Laser-optical methods for monitoring the biomechanical properties of the anterior part of the eye

Ekaterina M. Kasianenko[a], Alexey V. Yuzhakov[a], Anastasia V. Golovchenko[b], Vladimir I. Siplivyi[b], Oleg G. Romanov[c,d], and Olga I. Baum[a]

[a]Institute of Photon Technologies, Federal Scientific Research Center "Crystallography and Photonics", Russian Academy of Sciences, Troitsk, Moscow, Russia
[b]I. M. Sechenov First Moscow State Medical University (Sechenov University), Department of Ophthalmology, Moscow, Russia
[c]Belarusian State University, Minsk, Belarus
[d]B. I. Stepanov Institute of Physics, National Academy of Sciences of Belarus, Minsk, Belarus

ABSTRACT

Biomechanics of eye tissues is an important parameter of the state of the ocular system and its study is of undoubted interest since there are several clinical situations in which an in vivo assessment of mechanical properties can help both in diagnosis and in treatment. The risk of developing glaucoma and keratoconus of the eye is associated with pathological changes in the biomechanical properties of such eye tissues as the cornea and sclera. Thus, the problem arises of studying tissue biomechanics and the possibility of influencing it. For this purpose, experiments were carried out to determine the dynamics of elastic properties of intact and modified tissue of the sclera and cornea of the pig's eye by OCT elastography and speckle interferometry. Internal stresses found by numerical simulation from a comparison of subsequent OCT frames demonstrate a dependence on the biomechanics of the tissue sample. It was also shown that the time and temperature dependences of the contrast and correlation functions in speckle interferometry make it possible to track the onset of structural changes in the tissues during repetitively pulsed laser heating. A comparison was made in the behaviour of these curves for the central and peripheral regions of the cornea. The results obtained and their repeatability allow us to conclude that the speckle interferometry can be used as the basis for a system for monitoring structural changes in the cornea associated with the thermal effect of laser radiation. OCT elastography is a sensitive method for studying the biomechanical properties of eye tissues (cornea and sclera) under laser exposure, reflecting the dependence on the intraocular pressure of the eye. This method can be used as the basis for a control system in the development of medical technology for influencing the sclera and cornea of the eye.

Keywords: eye biomechanics, cornea, sclera, glaucoma, keratoconus, intraocular pressure, OCT elastography, speckle interferometry method

1. INTRODUCTION

Biomechanics of eye tissues is an important parameter of the state of the ocular system and its study is of undoubted interest since there are several clinical situations in which an in vivo assessment of mechanical properties can help both in diagnosis and in treatment. One of the common complications of keratorefractive surgery is iatrogenic corneal ectasia associated with a weakening of the strength properties of the cornea 1. The currently available methods for the timely detection of this pathology are imperfect since they make it possible to diagnose only by the presence of late structural deformities of the cornea. Timely detection of a decrease in corneal strength will allow diagnosing 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 the intraocular pressure. Thus, this article is devoted to the study of the biomechanics of the sclera and cornea of the eye.

Further author information: (Send correspondence to Ekaterina M. Kasianenko)
Ekaterina M. Kasianenko: E-mail: ekkassianenko@gmail.com, Telephone: +79104648261

The mechanical properties of the human eye are believed to play an important role in the regulation of intraocular pressure (IOP). In addition, the modulus of elasticity of the cornea and, apparently, other ocular tissues is a function of IOP. Since the human eye partially retains its shape by regulating IOP, its magnitude can be a valuable clinical parameter in helping diagnose and treat diseases such as glaucoma.

The following devices are currently used in clinical practice: Ocular Response Analyzer (Reichert, Ophthalmic Instruments, USA) 2,3 and Corvis-ST (OCULUS, Optikgerate GmbH, Wetzlar, Germany) 4,5. Both devices (and their counterparts) use a calibrated air stream to deform the cornea in the central region, and then analyze the movement of the cornea under its influence. The data obtained characterize the biomechanical properties of the cornea as a whole, but do not give an idea of its local properties, which can be useful in preclinical diagnosis of keratoconus and in refractive surgery.

Our studies have shown a possible practical implementation of the modification of the porous structure of the sclera in order to increase the outflow of fluid for the treatment of glaucoma 6,7, which is based on the impact in the paralimbal region of the eye. It has been shown that the modification influencing the change in the outflow of intraocular fluid can be carried out both in the trabecular and in the paralimbal region of the eye 8,9. But the correctness of the measurement of intraocular pressure in order to monitor it during treatment and for early diagnosis remains questionable, since it depends on the biomechanical properties of the eye tissues.

Thus, the relevance of studying the biomechanics of eye tissues is beyond doubt, and the data presented in this article can serve as the basis for the development of a method taking into account the biomechanical properties of the eye membrane for measuring intraocular pressure that has no analogues in the world, and a method for detecting iatrogenic pathology at early stages of development.

2. MATERIALS AND METHODS

2.1 Biological material

The study of the biomechanics of the sclera and cornea was carried out on *ex vivo* pig eyes, stored at a temperature of 4 °C in saline for no more than 48 hours until the experiment was carried out. Right before the experiments they were thawed at the room temperature and placed in physiological saline to prevent drying. To prevent excessive absorption of the surface water samples were slightly dried directly before conducting the experiment. Sample size of each iteration of the experiment is at least 5. To create small deformations in the tissue, we used an LS-1.56 fiber laser (IPG Photonics Corp.) operating at a wavelength of 1.56 μm, with an output power of up to 5 W and the ability to control the duration of laser pulses and interpulse pauses. The measurement of intraocular pressure was carried out using a Schiotz tonometer, for which the normal true IOP level is 10 to 21 mm Hg 10. Intraocular pressure was changed by equatorial concentric compression of the optic nerve of the eye.

2.2 OCT elastography

OCT technology of visualization of eye structures is used to diagnose keratoconus and to monitor it's treatment 11 and damaged of the ocular surface 12, 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 13, which can represent a good basis for a control system for laser modification methods and treatment of eye pathologies 14.

For this purpose, experiments were carried out to determine the dynamics of elastic properties of intact and modified tissue of the sclera and cornea of a pig's eye using a setup created at the Institute of Applied Physics, Russian Academy of Sciences, Nizhny Novgorod, Russia by a group led by Vladimir Y. Zaitsev. The OCT sensor was positioned perpendicular to the tissue surface (Fig. 1).

For the cornea, irradiation was carried out along the optical axis of the cornea with a pulse duration of 100 ms and a pause between pulses of 1900 ms, the total duration of irradiation was 10 seconds. For the sclera, irradiation was carried out in the Pars plana region with a pulse duration of 200 ms and a pause between pulses of 200 ms, the total duration of irradiation was 2 seconds.

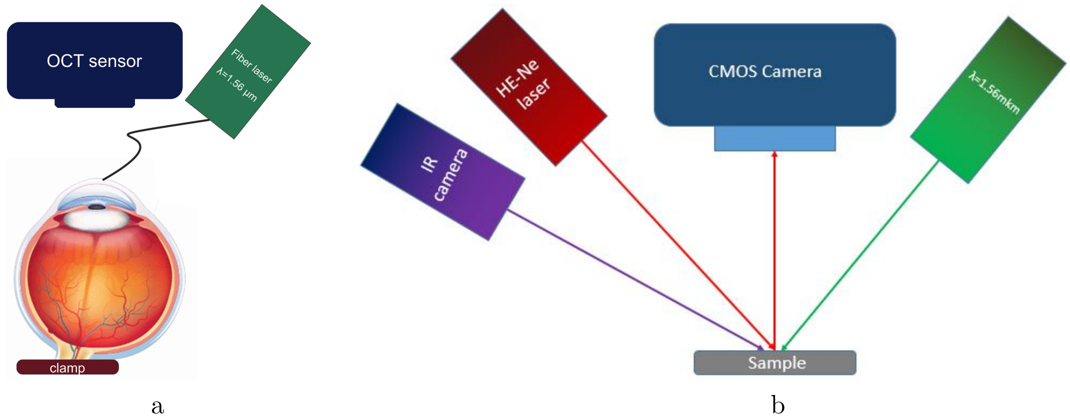

Figure 1. Experimental setup diagram: a – OCT - elastography, b - laser speckle interferometry

2.3 Laser speckle interferometry

Laser speckle interferometry is a simple, safe, and non-contact method that is widely used both in materials science and medicine to assess the surface properties of samples (roughness, deformation) or to assess the movement of scattering centers inside samples (for example, to assess the blood flow velocity) 15–22.

Irradiating medium with a large quantity of light-scattering particles with coherent light results in a random interference which can be captured with camera. Camera catches the changes of intensity occurring due to motion of scattering particles and thus fluctuations in the interference pattern. Temporal and spatial statistics of the recorded speckle frames contain information about the movement. So one can connect known processes occurring during heating of the sample and data gained from analysis of the speckle-contrast frames.

For laser speckle interferometry the irradiation mode was: pulse-periodic mode, power density 15-56 W/cm^2, exposure time 15-40 s, pulse duration and the interval between pulses 500 and 300 ms, respectively. After the normal reflection probe beam is caught by a CMOS camera (Videozavr, VZ-M50S, 1296 × 972 pixels, 21 $frames/s$) so we can process the obtained images and estimate statistical changes of speckle pattern. Observation of the surface temperature was made by IR camera FLIR A615 (Fig. 1). We took into the consideration the following values: the ratio between the standard deviation and mean intensity as a contrast value and the Pearson correlation coefficient between the consequently obtained intensity images.

3. RESULTS AND DISCUSSION

The magnitude of deformations obtained under laser action on the corneal region at different pressures inside the eye was measured by OCT elastography Fig. 2

As it was found from OCT images of interframe shift at increased pressure, the corneal tissues under laser action practically do not experience interframe displacements, and, therefore, the response to a single pulse is a small peak of stress in the tissue with rapid relaxation. However, over the entire time of laser exposure, tensile deformation accumulates in the tissue. At normal pressure, the tissue reacts to a single laser pulse with a higher amplitude, but the sequence of pulses does not lead to the accumulation of internal stresses. Reduced eye pressure leads to a slower response of the system to laser action, and relaxation of stresses after a laser pulse is much slower.

The higher the intraocular pressure, the more internal stresses are created with the same laser action on the cornea, due to which tensile deformations accumulate. This may be due to the fact that the use of non-destructive laser action allows for a short-term decrease in the elastic properties of the cornea, and the increased intraocular pressure leads to fluidity, creating new crosslinks upon subsequent cooling. If the impact is on the cornea, which is under normal and lower pressure, stretching deformations are associated with the movement of the tissue during the impact, and not with the accumulation of deformations inside the tissue.

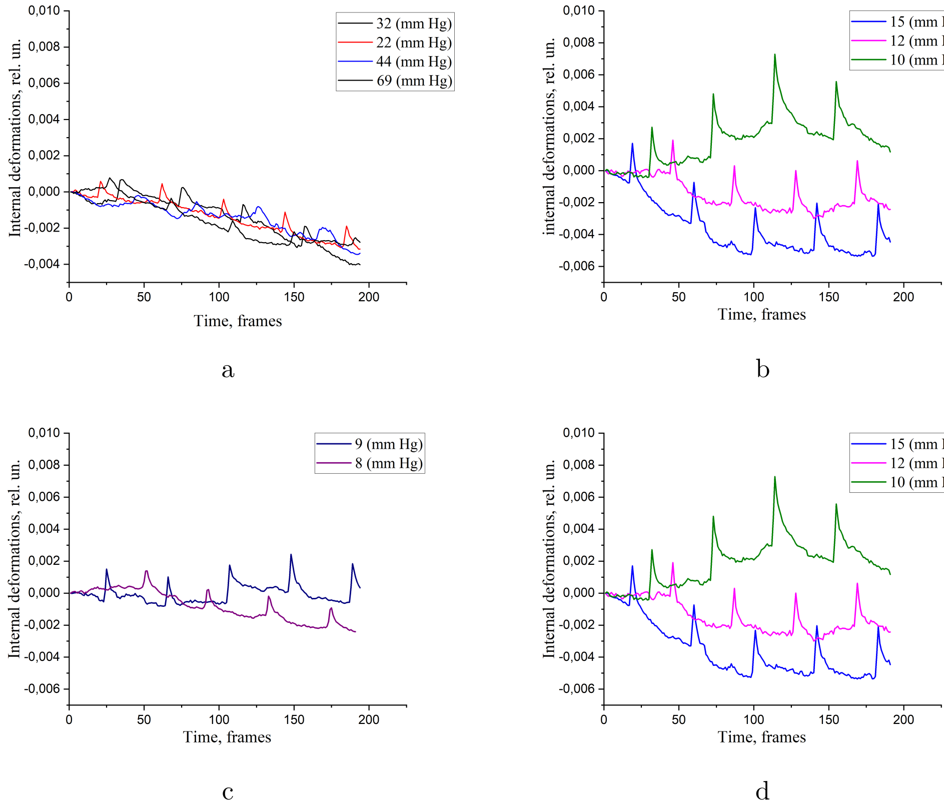

Figure 2. Dependence of internal deformations during laser action on the cornea on the IOP value of the eye

The dependence of the magnitude of the deformation for the sclera on the intraocular pressure has a clearer and more expressed character (Fig. 3).

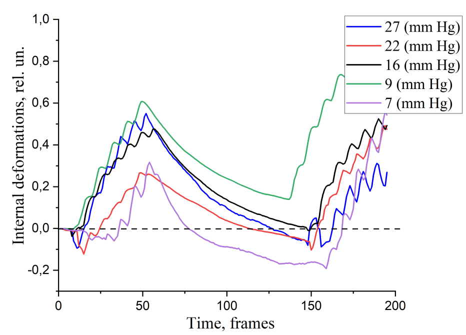

Figure 3. Graphs of internal deformations of the scleral tissue during laser exposure for various IOP

As a result, graphs of the dependence of internal stresses in the tissue during laser exposure at various IOP from 7 $mmHg$ up to 30 $mmHg$ were obtained. The analysis of these graphs showed that for normal pressure (16 $mmHg$)(Fig. 3 black line) the clearest picture of the tissue response to a laser pulse is observed - a clear increase in deformations with their rapid and complete relaxation after the completion of irradiation. Whereas for IOP above or below the norm, there is an indistinct tissue response to laser action and not complete relaxation of internal stresses. Moreover, for an IOP of 16 $mmHg$ the maximum of internal stresses remained at a depth of 30 μm from the scleral surface, while for other values it was shifted in depth to a depth of 60 to 200 μm.

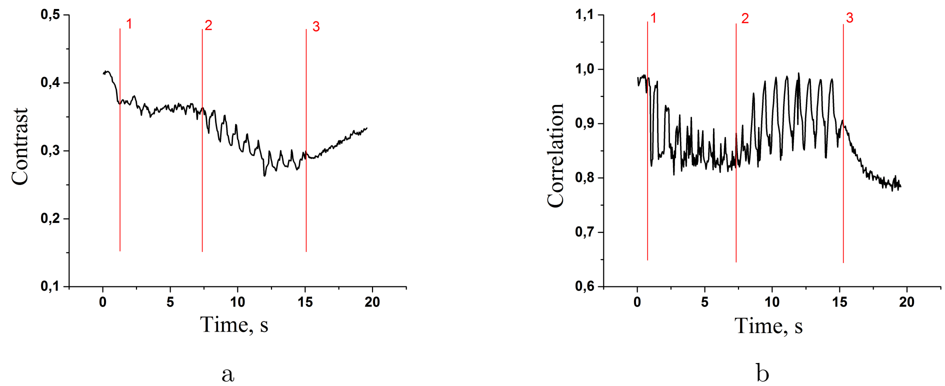

Figure 4. Temporal dependences of contrast (a) and correlation coefficient (b) during heating of the cornea

The values of the contrast and correlation functions were measured for cornea for a pulse-periodic laser heating regime at 56 W/cm^2, power density. In the comparative graphs (Fig. 4), presenting the dependence of the contrast function and the correlation on time, the motion of tissue inhomogeneities is noted, associated with its periodic thermal expansion and contraction due to the laser operation mode. Several regions can be outlined on them: Line 1 – heating start; Region 1-2 – process of heating with no notable changes in contrast curve and diminishing oscillations in correlation curve due to enlarging of average size of scattering centers; Line 2 – overcoming of the limit of plasticity;Region 2-3 – further heating lowering the value of contrast and maximizing oscillations of correlation due to more active movement of existing scattering centers and appearing of new ones; Line 3 and further – end of heating and then cooling process.

Results demonstrated in the Fig. 4 shows that speckle interferometry technique is able to track the beginning of the structural changes in the eye tissues thus indicating the potential use of this method as a control system.

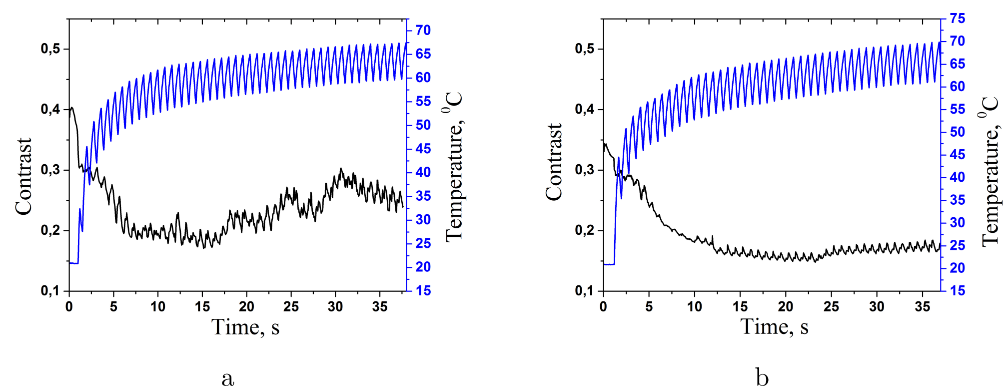

Figure 5. Temporal dependences of contrast and temperature during pulse-periodic heating of the peripheral (a) and central (b) areas of the cornea

For next experiment we lowered power density to 20 W/cm^2 and prolonged exposure time to 40 seconds for better comparison of the results. Speckle images for central and peripheral regions of the cornea were obtained and statistics were measured. The oscillation amplitude of the contrast function for a region located in the peripheral part of the cornea (Fig. 5a) is noticeably larger compared to the oscillation amplitude for the center (Fig. 5b).

The difference in behavior of the contrast time dependences for central and peripheral regions of the cornea shows that central parts have higher thermal resistance. This was already shown by our group in the past but through other means 23.

Time dependences of contrast were obtained for the reversibility experiments. The samples were irradiated for 20 seconds with power density of 15 W/cm^2, which corresponds to regime of stress relaxation (Fig. 6a), then they were soaked in saline for 5 minutes, and a 20-second irradiation was repeated (Fig. 6b). A qualitative similarity for the contrast function and temperature profiles was shown on the obtained graphs. The scatter of the results of repeated experiments lies within 10 % while maintaining the qualitative shape of the curves.

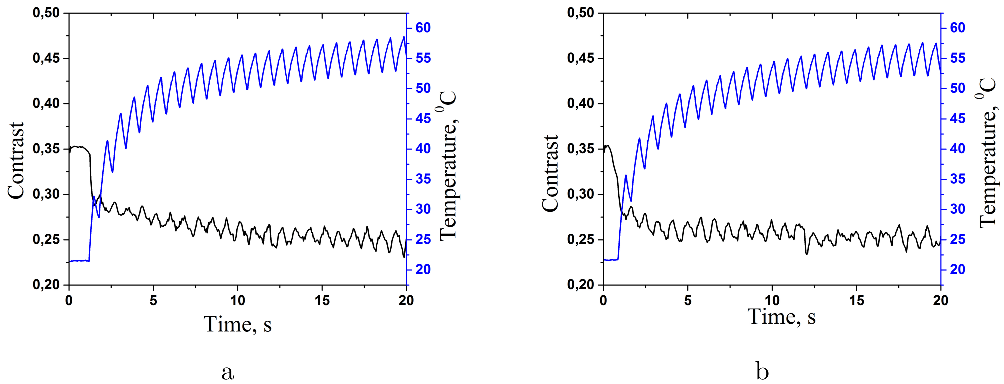

Figure 6. Temporal dependences of contrast and temperature during initial (a) and repeated (b) pulse-periodic heating of the cornea

The obtained graphs for the reversibility experiments showed a qualitative similarity in the rate of decrease in the contrast function and the similarity of temperature profiles. The maximum achieved temperature also coincides, which allows us to conclude that the thermomechanical characteristics of the cornea are restored thus adding an argument for the safety of stress relaxation irradiation

4. CONCLUSION

Using the methods of speckle interferometry and optical elastography, the main regularities of changes in the biomechanical properties of the sclera and cornea in the course of laser exposure at various intraocular pressures have been revealed. So for the cornea, the use of non-destructive laser action, which allows for a short-term decrease in its elastic properties, with increased intraocular pressure relative to the norm, leads to fluidity, creating new cross-links with subsequent cooling. And for the sclera with normal IOP, the maximum of internal stresses corresponds to a depth of 30 μm from its outer surface, while with a decrease or increase in IOP relative to the norm, the maximum of internal stresses shifts in depth.

The results obtained have shown that it is possible to track the onset of structural changes in the corneal tissues during pulse-periodic laser heating by laser speckle interferometry. It is shown that curves of contrast time dependences behave different for central and peripheral regions of the cornea. Though laser speckle interferometry requires further tuning to be more sensitive and have some better spatial and time resolutions it proved itself as a stable basis for the control system during stress relaxation cornea laser procedures.

ACKNOWLEDGMENTS

This work was supported by the Ministry of Science and Higher Education of Russian Federation within the State assignment FSRC “Crystallography and Photonics” RAS in part “Laser-induced control of pore formation depth due to additional pressures” and by an international grant by Russian Foundation for Basic Research

(RFBR) (Project No. 20-52-00041 Bel_a) and by the Belarusian Republican Foundation for Fundamental Research (project F20R-071) in part of "Dynamics of biomechanical properties of the cornea and sclera under laser exposure, taking into account intraocular pressure".

REFERENCES

[1] Roberts, C. J. and Dupps Jr, W. J., "Biomechanics of corneal ectasia and biomechanical treatments," *Journal of Cataract & Refractive Surgery* **40**(6), 991–998 (2014).

[2] Kaushik, S. and Pandav, S. S., "Ocular response analyzer," *Journal of current glaucoma practice* **6**(1), 17 (2012).

[3] Atalay, E., Özalp, O., Erol, M. A., Bilgin, M., and Yildirim, N., "A combined biomechanical and tomographic model for identifying cases of subclinical keratoconus," *Cornea* **39**(4), 461–467 (2020).

[4] Ramm, L., Herber, R., Spoerl, E., Raiskup, F., Pillunat, L. E., and Terai, N., "Intraocular pressure measurement using ocular response analyzer, dynamic contour tonometer, and scheimpflug analyzer corvis st," *Journal of ophthalmology* **2019** (2019).

[5] Matsuura, M., Hirasawa, K., Murata, H., Yanagisawa, M., Nakao, Y., Nakakura, S., Kiuchi, Y., and Asaoka, R., "The relationship between corvis st tonometry and ocular response analyzer measurements in eyes with glaucoma," *PLoS One* **11**(8), e0161742 (2016).

[6] Baum, O. I., Sobol, E. N., Bolshunov, A. V., Fedorov, A. A., Khomchik, O. V., Omelchenko, A. I., and Shcherbakov, E. M., "Microstructural changes in sclera under thermo-mechanical effect of 1.56 μm laser radiation increasing transscleral humor outflow," *Lasers in surgery and medicine* **46**(1), 46–53 (2014).

[7] Baum, O., Wachsmann-Hogiu, S., Milner, T., and Sobol, E., "Laser-assisted formation of micropores and nanobubbles in sclera promote stable normalization of intraocular pressure," *Laser Physics Letters* **14**(6), 065601 (2017).

[8] Olga, B., Georgy, Z., Andrej, B., Aleksey, Y., Alexander, O., Maria, O., and Emil, S., "Laser effect on paralimbal and trabecular zones of the eye enchases hydraulic conductivity of the sclera toward normalization of the intraocular pressure," *Journal of Biomedical Photonics & Engineering* **3**(1) (2017).

[9] Baum, O. I., Yuzhakov, A. V., Bolshunov, A. V., Siplivyi, V. I., Khomchik, O. V., Zheltov, G. I., et al., "New laser technologies in ophthalmology for normalisation of intraocular pressure and correction of refraction," *Quantum electronics* **47**(9), 860 (2017).

[10] Murgatroyd, H. and Bembridge, J., "Intraocular pressure," *Continuing Education in Anaesthesia, Critical Care and Pain* **8**(3), 100–103 (2008).

[11] Gokul, A., Vellara, H. R., and Patel, D. V., "Advanced anterior segment imaging in keratoconus: a review," *Clinical & experimental ophthalmology* **46**(2), 122–132 (2018).

[12] Thomas, B. J., Galor, A., Nanji, A. A., El Sayyad, F., Wang, J., Dubovy, S. R., Joag, M. G., and Karp, C. L., "Ultra high-resolution anterior segment optical coherence tomography in the diagnosis and management of ocular surface squamous neoplasia," *The ocular surface* **12**(1), 46–58 (2014).

[13] Zaitsev, V. Y., Matveyev, A. L., Matveev, L. A., Gelikonov, G. V., Omelchenko, A. I., Baum, O. I., Avetisov, S. E., Bolshunov, A. V., Siplivy, V. I., Shabanov, D. V., et al., "Optical coherence elastography for strain dynamics measurements in laser correction of cornea shape," *Journal of biophotonics* **10**(11), 1450–1463 (2017).

[14] Baum, O. I., Zaitsev, V. Y., Yuzhakov, A. V., Sviridov, A. P., Novikova, M. L., Matveyev, A. L., Matveev, L. A., Sovetsky, A. A., and Sobol, E. N., "Interplay of temperature, thermal-stresses and strains in laser-assisted modification of collagenous tissues: Speckle-contrast and oct-based studies," *Journal of biophotonics* **13**(1), e201900199 (2020).

[15] Briers, D., Duncan, D. D., Hirst, E. R., Kirkpatrick, S. J., Larsson, M., Steenbergen, W., Stromberg, T., and Thompson, O. B., "Laser speckle contrast imaging: theoretical and practical limitations," *Journal of biomedical optics* **18**(6), 066018 (2013).

[16] Boas, D. A. and Dunn, A. K., "Laser speckle contrast imaging in biomedical optics," *Journal of biomedical optics* **15**(1), 011109 (2010).

[17] Neganova, A. Y., Postnov, D. D., Jacobsen, J. C. B., and Sosnovtseva, O., "Laser speckle analysis of retinal vascular dynamics," *Biomedical optics express* **7**(4), 1375–1384 (2016).

[18] Postnov, D. D., Holstein-Rathlou, N.-H., and Sosnovtseva, O., "Laser speckle imaging of intra organ drug distribution," *Biomedical optics express* **6**(12), 5055–5062 (2015).

[19] Abdurashitov, A. S., Lychagov, V. V., Sindeeva, O. A., Semyachkina-Glushkovskaya, O. V., and Tuchin, V. V., "Histogram analysis of laser speckle contrast image for cerebral blood flow monitoring," *Frontiers of Optoelectronics* **8**(2), 187–194 (2015).

[20] Postnov, D. D., Sosnovtseva, O., and Tuchin, V. V., "Improved detectability of microcirculatory dynamics by laser speckle flowmetry," *Journal of biophotonics* **8**(10), 790–794 (2015).

[21] Abdurashitov, A., Bragina, O., Sindeeva, O., Sindeev, S., Semyachkina-Glushkovskaya, O. V., and Tuchin, V. V., "Off-axis holographic laser speckle contrast imaging of blood vessels in tissues," *Journal of biomedical optics* **22**(9), 091514 (2017).

[22] Hajjarian, Z., Nia, H. T., Ahn, S., Grodzinsky, A. J., Jain, R. K., and Nadkarni, S. K., "Laser speckle rheology for evaluating the viscoelastic properties of hydrogel scaffolds," *Scientific reports* **6**(1), 1–12 (2016).

[23] Yuzhakov, A. V., Sviridov, A. P., Baum, O. I., Shcherbakov, E. M., and Sobol, E. N., "Optical characteristics of the cornea and sclera and their alterations under the effect of nondestructive 1.56-μm laser radiation," *Journal of Biomedical Optics* **18**(5), 058003 (2013).