Study of Laser-Induced Microdeformations of the Cornea Using Phase-Sensitive Optical Coherent Elastography

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Abstract. In many clinical cases, knowledge of the biomechanical properties of the cornea will allow for early diagnosis and also contribute to the success of treatment. The methods existing in the clinic characterize the biomechanical properties of the cornea as a whole, but do not give an idea of its local properties. One of the promising approaches to measure local changes in biomechanics is optical coherence elastography (OCE) based on phase-sensitive optical coherence tomography (OCT). In this work, the OCE method, based on the registration of small tissue deformations under an applied load, showed that the appearance and propagation of mechanical waves due to laser exposure depend on the loading of the studied biological tissue due to its tension with the application of various intraocular pressures (IOP). An analysis of inter-frame differential OCT images showed that the width of the laser impact zone on the tissue increases with increasing of IOP. An analysis of the strain amplitudes depending on the IOP at a given point revealed a correlation with the IOP value and made it possible to fix the fluidity threshold for the sample under consideration in the given experimental geometry. © 2022 Journal of Biomedical Photonics & Engineering.

Keywords: intraocular pressure; phase-sensitive optical coherent elastography; cornea; keratoconus; biomechanics.

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1 Introduction

The study of the biomechanics of the cornea is of undoubted interest, since there are a number of clinical situations in which an intravital assessment of mechanical properties can help both in diagnosis and in treatment. One of the most common complications of keratorefractive surgery is iatrogenic keratoconus associated with a weakening of the strength properties of the cornea. The currently available methods for the timely detection of this pathology are imperfect, since they make it possible to make a diagnosis only in the presence of late structural deformations of the cornea. Timely detection of a decrease in the strength of the cornea would make it possible to diagnose the problem at an earlier stage and significantly reduce the risk of iatrogenic pathology. In addition, with a decrease in the strength of the cornea, there is a problem with the accuracy of determining intraocular pressure. At present, the interest in the study of the biomechanics of the trabecular apparatus is quite high. The results of the study of the mechanical strength and biochemical composition of the isolated samples of trabecular tissue show an increase in the rigidity of this structure with glaucoma. In addition, they directly correlate with the degree of intraocular fluid outflow, and, consequently, with changes in intraocular pressures (IOP) levels. The main disadvantage of such direct measurements on samples is the very high dependence of the mechanical properties of tissues on a huge number of poorly controlled factors, such as sample hydration, careful sample preparation, patient age, individual variability, and localization of the initial sample location in the eye. As a result, the resulting data have a large scatter and can only be used to a limited extent with various theoretical constructions in the clinical prediction of the behavior of a particular eye.

Now in clinical practice, devices such as Ocular Response Analyzer (Reichert, Ophthalmic Instruments, USA) [1–7] and Corvis-ST (OCULUS, Optikgerate GmbH, Wetzlar, Germany) have found application [8–11]. Both devices (and their analogues) use a calibrated air flow to deform the cornea in the central region, and then analyze the movement of the cornea under its influence. The main purpose of these devices is to accurately measure the IOP, taking into account the individual characteristics of the cornea of a particular patient. However, in addition to their main purpose, they provide an opportunity to assess the biomechanical properties of the cornea. The obtained data characterize the biomechanical properties of the cornea generally but do not give an idea of its local properties, which can be useful in the preclinical diagnosis of keratoconus and in refractive surgery. Alternative methods for studying the biomechanics of the eye, such as Brillouin scattering [12, 13], ultrasonic elastography [14, 15], atomic force microscopy [16, 17] provide the opportunity to study local biomechanical properties but have their limitations and are currently not available to use in the clinic. One of the promising approaches that allows one measuring local changes in biomechanics is optical coherent elastography based on phase-sensitive optical coherence tomography [16–23]. OCT technology of visualization of eye structures is used to diagnose keratoconus and to monitor its treatment [24] and damaged ocular surface [25] and other eye diseases. Using this method, it is possible to identify the initial stages of diseases that are not available with a slit lamp analysis. Thus, over the years, OCT has established itself as a standard and reliable method for the analysis of eye tissue. Moreover, the OCE method is being actively developed, which makes it possible to build “maps” of tissue elasticity. The high resolution of the OCE method in terms of analysis time allows visualizing the dynamics of deformations in the eye tissues at millisecond pulses of laser exposure [22]. The high sensitivity of the method to microscopic shifts makes it possible to register tissue deformations invisible to the naked eye as a result of short-term laser exposure [26, 27], which provides information on local biomechanical properties in this zone [20–22].

The present study was carried out in order to investigate the possibilities of phase-sensitive optical coherent elastography to register laser-induced microdeformations of the cornea under various mechanical stresses.

2 Materials and Methods

The study was conducted on 4 enucleated eyes of laboratory rabbits of the chinchilla-gray breed. The study plan was approved by the local ethics committee. All procedures followed the principles set out in the 1975 Declaration of Helsinki and its 2000 revision.

Four hours after enucleation, the eyes were fixed in a laboratory setup, see Fig. 1. The pressure inside the eye was maintained using a system of communicating vessels – a needle with a diameter of 0.45 mm was inserted through the cornea into the anterior chamber of the eye, connected to a bulb of sodium chloride solution fixed on a vertical stand at a certain level. The movement of the bulb along this vertical stand made it possible to change the IOP and maintain it unchanged during the laser exposure. Evaluation of IOP was carried out by the Schiotz impression tonometer. The values were recorded in mm Hg.

Laser irradiation of the tissue was carried out with an Erbium fiber laser with a wavelength of 1.56 μm. The irradiation power was chosen to be minimal so as not to cause damage to the tissue. The pulse duration is 100 ms. To study the propagation of the deformation pattern we used an OCT elastography unit, previously used to study eye tissues [22–24], and created at the Institute of Applied Physics, Russian Academy of Sciences, Nizhny Novgorod, by a group led by V. Yu. Zaitsev, with an imaging area of 4 mm wide and 2 mm deep, the setup made it possible to obtain the dependence of internal strains on time at a rate of 80 kHz for spectral bands and 20 Hz for B-scans. The study of the cornea was carried out in the central zone along the axis of the pupil.

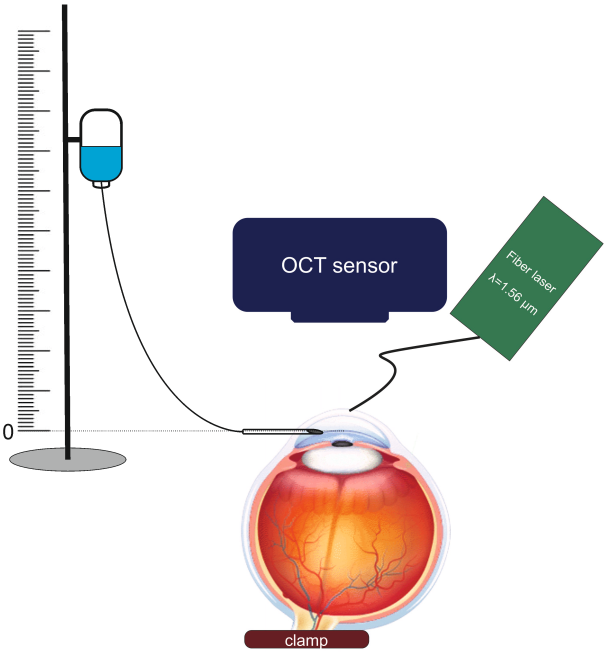


Fig. 1 The experimental setup for the study of laser-induced microdeformations of the cornea with different IOP by the optical coherent elastography.

Since the scanning frequency did not coincide with the frequency of laser pulses, from the recorded series of scans, the maxima of the width of the zone were selected, in which optocoherent elastography detected a phase change, which means that the tissue responded to laser exposure – tissue displacement and elastic wave propagation.

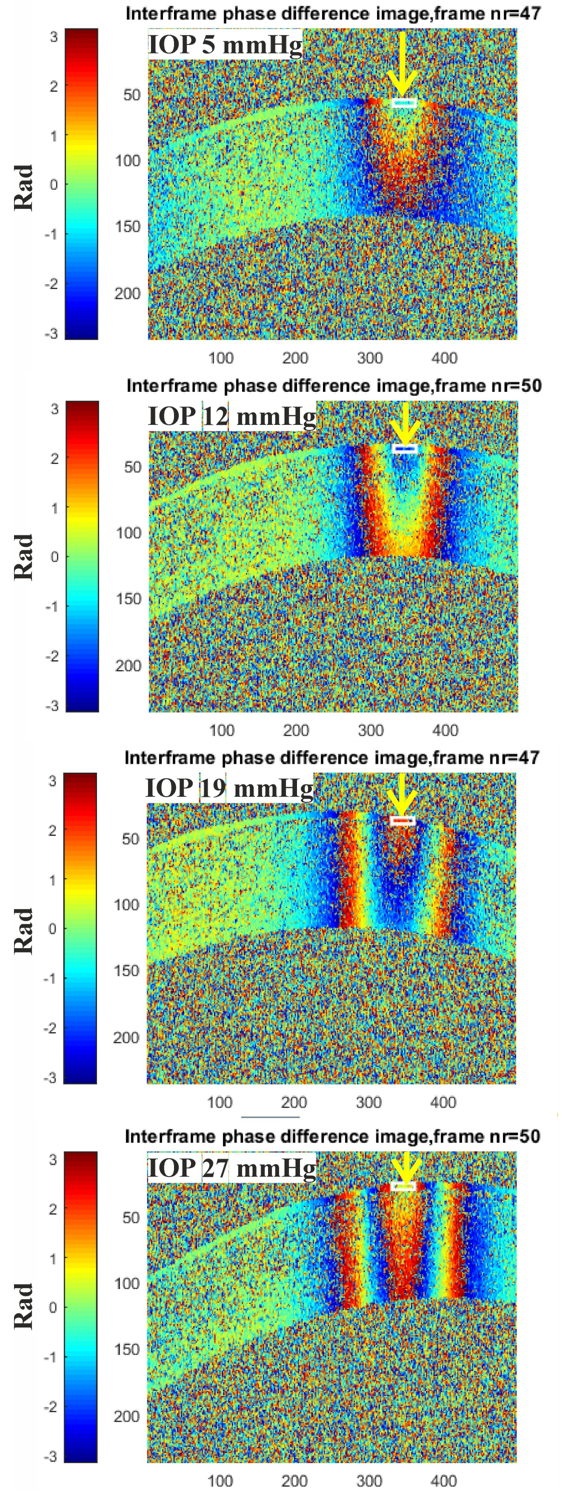


Fig. 2 Inter-frame phase difference between a pair of B-scans at the initial moment of the first laser exposure for different IOP values of the rabbit eye.

The relationship between IOP at the time of the study (and hence the mechanical stress of the cornea) and the characteristic region of elastic wave propagation under laser exposure was estimate using the Pearson parametric correlation coefficient.

Statistical analysis was performed using R version 4.1.1 (R Foundation for Statistical Computing).

3 Results

For experimental samples, no visible changes in the cornea were found in any case at the site of laser heating.

Fig. 2 shows the cornea of the eye in a depth section, along the axes the coordinates of the position in space in pixels are plotted. The axis of laser exposure is marked with a yellow arrow. The inter-frame phase difference between two consecutive B-scans exhibiting multiple phase wrapping is shown. Analysis of inter-frame differential OCT images showed that the width of the laser impact zone (area of different color – phase wrapping area) on the tissue depends on IOP (Fig. 2). Fig. 2 shows the first frame for the first laser pulse with a duration of 100 µs at different IOP of the eye (frame number 47 or 50 depending on start of recording).

Obviously, at low values of IOP, the effect of laser exposure is limited to a small area, both along the depth of the tissue and perpendicular to the axis of action. However, with an increase in IOP, the area of tissue response to laser exposure also increases.

Since the scanning frequency did not coincide with the frequency of laser pulses, frames were selected from the recorded series of scans corresponding to the maximum of the zone of phase change in the tissue, which, in fact, corresponds to the area of tissue displacement under the action of laser exposure. The characteristic size of the region of phase change was taken at half the height of the cornea with a decrease in the phase modulus by a factor of *e*.

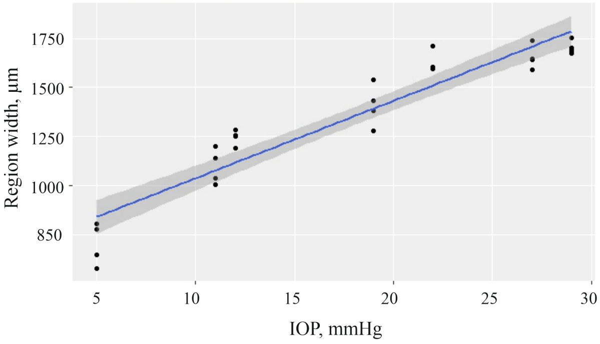
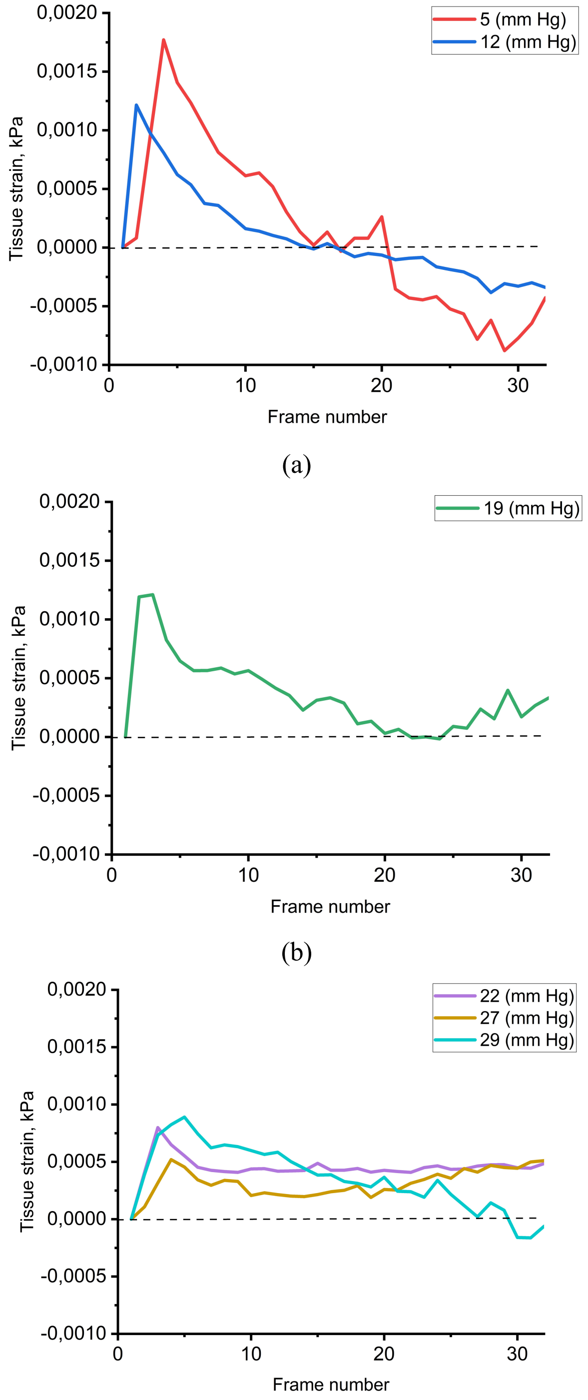


Fig. 3 Scatterplot; horizontally – IOP in mm Hg, vertically – horizontal size of the response area to laser exposure in microns.

Statistical analysis showed a significant correlation between the level of IOP and the characteristic size of laser-induced microdeformation (Fig. 3). The value of the Pearson correlation coefficient was 0.94 (95% confidence interval from 0.88 to 0.97), $p < 5\times10^{-14}$.



(a)

(b)

(c)

Fig. 4 Graphs of the dependence of the amplitude of tissue strain under laser exposure of the same power on different values of IOP: (a) for IOP 5, 12 mm Hg, (b) for IOP 19mm Hg, (c) for IOP more than 20 mm Hg.

The range of propagation of the elastic wave front from the axis of laser action also differed over time for different values of IOP. So, for low IOP values, the wave propagation under laser exposure had a small depth, while at an increased IOP, the region had a significantly larger area. The wave decay rate at low IOP was higher than for high IOP.

An analysis of the amplitudes of deformations at a selected point at an equal distance from the center of laser exposure revealed the following regularities (Fig. 4): since low-power laser exposure was used in the work, which did not lead to a change or damage of the tissue structure, for a normal IOP value (19 mm Hg) deformation during laser exposure did not accumulate and relaxed completely. For low IOP, the amplitude of deformities is higher than for normal and high IOP. However, there is a rapid relaxation and reversal of the strain sign, which occurs because the tissue is not under pressure and therefore subject to oscillation. With an increase in IOP, the amplitude of deformities decreases, but the duration of their existence in the tissue becomes longer. With an increase in IOP up to 29 mm Hg laser exposure in the selected range of parameters leads to tissue fluidity, which is expressed in an increase in the amplitude of deformation and a change in their sign during relaxation.

4 Discussion

Current clinical measurements of IOP are based on indirect methods with limited accuracy because the biomechanics of the eye cannot yet be taken into account for every patient. Available systems used to measure IOP *in vivo*, such as Goldmann tonometry, Ocular Response Analyzer, dynamic contour tonometry, and non-contact tonometry, can be improved by calibration methods that take into account the mechanical properties of the cornea.

Almost all currently existing methods for assessing the biomechanical properties of biological tissues require the presence of some kind of mechanical effect on it, followed by an assessment of the deformation response. Thus, the Ocular Response Analyzer, Corvis-ST devices and their analogues used today in the clinic register the response of the cornea to a calibrated air flow acting on a sufficiently large area, which does not allow assessing the local properties of the tissue. The combination of the precise mechanical action of laser tissue heating and the sensitive technique of recording induced microdeformations using phase-sensitive coherent elastography can provide data on the local biomechanical properties of the cornea and map the biomechanical properties of the corneal tissue.

A significant reliable correlation between IOP and the recorded characteristic size of the response zone to laser-induced exposure shows the fundamental possibility of recording the mechanical stress of the cornea in a small neighborhood around the heating zone.

The development of the methodology for mapping the cornea and the improvement of methods for measuring the dynamics of the biomechanical parameters of eye tissues can be used as the basis for a method for diagnosing and monitoring the treatment of glaucoma, taking into account the biomechanical properties of eye tissues, as well as identifying a safety criterion for laser-controlled changes in the biomechanics of eye tissues. And the high resolution of the OCE method in terms of analysis time allows visualizing the dynamics of changes in the response zone in the tissues of the eye under millisecond laser pulses, which can be a good basis for a control system of laser modification methods and treatment of eye pathologies.

5 Conclusions

Light is a non-destructive and information-intensive tool for studying biological tissues; the penetrating power of light is of particular relevance in the development of monitoring systems. Since an inherent property of light is the ability to repeatedly scatter, interacting with the components of biological tissues, the construction of clear images from the depth of the tissue is related with certain difficulties associated with the noise interference of multiply scattered radiation. To reduce noise and enhance the useful signal, methods are being developed based on the use of light coherence, as in the OCE method used in this study.

In this work, the OCE method, based on the registration of small tissue deformations under an applied load, showed that the appearance and propagation of mechanical waves due to laser exposure depend on the loading of the biological tissue due to its tension with the application of various IOPs. An analysis of inter-frame differential OCT images showed that the width of the laser impact zone on the tissue increases with increasing of IOP. An analysis of the strain amplitudes depending on the IOP at a given point revealed a correlation with the IOP value and made it possible to fix the fluidity threshold for the sample under consideration in the given experimental geometry.

In the future, the combination of the precision mechanical action of laser tissue heating and the registration of induced microdeformation using phase-sensitive coherent elastography can provide data on the local biomechanical properties of the cornea and more accurate data on the state of the IOP system of the eye, taking into account the individual characteristics of each patient.

Disclosures

All authors declare that there is no conflict of interests in this paper.

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