Ultrasound in Med. & Biol., Vol. 41, No. 5, pp. 1461–1472, 2015

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2014.12.017

● *Original Contribution*

MEASUREMENT OF QUANTITATIVE VISCOELASTICITY OF BOVINE CORNEAS BASED ON LAMB WAVE DISPERSION PROPERTIES

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(*Received* 11 *August* 2014; *revised* 11 *December* 2014; *in final form* 15 *December* 2014)

Abstract—The viscoelastic properties of the human cornea can provide valuable information for clinical applications such as the early detection of corneal diseases, better management of corneal surgery and treatment and more accurate measurement of intra-ocular pressure. However, few techniques are capable of quantitatively and non-destructively assessing corneal biomechanics *in vivo*. The cornea can be regarded as a thin plate in which the vibration induced by an external vibrator propagates as a Lamb wave, the properties of which depend on the thickness and biomechanics of the tissue. In this study, pulses of ultrasound radiation force with a repetition frequency of 100 or 200 Hz were applied to the apex of corneas, and the linear-array transducer of a SonixRP system was used to track the tissue motion in the radial direction. Shear elasticity and viscosity were estimated from the phase velocities of the A0 Lamb waves. To assess the effectiveness of the method, some of the corneas were subjected to collagen cross-linking treatment, and the changes in mechanical properties were validated with a tensile test. The results indicated that the shear modulus was 137 ± 37 kPa and the shear viscosity was 3.01 ± 2.45 mPa·s for the group of untreated corneas and 1145 ± 267 kPa and was 0.16 ± 0.11 mPa·s for the treated group, respectively, implying a significant increase in elasticity and a significant decrease in viscosity after collagen cross-linking treatment. This result is in agreement with the results of the mechanical tensile test and with reports in the literature. This initial investigation illustrated the ability of this ultrasound-based method, which uses the velocity dispersion of low-frequency A0 Lamb waves, to quantitatively assess both the elasticity and viscosity of corneas. Future studies could discover ways to optimize this system and to determine the feasibility of using this method in clinical situations. (E-mail: chenxin@szu.edu.cn) © 2015 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Ultrasound, Elastography, Lamb waves, Corneas, Viscoelasticity, Radiation force, Cross-linking therapy.**

INTRODUCTION

The cornea is the transparent front of the eye and contributes the most to the eyes' focusing power. The biomechanics of the cornea plays an important role in maintaining its normal functions and affects its responses to disease and surgery. Techniques for accurately characterizing corneal mechanical properties *in vivo* in a non-destructive fashion will be widely applicable in clinical ophthalmology. Potential applications include patient-specific biomechanical optimization of corneal and keratorefractive surgery, early detection of corneal ectatic disorders, better management of corneal treatment, more accurate measurement of intra-ocular pressure (IOP), quantitative assessment of corneal wound healing and evaluation of the biomechanical performance of tissue-engineered corneas (Dupps et al. 2007). Ectatic corneal disorders include keratoconus and ectasia after laser *in situ* keratomileusis (LASIK) and manifest as changes in corneal mechanical and optical properties (Ambekar et al. 2011). These are the second most common indications for keratoplasty (Binder et al. 2005), which is surgery on corneas where the damaged or diseased tissue is replaced by donated corneal tissue in its entirety or in part. On the basis of epidemiologic studies, the incidence of keratoconus is estimated to be

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approximately 0.5‰ in the general population (Kennedy et al. 1986). The growth in the popularity of LASIK has caused concern about the serious complications of corneal ectasia after LASIK. Currently no specific test or measurement is diagnostic of a corneal ecstatic disorder (Binder et al. 2005). Developing an accurate, non-invasive and *in situ* measurement technique for corneal viscoelasticity will facilitate the understanding of the pathogenesis and early diagnosis of ectatic corneal disorders. Accurate knowledge of the mechanical properties of the cornea is also important for the estimation of risk factors caused by abnormal mechanical properties of the cornea before refractive surgery and, thus, the prevention of severe complications (Binder 2007). Moreover, individual differences in corneal biomechanics significantly affect the accuracy of the tonometric measurement of IOP, one of the most significant clinical factors in ophthalmology, especially in the evaluation of patients at risk for glaucoma (Liu and Roberts 2005). It has been found by both analytical analysis and experimentation that stiffer corneas lead to overestimation, whereas more compliant corneas lead to underestimation of the IOP (Liu and Roberts 2005; Tang et al. 2012). Determination and monitoring of corneal viscoelastic properties will thus help us in studying the complex relationships between these ocular factors and in improving the accuracy of IOP measurement.

Early studies attempted to determine the biomechanical properties of corneas with tensile tests or inflation tests on animal corneas or donors. However, the results of such destructive *ex vivo* tests were insufficient for accurate characterization of human corneas under *in vivo* conditions. Thus, there is a need for techniques that are capable of accurately assessing the corneal biomechanical properties *in vivo* in a non-destructive fashion. Currently, the ocular response analyzer (ORA) is the only commercially available medical device capable of measuring corneal biomechanics *in vivo*. The ORA uses a puff of air to deflect the cornea while an infrared beam tracks changes in the shape of the anterior cornea during the inward and outward deviation, providing a parameter called corneal hysteresis (CH) as an indicator of corneal viscoelasticity. However, the complex relationship between corneal biomechanical characteristics and CH has not been clearly determined (Kotecha et al. 2006; Lau and Pye 2011; Narayanaswamy et al. 2011).

Much effort has been exerted to develop methods that can characterize corneal biomechanics accurately and explicitly. Ultrasound elastography has been investigated extensively over the past two decades because it is a safe, cost-effective and easy-to-use medical imaging modality. Some researchers have also explored the possibility of adapting ultrasound elastography for characterization of the biomechanics of corneas. Hollman et al. (2002) proposed an ultrasound elasticity microscope system for strain imaging of corneal tissue with a compression plate on the corneal surface of *ex vivo* porcine eyes. This method provided an image of the relative strain distribution rather than a quantitative estimate of Young's modulus. Tanter et al. (2009) acquired a quantitative measurement of the Young's modulus *ex vivo* on porcine corneas based on their proprietary Supersonic Shear Imaging (SSI) system, which is an innovative ultrasound scanner with a very high frame rate. Shih et al. (2013) designed a dual confocal ultrasound transducer for both the excitation and detection of tissue movement and obtained a high-resolution strain image based on qualitative acoustic radiation force imaging techniques. Urs et al. (2014) reported the use of acoustic radiation force imaging as non-invasive method for evaluating corneal biomechanical changes induced by cross-linking therapy. In addition to ultrasound elastography, several other techniques have been proposed in recent years. Liu's group described a quantitative ultrasound spectroscopy method for *in vivo* characterization of corneal biomechanical properties (He and Liu 2009; Liu et al. 2007). Dupps et al. (2007) proposed surface wave elastometry of the cornea via regional and directional measurements of the surface wave velocity, which is a function of corneal stiffness. Li et al. (2012) introduced an all-optical measurement of corneal elasticity that used a pulsed laser to excite surface acoustic waves and an optical coherence tomography system to record wave propagation. Dorronsoro et al. (2012) reported dynamic optical coherence tomography measurement of corneal deformation with an air puff in normal and cross-linked corneas. Scarcelli et al. (2012, 2013) developed Brillouin optical microscopy for mapping the corneal modulus in three dimensions with high spatial resolution.

The principle underlying a majority of quantitative elastography techniques is the relationship between shear wave propagation properties and tissue viscoelasticity, which is based on the assumption that the tissue is an infinite, homogeneous medium. This principle allows researchers to estimate the viscoelasticity properties based on models that describe this relationship. However, application of these models to plate-like tissues, such as heart walls, vessel walls and cornea, is inappropriate. When a tissue is similar to a thin plate, there is a strong contrast in shear velocity between it and the surrounding medium. Strong reflection and mode conversions at these interfaces partially guide propagated waves. The elastic waves propagating in infinite and thin elastic plates are known as Lamb waves. Lamb waves propagate with multiple modes that have highly dispersive behaviors. Only the zero-order symmetric (S0) and zero-order anti-symmetric (A0) modes are found in the low-frequency range.