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Measurements of Ocular Properties in Response to Intraocular Pressure Changes Using an Ultrasonic System

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Abstract— **An ultrasonic system was developed to measure the biomechanical properties of intact corneas and determine the effects of an elevated intraocular pressure (IOP) on these properties. Accurate measurement of IOP is essential for early detection of blinding disease, glaucoma. Inter-subject variations of biomechanical properties may have introduced significant errors to IOP measurements using the current gold standard – Goldmann Applanation Tonometry. Therefore, it is important to develop a non-invasive method for measuring corneal biomechanical properties in vivo. In this study, an ultrasonic measurement technique in combination with a mathematical model for wave propagation in thin layers was developed to estimate corneal properties and to differentiate the changes of the corneal properties in response to IOP changes in five enucleated porcine eyes. The measurements were performed with the IOPs adjusted at three different levels. Results showed that the ultrasonic method was sensitive to corneal property changes associated with IOP changes. We concluded that the ultrasonic method has the potential to implement non-invasive measurements of corneal properties in vivo.**

I. Introduction

GLAUCOMA is one of the leading causes of irreversible blindness [1]. Because it is typically asymptomatic before advanced optic nerve damage occurs, screening of glaucoma for its early detection and treatment is essential to prevent glaucoma-related blindness [2]. Unfortunately, a good screening test is not available to date. Although the use of Goldmann Applanation Tonometry is widespread and long-standing, it does not give satisfactory sensitivity and specificity [3-5]. Agencies such as National Eye Institute discourage the use of tonometry for glaucoma screening.

The inaccuracy of such method stems from its measurement mechanism. Applanation tonometry assumes applicability of the Imbert-Fick law, which considers corneas as infinitely thin, perfectly elastic, expandable and dry. Human corneas do not always satisfy these criteria. The variations in physiological parameters such as thickness or biomechanical properties have likely introduced significant errors to tonometry readings of IOP. Indeed, clinical and experimental studies have demonstrated non-negligible effects of cornea thickness on IOP measurements [4, 5]. Biomechanical properties were predicted to have even greater influence than corneal thickness [6]. Nevertheless, these effects remain unknown due to lack of accurate methods for measuring these properties in vivo. If the biomechanical properties can be measured in vivo, and that information be used to correct tonometry readings, accuracy of IOP prediction will be significantly improved.

In this study, we developed an ultrasonic model and system to non-invasively measure corneal properties in ex vivo porcine eyes. Porcine eyes were used in the current study, as regularly in preclinical studies, because of their similar properties to human eyes and their availability [9]. Understanding corneal responses to elevated IOPs under normal and abnormal conditions is of particular interest to improve predictive constitutive models for corneal biomechanics [7]. In this study, the IOPs of the porcine eyes were adjusted to various levels of clinical significance, and the effects of IOP on corneal properties were determined.

II. Materials And Method

A. Experimental setup

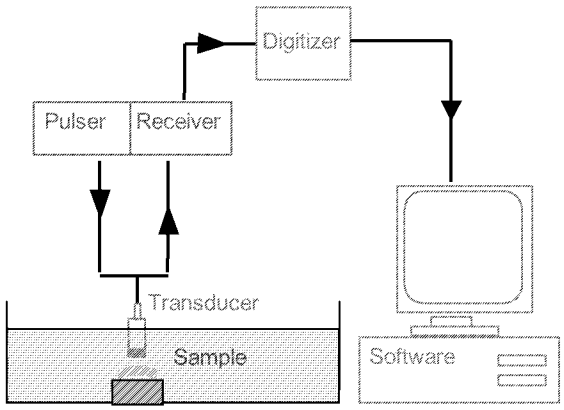

Fig. 1: Ultrasonic measurement system.

Five porcine eyes were obtained from local slaughter place. The eyes were immediately immersed in 8% Dextran/saline solution after obtained. All porcine eyes were immersed in 8% Dextran/saline during ultrasonic measurements (Fig. 1). A broadband ultrasound transducer (10 MHz, XMS,

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Panametrics-NDT), driven by a pulser-receiver (Panametrics-NDT, 5900PR), was used for all ultrasonic measurements. The ultrasonic RF signals were recorded by a 500 MHz/8-bit digitizer (Acqiris, DP105). The X, Y, Z position and angle of the transducer were adjustable. The distance between the transducer and the apex of the cornea was kept the same for all measurements. All ultrasonic measurements were finished in six hours.

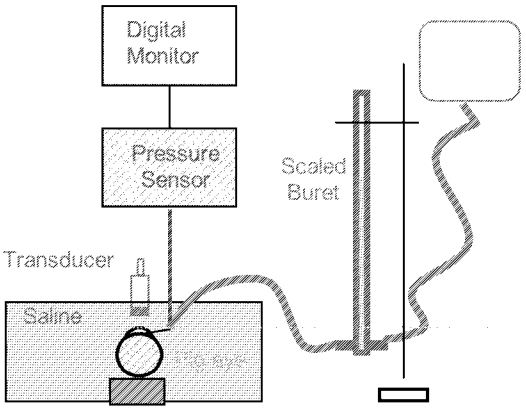

Fig. 2: Pressure control system.

To control the intraocular pressure (IOP) of the porcine eyes, the anterior chamber of the eyes were connected to a tubing system using a 25G needle. Fig. 2 shows the pressure control system. A saline reservoir was used to adjust the height of the saline column in the buret. The IOP was controlled by the column and monitored by a pressure sensor (Omega Px154) and a digital monitor (Omega DP 25B).

B. Wave propagation model

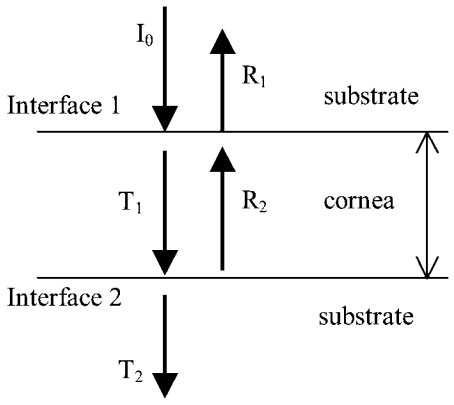

Fig. 3: Wave propagates through an embedded thin layer.

A mathematical model of elastic wave propagation was used [8] to simulate ultrasound wave propagation in porcine corneas immersed in liquid bath. Flat sample surfaces were assumed in the model. Mechanically, the system is composed of a thin layer embedded between two continuous subspaces as shown in Fig. 3. The time harmonic longitudinal wave propagating along the positive direction of x coordinated can be expressed as:

$$u(x,t) = A \cdot e^{i(kx-\omega t)} \tag{1}$$

where u is the displacement field along x direction, A is the amplitude of initial wave, ω is the angular frequency, and k is the wave number. The stress fields within the layer were derived by using constitutive relationships for isotropic materials. The reflection coefficient from the thin layer is defined as the ratio between the magnitude of the reflected wave AR1 and that of original wave (reference wave) A_i (Figure 3). The reflection coefficient can be solved by enforcing the continuity conditions at the interface between the layer and the substrates. The stress and displacement at the layer substrate interfaces was described by the following equations:

Interface 1:
$$\sum \sigma_1^+ = \sum \sigma_1^- \tag{2}$$
$$\sum u_1^+ = \sum u_1^- \tag{3}$$

Interface 2:
$$\sum \sigma_2^+ = \sum \sigma_2^- \tag{4}$$
$$\sum u_2^+ = \sum u_2^- \tag{5}$$

where σ_i are the stress and u_i are the displacements. The subscript i represents the interface number. The normalized magnitudes of transmission and reflection can be solved from above equations, if the incident wave is known. By calculating reflection coefficients at a given range of frequencies, a reflection spectrum was obtained.

C. Inverse algorithm

The physical properties of the porcine corneas were reconstructed using an inverse algorithm. The inverse algorithm searched the multidimensional parameter space to minimize the following error function:

$$\varepsilon = \sum_{i=1}^{n} \left(\left| R^e(f_i) \right| - \left| R^t(f_i) \right| \right)^2 \tag{6}$$

where n is the number of the data points at different frequencies; Re and Rt are the experimental and theoretical reflection coefficients, respectively; ε is the total error between experimental reflection spectra and the reconstructed spectra. A MabLab program based on the non-linear least square optimization algorithm performed the minimization search.

III. Results

To differentiate the change of corneal biomechanical properties due to IOP variations, porcine eyes maintained under different IOP levels were investigated. Clinically, patient with IOP below 21 mmHg will be considered as normal. Based on the clinical threshold, three different IOP levels, normal (20 mmHg), abnormal (30 mmHg), and dangerous (40 mmHg), were chosen to mimic the different IOPs in human eyes.

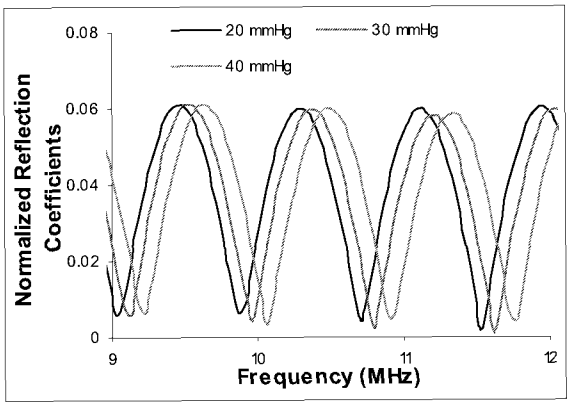

Fig. 4: The spectrum of reflection signals with different IOPs.

The ultrasonic spectra from one porcine eye under three different IOPs are presented in Fig. 4. The spectra were obtained by applying Fast Fourier Transform to the ultrasonic wave signals. Due to the thin layer nature of corneas, the spectra had alternating peaks and troughs caused by interference of the two reflections from the anterior and posterior surfaces of corneas

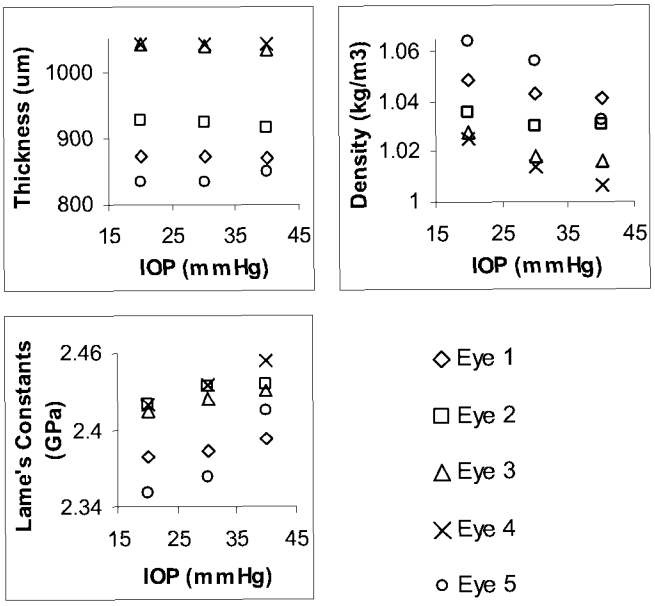

Fig. 5: Reconstructed properties of porcine corneas.

Fig. 5 presents the reconstructed parameters of the five corneas at different IOPs. As IOP increased, the thickness of the corneas generally decreased (mean=-9.4×10^{-2} μm/mmHg); density was decreased (mean=-5.0×10^{-4} (g/cm^3)/mmHg); and stiffness was increased (mean=0.77 MPa/mmHg).

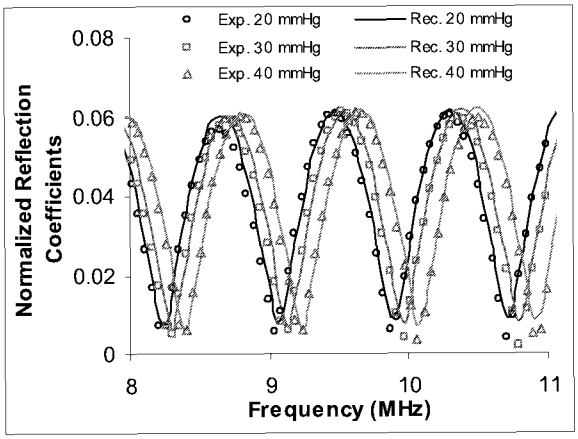

Fig. 6: Comparison of theoretical and experimental spectrum.

Fig. 6 shows the results of curve fitting of the spectra measured experimentally and that calculated from the reconstructed parameters. Experimental data from the same eye in Fig. 4 was used. The theoretical spectra were in good agreement with the experimental spectra.

IV. Discussion

In this study, an ultrasonic model and system for in vivo measurement of ocular biomechanical properties was developed. The ultrasonic system detected the biomechanical property changes in elevated IOPs of porcine eyes as evidenced by the changes in the measured spectra in Fig. 4. The spectral curves alone were not sufficient to determine which corneal properties changed and how they were changed due to changes in IOP, because all of the parameters affect the shape of the spectral curves. The parameter reconstruction (or property estimation) based on both model prediction and experimental measurements revealed that a heightened IOP caused a decrease in thickness, but an increase in stiffness (i.e., elastic constants) of the corneas. This result qualitatively agrees with that was reported in literature [7]. The reconstructed spectra agreed well with experimental results (Fig. 6), suggesting the reliability of the property reconstruction.

We observed that the decrease of the thickness was moderate for most eyes (Fig 5), and that the corneal thickness of eye 5 was increased, possibly due to unavoidable postmortem swelling of the cornea during the experiments. The thickness of cornea may have decreased more with the elevated IOPs if there were no swelling. The decreased density with the elevated IOP may also due to corneal swelling. If swelling were the dominant factor for stiffness change, we would have observed a decreased stiffness with elevated IOP because swelling is associated with softening. However, the stiffness consistently increased with elevated IOP, indicating the dominance of IOP effect. Cornea swelling, indicated by an opaque appearance over time, was observed during the experiments. This is because cornea stroma tends

to absorb water, which causes micro-structural changes of collagen fibrils imbedded in the stroma. To minimize swelling, corneal preservation media needs to be used. In addition, the postmortem processing of porcine eyes at slaughterhouses was not controllable in this study, which may have introduced significant biomechanical changes before ultrasonic measurements were performed. Freshly enucleated animal eyes will be obtained for future studies.

V. Conclusion

We have demonstrated the feasibility of an ultrasonic approach for non-destructive evaluation of the biomechanical properties of ex vivo porcine eyes. This approach appeared sensitive to small changes in corneal properties associated with changes in IOPs. Future work will focus on optimizing the system and the model for in vivo non-invasive determination of corneal properties in human eyes.

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