, "Vibro-acoustography Imaging of Permanent Prostate Brachytherapy seeds in an excised human prostate - Preliminary Results and Technical Feasibility," *Ultrasonics*, vol. 49, no. 3, pp. 389-394, 2009.

[28] F. G. Mitri, B. J. Davis, A. Alizad, J. F. Greenleaf, T. M. Wilson, L. A. Mynderse, and M. Fatemi, "Prostate Cryotherapy Monitoring Using Vibroacoustography: Preliminary Results of an Ex Vivo Study and Technical Feasibility," *IEEE Transactions on Biomedical Engineering*, vol. 55, no. 11, pp. 2584-2592, 2008.

[29] S. G. Chen, M. W. Urban, C. Pislaru, R. Kinnick, Y. Zheng, A. P. Yao, and J. F. Greenleaf, "Shearwave Dispersion Ultrasound Vibrometry (SDUV) for Measuring Tissue Elasticity and Viscosity," *IEEE Transactions on Ultrasonics Ferroelectrics and Frequency Control*, vol. 56, no. 1, pp. 55-62, 2009.

[30] J. Kemper, R. Sinkus, J. Lorenzen, C. Nolte-Ernsting, A. Stork, and G. Adam, "MR elastography of the prostate: Initial in-vivo application," *Rofo-Fortschritte Auf Dem Gebiet Der Rontgenstrahlen Und Der Bildgebenden Verfahren*, vol. 176, no. 8, pp. 1094-1099, 2004.