Quantifying the effects of hydration on corneal stiffness with optical coherence elastography

Manmohan Singh[a], Jiasong Li[a], Zhaolong Han[a,b], Srilatha Vantipalli[c], Salavat R. Aglyamov[a], Michael D. Twa[d,e], and Kirill V. Larin[a,f,g,*]

[a]Department of Biomedical Engineering, University of Houston, Houston, TX, USA; [b]School of Naval Architecture, Ocean and Civil Engineering, Shanghai Jiao Tong University, Shanghai, China; [c]College of Optometry, University of Houston, Houston, TX, US; [d]School of Optometry, University of Alabama at Birmingham, Birmingham, AL, USA; [e]Department of Biomedical Engineering, University of Alabama at Birmingham, Birmingham, AL, USA; [f]Interdisciplinary Laboratory of Biophotonics, Tomsk State University, Tomsk, Russia; [g]Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, TX, USA

*klarin@uh.edu

ABSTRACT

Several methods have been proposed to assess changes in corneal biomechanical properties due to various factors, such as degenerative diseases, intraocular pressure, and therapeutic interventions (e.g. corneal collagen crosslinking). However, the effect of the corneal tissue hydration state on corneal stiffness is not well understood. In this work, we induce low amplitude (< 10 μm) elastic waves with a focused micro air-pulse in fresh *in situ* rabbit corneas (n = 10) in the whole eye-globe configuration at an artificially controlled intraocular pressure. The waves were then detected with a phase-stabilized swept source optical coherence elastography system. Baseline measurements were taken every 20 minutes for an hour while the corneas were hydrated with 1X PBS. After the measurement at 60 minutes, a 20% dextran solution was topically instilled to dehydrate the corneas. The measurements were repeated every 20 minutes again for an hour. The results showed that the elastic wave velocity decreased as the corneal thickness decreased. Finite element modeling (FEM) was performed using the corneal geometry and elastic wave propagation speed to assess the stiffness of the samples. The results show that the stiffness increased from ~430 kPa during hydration with PBS to ~500 kPa after dehydration with dextran, demonstrating that corneal hydration state, apart from geometry and intraocular pressure, can change the stiffness of the cornea.

Keywords: Optical coherence elastography, cornea, hydration, tissue biomechanical properties, stiffness, Young's modulus

1. INTRODUCTION

The biomechanical properties of the cornea are linked to its form and function. Several diseases, such as keratoconus, and refractive procedures, such as LASIK and UV-A/riboflavin corneal collagen crosslinking (CXL) can alter corneal structure and corneal biomechanical properties, and subsequently, vision quality. CXL is intended to stiffen to the cornea and increase its strength to prevent degradation of visual acuity due to keratoconus or other pathologies. One of the primary components of the typical "Dresden" CXL protocol is the topical addition of a 20% Dextran solution [1]. However, recent research has brought the effects of tissue dehydration into question as a compounding factor of the stiffening induced by CXL. While there is a good understanding between the relationship between corneal hydration and thickness [2], the relationship between corneal hydration state and corneal biomechanical properties is not quite clear. Previous research has utilized uniaxial mechanical testing [3], inflation testing [4], and atomic force microscopy [5] to measure corneal biomechanical properties as a function to tissue hydration. However, the results are somewhat contradictory.

In this work, we utilize our previously described technique of air-pulse optical coherence elastography (OCE) to evaluate the biomechanical properties of *in situ* rabbit corneas [6]. The OCE measurements were then used in finite element method (FEM) simulations to quantify corneal biomechanical properties [7, 8].

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2. MATERIALS AND METHODS

Fresh mature (> 6 months) whole rabbit eyes (n=10) were obtained from Pel-Freez Biologicals (AR, USA). The samples were shipped overnight on ice and all measurements were performed within 24 hours upon receipt of the samples. A blunt surgical instrument was used to remove excess tissues such as muscles and the epithelium (to aid in tissue dehydration). Since the eye-globe intraocular pressure (IOP) can have a profound influence on the measured stiffness of the cornea [9], the IOP was set to a physiologically relevant 15 mmHg by our previously described artificial IOP control system [10]. Briefly, the eye-globes were placed in a custom holder and cannulated with two needles. One needle was connected via tubing to a pressure transducer, and the other needle was connected to a micro infusion pump. The system was controlled with a custom software to form a closed-loop feedback system.

A focused micro air-pulse induced low-amplitude (< 10 μm) displacements at the apex of the cornea [11], which then propagated through the corneal tissue as an elastic wave [6]. Details on the acquisition process can be found in our previous work [6]. In order to minimize the influence of anisotropy [12-15], all OCE measurements were made along the same meridian. For 60 minutes, 1X PBS was dropped every 5 minutes on the de-epithelized corneas. After 60 minutes, a 20% dextran solution was dropped on the corneas, also every 5 minutes. OCE measurements were taken every 20 minutes. The group velocity of the air-pulse induced elastic wave was calculated by a cross-correlation algorithm [16], and the corneal geometry and group velocity were used in the FEM simulations to obtain the stiffness of the corneas. The FEM simulations were performed similarly to our previous work [7, 8]. Briefly, a corneal model was constructed in the ANSYS 14.0 environment based on the averaged dimensions of the corneal samples at each given time point. The corneal tissue was assumed as linearly elastic and a fluid-structure interface was created at the posterior surface of the cornea in order to accurately replicate the cornea boundary conditions [8]. The mass density of the corneal tissue was set to 1062 kg/m^3 [17], the Poisson ratio was set to 0.49, the density of the aqueous humor was set to 1000 kg/m^3. A local perturbation was prescribed at the apex of the cornea, which was based on corresponding OCE-measured displacement profiles from the corneal apex. The Young's modulus of the cornea was adjusted incrementally until the error between the FEM-simulated elastic wave speed and OCE-measured elastic wave speed was less than 5%.

3. RESULTS

Figure 1 shows a typical rabbit cornea while it was dehydrated with the dextran solution. There is no noticeable change in thickness during the first 60 minutes. Once the dextran solution was applied, the cornea then quickly shrank. Figure 2(a) plots the central corneal thickness (CCT) of the samples as a function of time. There is no real change in CCT while PBS was added as the corneas went from ~670 μm at the 0 minute measurement to ~680 μm at the 60 minute measurement. Again, it is clear that after the addition of the dextran solution at 60 minutes, the CCT shrinks rapidly from ~680 μm at the 60 minute measurement to ~370 μm at the last OCE measurement at 120 minutes. Similarly, the OCE-measured elastic wave speed remains stable between ~3.2±0.2 m/s at 0 minutes and ~3.2±0.3 m/s at 60 minutes. The elastic wave speed then decreased to ~2.6 m/s as the cornea thinned at 120 minutes.

To quantify the corneal stiffness, FEM simulation were performed. The average error between the FEM-simulated elastic wave speed and OCE-measured elastic wave speed was 3.1±5.7%, demonstrating good agreement between the FEM simulations and OCE measurements. While PBS was added to the corneas, the Young's modulus remained fairly constant from ~500 kPa at 0 minutes to ~465 kPa at 60 minutes. Once the dextran solution was added, the corneal stiffness dramatically increased up to ~800 kPa at 120 minutes.

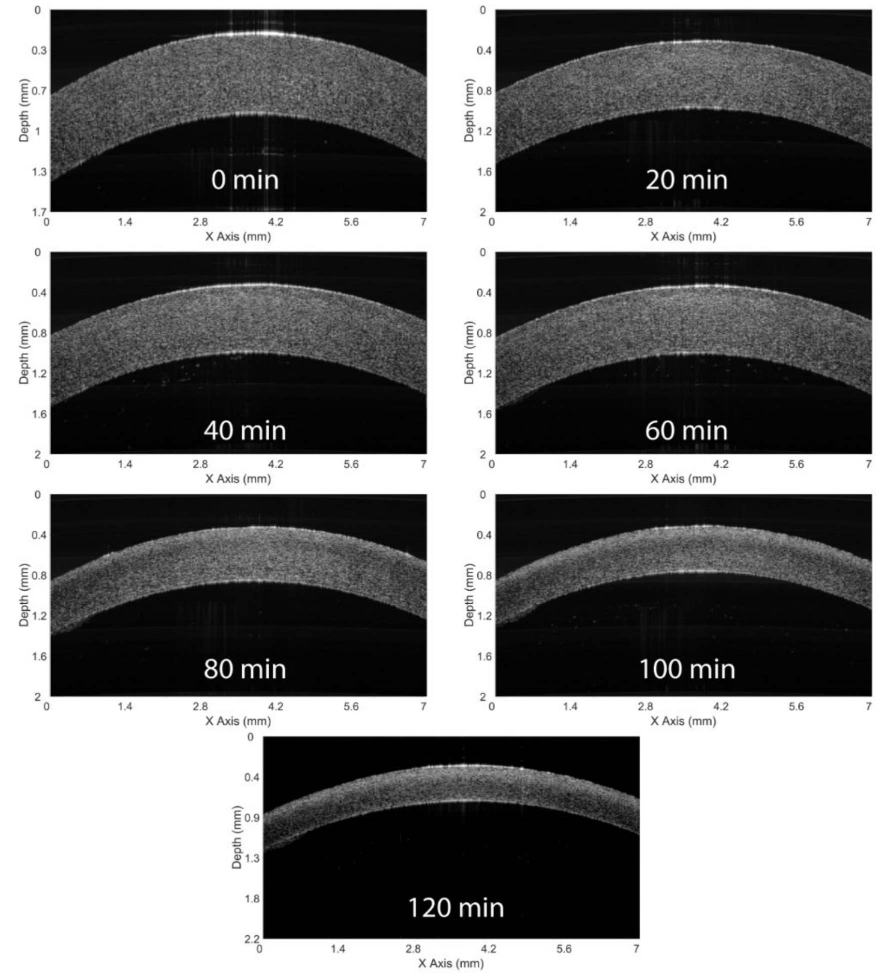

Figure 1. OCT structural images of a typical *in situ* rabbit cornea at the indicated times during the experiment. The 20% dextran solution was added after the 60 minute measurement.

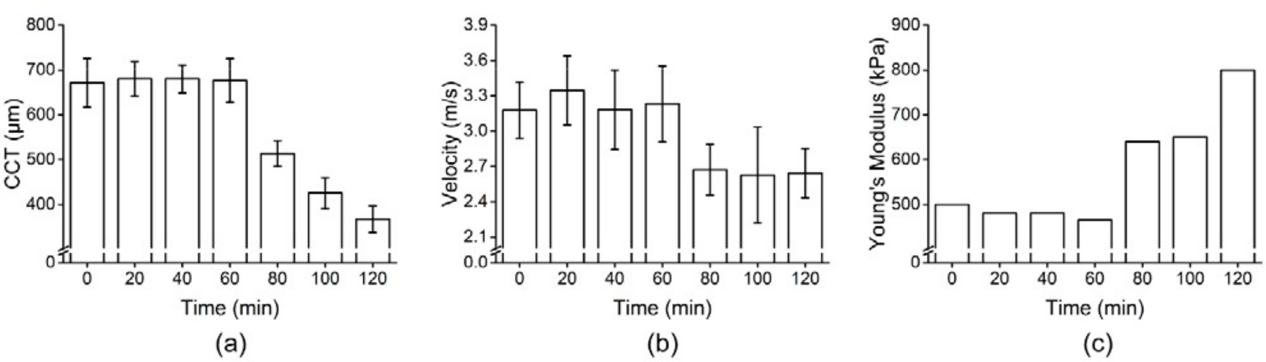

Figure 2. (a) Central corneal thickness (CCT) of the corneas (n=10) as a function of time. (b) The group velocity of the air-pulse induced elastic wave as a function of time.

4. CONCLUSIONS AND FUTURE WORK

OCE and FEM are a powerful combination for quantifying the biomechanical properties of the cornea. Our results show that a 20% dextran solution thins the cornea quickly, which also causes a decrease in the velocity of an air-pulse induced elastic wave. However, FEM simulations demonstrate that the stiffness of the cornea increased drastically as the corneas thinned. Therefore, the hydration state of the cornea, along with its geometry, are significant factors that contribute to the stiffness of the cornea and must be considered when quantifying corneal biomechanical properties. Our future work will entail the quantification of viscoelasticity and development of higher frequency excitation techniques to minimize the influence of boundary conditions and increase the spatial resolution of the air-pulse OCE technique.

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