Ultrasound in Med. & Biol., Vol. 00, No. 00, pp. 1−6, 2018

0301-5629/$ - see front matter

ELSEVIER

https://doi.org/10.1016/j.ultrasmedbio.2018.10.009

● *Technical Note*

TRANSVAGINAL ULTRASOUND VIBRO-ELASTOGRAPHY FOR MEASURING UTERINE VISCOELASTICITY: A PHANTOM STUDY

Xiaoming Zhang,* Boran Zhou,* Wendaline M. VanBuren,* Tatnai L. Burnett,[†] and John M. Knudsen*

* Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA; and [†] Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, Minnesota, USA

(*Received* 15 *August* 2018; *revised* 4 *October* 2018; *in final from* 5 *October* 2018)

Abstract—The purpose of this research was to determine the feasibility of a transvaginal ultrasound vibro-elastography (TUVE) technique for generating and measuring shear wave propagation in the uterus. In TUVE, a 0.1-s harmonic vibration at a low frequency is generated on the abdomen of a subject *via* a handheld vibrator. A transvaginal ultrasound probe is used to measure the resulting shear wave propagation in the uterus. TUVE was evaluated on a female ultrasound phantom. The shear wave speeds in the region of interest of the uterus of the female ultrasound phantom were measured in the frequency range of 100−300 Hz. The viscoelasticity was analyzed based on the wave speed dispersion with frequency. The measurement of shear wave speed suggests that the uterus of this female ultrasound phantom is much stiffer than the human uterus. This research illustrates the feasibility of TUVE for generating and measuring shear wave propagation in the uterus of a female ultrasound phantom. We will further evaluate TUVE in patients, both normal controls and those with uterine diseases such as adenomyosis. (E-mail: zhang.xiaoming@mayo.edu)

Key Words: **Transvaginal ultrasound vibro-elastography, Shear wave speed, Uterus viscoelasticity, Adenomyosis.**

INTRODUCTION

The uterus is an organ that provides easy access for the diagnosis of pathologies such as endometrial hyperplasia and endometrial cancer by endometrial biopsy. Other pathologies are more challenging to diagnose without major surgery, including entities such as adenomyosis, smooth muscle tumors of uncertain malignant potential and leiomyosarcoma. In such cases, needle biopsy can be attempted; however, needle biopsy sensitivity depends on several factors, including the extent of disease, number of biopsy specimens, sampling site, needle gauge and operator experience (Levgur 2007).

Transvaginal ultrasound (TVUS) is a non-invasive imaging modality used to evaluate these diseases, especially in women with pre-malignant endometrial lesions. An endometrial thickness $\leq$5 mm is associated with a low risk of endometrial disease (Goldstein et al. 1990; Karlsson et al. 1995). The American College of Obstetricians and Gynecologists (2009) advises that an endometrial thickness $\leq$4 mm evaluated by TVUS is effective as the first diagnostic step in women with postmenopausal bleeding. The Society of Radiologists in Ultrasound (SRU) suggests that an endometrial thickness $\leq$5 mm is an effective diagnosis for women with postmenopausal bleeding (Goldstein et al. 2001). TVUS is increasingly used for diagnosing adenomyosis, with sensitivity and specificity of 72% and 81%, respectively (Champaneria et al. 2010).

Some studies use strain elastography to diagnose adenomyosis and uterine leiomyomas (Frank et al. 2015; Stoelinga et al. 2014; Tessarolo et al. 2011). However, strain elastography is a subjective technique. Moreover, conventional TVUS also provides information on the echotexture of the myometrium, where tissue viscoelasticity may change in adenomyosis (Hanafi 2013). Yet, it is unable to quantify the tissue viscoelasticity to evaluate disease development and progression.

The purpose of this study was to illustrate the feasibility of using a transvaginal ultrasound vibro-elastography (TUVE) technique to measure uterine elastic

Address correspondence to: Xiaoming Zhang, Department of Radiology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. E-mail: zhang.xiaoming@mayo.edu

properties. In addition to imaging, TUVE provides the viscoelasticity of the uterus, which may be useful for evaluating uterine diseases that are currently difficult to diagnose.

METHODS

A female ultrasound phantom (General Pathology Transvaginal Ultrasound Training Model, Blue Phantom, CAE Healthcare, Sarasota, FL, USA) was used in this study. In the TUVE technique, a 0.1-s harmonic vibration is generated on the abdomen of the phantom using a handheld vibrator (Model FG-142, Labworks Inc., Costa Mesa, CA, USA) mounted on a stand (Fig. 1a). In this research, five exciting frequencies were used to measure the shear waves: 100, 200, 300, 400 and 500 Hz. The excitation signal at a frequency was amplified by an audio amplifier (Model D150 A, Crown Audio Inc., Elkhart, IN, USA). The handheld shaker applies local excitation on the abdomen through a 3-mm-diameter indenter (Kubo et al. 2018a, 2018b). The resulting wave propagation in the uterus is measured using a transvaginal ultrasound probe (GE-IC5-9-D, GE Healthcare, Madison, WI, USA) with a central frequency of 5.682 MHz. A Verasonics (Kirkland, WA, USA) ultrasound system is used. The Verasonics ultrasound system can collect up to a few thousand imaging frames per second using a plane-wave pulse transmission method (Cheng et al. 2018; Kubo et al. 2018a, 2018b). Figure 1(b) is a typical B-mode image of the phantom.

The techniques for measuring the shear wave in response to the mechanical vibration, as illustrated in the B-mode imaging area (Fig. 1b), are summarized as follows. The radiofrequency (RF) data of the ultrasound echo are obtained first. By demodulation of the RF data using quadrature detection, the IQ data of ultrasound signals are processed. Cross-correlation analysis of the ultrasound IQ data is used to calculate the motion at a location in the ultrasound imaging area (Clay et al. 2018; Hasegawa and Kanai 2006). Tracking the wave propagation in both the horizontal and vertical directions allows the wave speed at a pixel in the B-mode imaging area to be measured and the speed map of the entire B-mode imaging area to be obtained (Song et al. 2014).

The shear wave speed is related to elasticity by

$$c_s = \sqrt{\frac{\mu}{\rho}} \tag{1}$$

where μ is shear modulus and ρ is mass density.

The measurement of wave speeds at multiple frequencies enables calculation of both elasticity μ_1 and viscosity μ_2 using the Voidt model. Equation (1) can be modified as (Zhang et al. 2018a)

$$c_s = \sqrt{\frac{2\left(\mu_1^2 + \omega^2\mu_2^2\right)}{\rho\left(\mu_1 + \sqrt{\mu_1^2 + \omega^2\mu_2^2}\right)}} \tag{2}$$

where ω is the angular frequency.

Given the measured shear wave speeds at different frequencies, the material parameters associated with Voigt's model were identified by using the

(a) (b)

Fig. 1. (a) Experimental setup for transvaginal ultrasound vibro-elastography of a female ultrasound phantom. (b) Typical B-mode image of the phantom.

Levenberg−Marquardt non-linear, least-squares algorithm for minimizing the objective function, which reflects the agreement between measured and predicted shear wave speeds at different excitation frequencies, yielding unique estimates of the material parameters (Prim et al. 2016; Suh and Bai 1998; Zhou et al. 2014). Residual error is the output of the objective function

$$\Omega = \sum_{n=1}^{N} \left(c_n^T - c_n^E\right)^2 \tag{3}$$

where the superscripts E and T refer to the experimentally measured and theoretically calculated values of shear wave speed, and subscript n indicates a particular experimental state. The ranges over which parameter values were sought were identical with limiting values based on the physical meaning of each parameter. Multiple iterations of functional minimization were performed to ensure that the obtained parameter values were insensitive to the initial guesses within the prescribed ranges.

RESULTS

The shear wave speed in the region of interest (ROI) of the uterus of the female ultrasound phantom, as illustrated in Figure 2, is 7.50 ± 3.15 m/s at 100 Hz. The results are expressed as the mean ± standard deviation in the ROI. Three measurements were performed at each frequency. The average shear wave speed for the three measurements in the ROI of the uterus was 7.26 ± 0.21 m/s at 100 Hz. The average shear wave speeds were 6.99 ± 0.05 m/s at 150 Hz, 6.43 ± 0.03 m/s at 200 Hz, 6.77 ± 0.02 m/s at 250 Hz and 7.62 ± 0.01 m/s at 300 Hz in the ROI of the uterus. Figure 3 illustrates the wave speed dispersion with frequency, from which both the elasticity and viscosity of the uterus can be estimated from eqn (2). The shear elasticity μ_1 and shear viscosity μ_2 are estimated in Figure 3, respectively, as 46.63 kPa and 9.58 Pa·s.

DISCUSSION

Transvaginal ultrasound vibro-elastography is a non-invasive technique for generating and detecting the shear wave speed of the uterus. Shear wave propagation

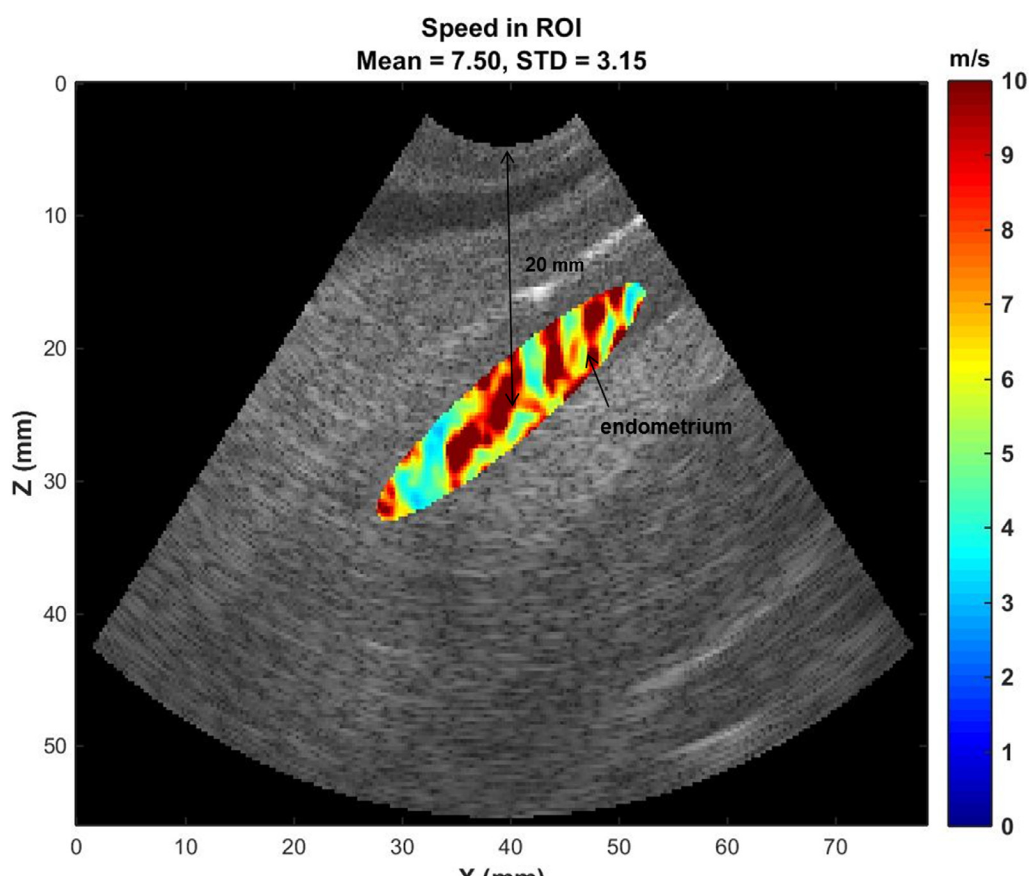

Fig. 2. Measurement of shear wave speed at 100 Hz in the region of interest of the uterus. The distance between the region of interest and the probe is approximately 20 mm. ROI = region of interest; STD = standard deviation.

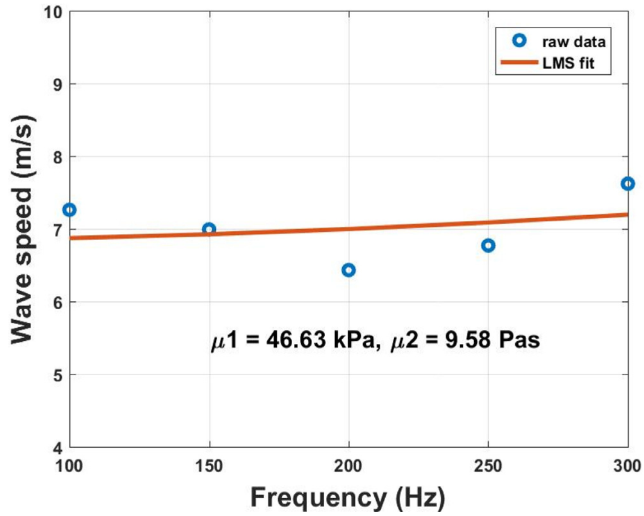

Fig. 3. Estimation of both elasticity and viscosity from the wave speed dispersion curve. LMS = least mean squares.

in the uterus is generated by applying a small, local, 0.1-s harmonic vibration on the abdomen of a subject. A transvaginal ultrasound probe is used to measure the resulting shear wave propagation in the uterus. The shaker was typically positioned 5−10 mm away from the ultrasound transducer in our previous studies measuring wave speeds of lung, skin and penis (Zhang et al. 2018b, 2018c). In this technique for vaginal application, there is no need to specify this distance.

The results obtained in this study are in agreement with published results. The dynamic response of the phantom manifesting as shear wave speed dispersion with excitation frequency is qualitatively similar to that of soft biological tissues (Dai et al. 2014). The wave speed values of the phantom obtained in this study are in the same range as reported by Zhang et al. (2018b). The Young's modulus was reported as 22.6−274.2 kPa by Acar et al. (2016); values obtained on the phantom fall in that range.

Currently, most shear wave elastography (SWE) techniques use ultrasound radiation force (URF) to generate tissue motion. However, URF may not be applied to some tissues such as the lung because the relatively high-intensity ultrasound energy may cause alveolar hemorrhage or lung injury (Zachary et al. 2006). In addition, a long period of ultrasound pulses with relatively high-intensity ultrasound energy may damage the ultrasound system itself—for example, high-voltage drop and probe element damage, in our experience. SWE has been used to measure the shear wave speed of *ex vivo* cervix (Carlson et al. 2014) and *in vivo* cervix (Muller et al. 2015). Compared with SWE, TUVE can easily and safely generate high-displacement tissue motion in a large area of the female organ. Because the aperture of a transvaginal ultrasound probe is typically small, it is difficult to generate large motion in the uterus. The probe may be easily damaged by the generation of high-displacement tissue motion. SWE may be useful for a small area of cervix but may be difficult to generate the shear wave propagation over a large area of uterus. External mechanical excitation of wave propagation can be used to measure the elastic properties of other vulnerable tissues such as the lungs (Zhang et al. 2017, 2018a, 2018b, 2018c) and eyes (Sit et al. 2018; Zhou et al. 2017).

This study determined the feasibility of using TUVE to generate and measure shear wave propagation in the uterus of a female ultrasound phantom. These measurements of shear wave speed suggest that the uterus of this phantom is much stiffer than the human uterus. In a study on measurement of the human cervix (Muller et al. 2015), shear wave speed ranged from 1.2 to 1.8 m/s. In another study measuring the shear wave speed of an excised uterus (Carlson et al. 2014), the shear wave speeds were between 2.11 and 3.56 m/s depending on the location on the cervix. It should be easier to generate shear wave propagation in the human uterus. We are working on clinical protocols to evaluate this technique in patients. We plan to start evaluating this technique initially in patients with adenomyosis. This technique may be useful for other uterine diseases such as endometrial lesions, uterine leiomyomas and adenomyomas.

Although this was a technique feasibility study on a female ultrasound phantom, the objective is to use the technique to study patients with disease of the uterus. On the basis of this feasibility study, we planned a pilot study on some patients and control patients. We are confident of the clinical use of the technique because it is tolerable and easily performed. A sonographer can apply the mechanical vibration on a subject's abdomen using the handheld vibrator. The sonographer can also use the transvaginal ultrasound probe to collect the ultrasound data at the same time. In another option, the small vibrator can be placed on the subject's abdomen using a flexible holder so that the sonographer operates only the transvaginal ultrasound probe. The technique's advantage is that the low-frequency mechanical wave can propagate over large areas, such as from the subcutaneous tissue to the uterus. The wave speed measurement, however, is local and dependent only on local elastic properties of tissue. Therefore, the wave speed measurement of the uterus is only dependent on the elastic properties of the uterus and is independent of the location of wave excitation, which is on the abdomen. This technique may be improved by combining a miniature vibrator and the transvaginal ultrasound probe into a single device.

CONCLUSIONS

We have described the use of a TUVE technique for generating and measuring shear wave propagation in the uterus of a female ultrasound phantom. The shear wave propagation in the uterus was successfully generated on the abdomen of the phantom using a handheld vibrator. A transvaginal ultrasound probe was used to measure the shear wave speed in the ROI of the uterus between 100 and 300 Hz. The viscoelasticity can be obtained from the wave speed dispersion with frequency. This proof-of-concept study illustrates the feasibility of using TUVE to generate and measure shear wave propagation in the uterus of a female ultrasound phantom. We will further evaluate TUVE for patients with uterine diseases such as adenomyosis.

REFERENCES

Acar S, Millar E, Mitkova M, Mitkov V. Value of ultrasound shear wave elastography in the diagnosis of adenomyosis. Ultrasound 2016;24:205–213.

American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 440: The role of transvaginal ultrasonography in the evaluation of postmenopausal bleeding. Obstet Gynecol 2009;114:409–411.

Carlson LC, Feltovich H, Palmeri ML, Dahl JJ, Munoz del Rio A, Hall TJ. Estimation of shear wave speed in the human uterine cervix. Ultrasound Obstet Gynecol 2014;43:452–458.

Champaneria R, Abedin P, Daniels J, Balogun M, Khan KS. Ultrasound scan and magnetic resonance imaging for the diagnosis of adenomyosis: Systematic review comparing test accuracy. Acta Obstet Gynecol Scand 2010;89:1374–1384.

Cheng YS, Zhou B, Kubo K, An KN, Moran SL, Amadio PC, Zhang X, Zhao C. Comparison of two ways of altering carpal tunnel pressure with ultrasound surface wave elastography. J Biomech 2018;74:197–201.

Clay R, Bartholmai BJ, Zhou B, Karwoski R, Peikert T, Osborn T, Rajagopalan S, Kalra S, Zhang X. Assessment of interstitial lung disease using lung ultrasound surface wave elastography: A novel technique with clinicoradiologic correlates. J Thorac Imaging. doi: 10.1097/RTI.0000000000000334 Published online ahead of print.

Dai Z, Peng Y, Mansy HA, Sandler RH, Royston TJ. Comparison of poroviscoelastic models for sound and vibration in the lungs. J Vibration Acoustics 2014;136 050905.

Frank M, Schäfer S, Möllers M, Falkenberg M, Braun J, Möllmann U, Strube F, Fruscalzo A, Amler S, Klockenbusch W. Importance of transvaginal elastography in the diagnosis of uterine fibroids and adenomyosis. Birth 2015;15:16.

Goldstein RB, Bree RL, Benson CB, Benacerraf BR, Bloss JD, Carlos R, Fleischer AC, Goldstein SR, Hunt RB, Kurman RJ, Kurtz AB, Laing FC, Parsons AK, Smith-Bindman R, Walker J. Evaluation of the woman with postmenopausal bleeding: Society of Radiologists in Ultrasound-sponsored consensus conference statement. J Ultrasound Med 2001;20:1025–1036.

Goldstein SR, Nachtigall M, Snyder JR, Nachtigall L. Endometrial assessment by vaginal ultrasonography before endometrial sampling in patients with postmenopausal bleeding. Am J Obstet Gynecol 1990;163:119–123.

Hanafi M. Ultrasound diagnosis of adenomyosis, leiomyoma, or combined with histopathological correlation. J Hum Reprod Sci 2013;6:189.

Hasegawa H, Kanai H. Improving accuracy in estimation of artery-wall displacement by referring to center frequency of RF echo. IEEE Trans Ultrason Ferroelectr Freq Control 2006;53:52–63.

Karlsson B, Granberg S, Wikland M, Ylostalo P, Torvid K, Marsal K, Valentin L. Transvaginal ultrasonography of the endometrium in women with postmenopausal bleeding—A Nordic multicenter study. Am J Obstet Gynecol 1995;172:1488–1494.

Kubo K, Cheng YS, Zhou B, An KN, Moran SL, Amadio PC, Zhang X, Zhao C. The quantitative evaluation of the relationship between the forces applied to the palm and carpal tunnel pressure. J Biomech 2018a;66:170–174.

Kubo K, Zhou B, Cheng YS, Yang TH, Qiang B, An KN, Moran SL, Amadio PC, Zhang X, Zhao C. Ultrasound elastography for carpal tunnel pressure measurement: A cadaveric validation study. J Orthop Res 2018b;36:477–483.

Levgur M. Diagnosis of adenomyosisa: Review. J Reprod Med 2007;52:177–193.

Muller M, Ait-Belkacem D, Hessabi M, Gennisson JL, Grange G, Goffinet F, Lecarpentier E, Cabrol D, Tanter M, Tsatsaris V. Assessment of the cervix in pregnant women using shear wave elastography: A feasibility study. Ultrasound Med Biol 2015;41:2789–2797.

Prim DA, Zhou B, Hartstone-Rose A, Uline MJ, Shazly T, Eberth JF. A mechanical argument for the differential performance of coronary artery grafts. J Mech Behav Biomed Mater 2016;54:93–105.

Sit AJ, Kazemi A, Zhou B, Zhang X. Comparison of ocular biomechanical properties in normal and glaucomatous eyes using ultrasound surface wave elastography. Invest Ophthalmol Visual Sci 2018;59 1218−1218.

Song P, Manduca A, Zhao H, Urban MW, Greenleaf JF, Chen S. Fast shear compounding using robust 2-D shear wave speed calculation and multi-directional filtering. Ultrasound Med Biol 2014;40: 1343–1355.

Stoelinga B, Hehenkamp W, Brölmann H, Huirne J. Real−time elastography for assessment of uterine disorders. Ultrasound Obstet Gynecol 2014;43:218–226.

Suh JK, Bai S. Finite element formulation of biphasic poroviscoelastic model for articular cartilage. J Biomech Eng 1998;120:195–201.

Tessarolo M, Bonino L, Camanni M, Deltetto F. Elastosonography: A possible new tool for diagnosis of adenomyosis?. Eur Radiol 2011;21:1546–1552.

Zachary JF, Blue JP, Jr, Miller RJ, Ricconi BJ, Eden JG, O'Brien WD, Jr.. Lesions of ultrasound-induced lung hemorrhage are not consistent with thermal injury. Ultrasound Med Biol 2006;32:1763–1770.

Zhang X, Osborn T, Zhou B, Meixner D, Kinnick RR, Bartholmai B, Greenleaf JF, Kalra S. Lung ultrasound surface wave elastography: A pilot clinical study. IEEE Trans Ultrason Ferroelectr Freq Control 2017;64:1298–1304.

Zhang M, Wasnik AP, Masch WR, Rubin JM, Carlos RC, Quint EH, Maturen KE. Transvaginal ultrasound shear wave elastography for the evaluation of benign uterine pathologies: A prospective pilot study. J Ultrasound Med. Published online ahead of print. Available at: https://doi.org/10.1002/jum.14676.

Zhang X, Zhou B, Kalra S, Bartholmai B, Greenleaf J, Osborn T. An ultrasound surface wave technique for assessing skin and lung diseases. Ultrasound Med Biol 2018b;44:321–331.

Zhang X, Zhou B, Miranda AF, Trost LW. A novel noninvasive ultrasound vibro-elastography technique for assessing patients with erectile dysfunction and Peyronie disease. Urology 2018c;116: 99–105.

Zhou B, Wolf L, Rachev A, Shazly T. A structure-motivated model of the passive mechanical response of the primary porcine renal artery. J Mech Med Biol 2014;14 1450033.

Zhou B, Sit AJ, Zhang X. Noninvasive measurement of wave speed of porcine cornea in *ex vivo* porcine eyes for various intraocular pressures. Ultrasonics 2017;81:86–92.