Title Page

Title: Diurnal variation of corneal tangent modulus in normal Chinese

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Conflict of Interest

Prof. David C.C. Lam has a patent WO2012163080 A1 pending to The Hong Kong University of Science and Technology (HKUST).

Keywords

Corneal biomechanics, tangent moudulus, stiffness, diurnal variation

Disclosure of funding

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Diurnal variation of corneal tangent modulus in normal Chinese

Abstract

Purpose. The aim of this study was to investigate the diurnal variation of corneal tangent modulus, measured using a novel corneal indentation device, in healthy Chinese subjects.

Methods. The central corneal thickness (CCT), mean central corneal radius (meanK), intraocular pressure (IOP), and corneal stiffness of 25 young adults aged 21-25 years (23.0 ± 1.0 years) were measured at 3-hour intervals from 09:00 to 21:00 in the course of 1 day. Corneal tangent modulus was calculated on the basis of corneal stiffness, CCT and meanK. Repeated-measures analyses of variance were performed to compare the diurnal changes in ocular parameters over time.

Results. Significant diurnal variations were observed in CCT and IOP ($p < 0.001$ and $p = 0.025$, respectively). Both parameters showed a decreasing trend throughout the day. MeanK and corneal stiffness did not show any significant diurnal changes ($p = 0.251$ and $p = 0.516$, respectively). Mean corneal tangent modulus across all measurements was 0.047 ± 0.085 MPa, and its diurnal rhythm ranged from 0.469 to 0.485 MPa. The variation was nonsignificant ($p = 0.526$).

Conclusion. The elastic properties of the cornea in healthy Chinese subjects were stable during wake time. The current study shows that the corneal indentation device obtains stable corneal biomechanics similar to other clinical device obtained. Future studies investigating the differences in corneal biomechanics among patients with various ocular conditions are warranted.

Introduction

It is conceivable that most anatomical and physiological parameters of the human eye exhibit diurnal variation. Investigations on corneal thickness and intraocular pressure (IOP) are well documented because of the ease of measurement with current clinical devices.[1-4] Knowledge about the daily fluctuations of these parameters is crucial for both clinical and scientific purposes such as predicting the risk of glaucoma progression and designing interventional studies.[5,6]

Corneal biomechanics describes the mechanical behavior of the cornea. It has been shown to induce measurement error by tonometry[7] and is associated with corneal diseases[8,9] and treatment.[10] Clinical studies on corneal biomechanics have been accelerated since the launch of two non-contact tonometers, the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Buffalo, NY) and the Corvis ST (Oculus, Wetzlar, Germany).

The ORA provides two empirically derived measurements, namely corneal hysteresis (CH), and corneal resistance factor (CRF). These 2 terms are not standard descriptions of material properties. Thus, they should be interpreted cautiously under controlled measurement conditions.[11-13]

Most studies have revealed no significant diurnal change for CH,[14-18] although 2 studies have reported that CH and CRF were elevated on awakening.[19,20] Upon the weakness of CH and CRF to detect diseased and surgically treated corneas, new waveform parameters are proposed by the manufacturer for further investigation.[21,22] The Corvis ST provides direct corneal deformation parameters, however, their repeatability are not satisfactory.[23-25] Until recently, no study has investigated the diurnal variation of the Corvis ST parameters. Some researchers performed Corvis measurements within a short duration to avoid the influence of diurnal variation.[26,27]

Elastic (Young's) modulus is the standard terminology describing the mechanical behavior of materials, which is calculated from stress (force per unit area) over strain (displacement per unit length). A higher elastic modulus indicates that the material is stiff. Elastic modulus remains constant in metals. It changes according to stress level in biological tissues. Thus, tangent modulus (an instantaneous slope at a specific stress) is used to represent the elastic properties of the cornea (supplemental digital content, graph 1).[28]

A novel corneal indentation device (CID) was developed to measure corneal biomechanics *in vivo*.[29] The CID measures the force (load) required to deform the cornea to a certain depth. A new parameter, corneal tangent modulus, was derived from a series of shell theory equations modeling the corneal deformation caused by corneal indentation. The device has been validated with a universal testing machine by using porcine eyes *ex vivo* and rabbit eyes *in vivo*.[29] A repeatability test on human subjects was established.[30] Before the CID is introduced in clinical studies, the diurnal variation of corneal tangent modulus requires careful investigation. The aim of current study was to determine the diurnal variation of corneal tangent modulus in healthy Chinese subjects during wake time.

Methods

Twenty-five healthy Chinese adults were recruited (17 men and 8 women). All subjects had unremarkable general and ocular health. Exclusion criteria included refractive sphere lower than -6.00 D, refractive cylinder higher than 2.00 D, rigid lens wear, current pregnancy, and history of refractive surgery or eye disease. Soft lens wearers were required to cease wearing lenses for 1 week before data collection. The study protocol was reviewed and approved by the ethics review board of Hong Kong Polytechnic University in accordance with the Declaration of Helsinki. Written consent was obtained from each subject. One eye was randomly selected where both eyes were eligible for the study.

The sequence of data collection proceeded as follows. The central corneal thickness (CCT) and mean central corneal radius (meanK) were measured using a corneal topographer (Pentacam; Oculus, Wezlar, Germany). Each subject was asked to fixate on an internal target while the measurement was automatically completed within 2 seconds after fixation alignment. A 25-image mode was used and 3 valid images were captured in which the Quality Specification (QS) indicated “OK”.

The CID was prepared as reported elsewhere.[30] In general, it was used on a slit-lamp unit (supplemental digital content, photo 1) with a foot switch connected to it. Following corneal anaesthesia by one drop of 0.4% Benoxinate, the indenter was moved toward the corneal center (supplemental digital content, photo 1) until a low pitch signal sounded, which indicated a stable pre-load at 0.001-0.1 N. When the foot switch was pressed, the indenter was actuated forward at 12 mm/s to indent the cornea to 1-mm depth and retracted immediately. The entire indentation process was completed in approximately 0.2 seconds. A valid measurement featured a smooth and linear load-displacement curve shown on the screen.[30] The CID measured corneal stiffness, which was the slope within a 0.3 to 0.6 mm corneal displacement. Three readings were recorded. Because corneal biomechanics depends on IOP,[29] Goldmann applanation tonometry (GAT) was performed immediately after the CID measurement. Two readings (GAT-IOP) were taken and the mean result was used for the analysis.

Determining corneal tangent modulus ($E|_{IOP}$) at a specific IOP involved substituting the raw data, including CCT, meanK and corneal stiffness ($S|_{IOP}$) into the generalized equation,

$$\mathrm{E}|_{\mathrm{IOP}} = \frac{a(r-t/2)\sqrt{1-\nu^2}}{t^2} \times \mathrm{S}|_{\mathrm{IOP}}\ ,$$ [29]

where *t* is the CCT, *r* is the meanK, *v* is the Poisson's ratio of the cornea and *a* is a geometry constant. The derivation of this geometry constant was discussed in our previous paper[30] and it is linearly related to *μ*, where *μ* is determined by

$$\mu = r_o \left[\frac{12\left(1-\nu^2\right)}{\left(r-{}^{t}/_{2}\right)^2 t^2}\right]^{1/4} .$$ [31]

The radius of a circular flat-surface indenter that is in full contact with the cornea is denoted as r_0.

The above data collection was repeated at 3-hour intervals from 09:00 to 21:00 over the course of 1 day, with a 30-minute tolerance before and after the scheduled time. Specifically that was from 8:30 to 9:30, 11:30 to 12:30, 14:30 to 15:30, 17:30 to 18:30 and 20:30 to 21:30.

Treatment of data

After data collection, for each subject, the means of all ocular parameters at all time points were calculated. The distributions of CCT, meanK, IOP, corneal stiffness and corneal tangent modulus did not differ significantly from a normal distribution (Shapiro-Wilk tests, $p > 0.05$). Hence, repeated-measures analyses of variance (ANOVA) were performed to compare the changes over time. In instances of significant differences, paired *t*-tests with Bonferroni adjustment were used for post-hoc comparisons. Correlations between IOP and the corneal properties in each session were investigated using Pearson bivariate correlations. Data analysis and graphical presentation was conducted using IBM SPSS version 23 (SPSS, IL, USA) and GraphPad Prism 5 (GraphPad Software, Inc., CA, USA), respectively. The statistical power was computed using G-power version 3.1.7 (Franz Faul, Universität Kiel, Germany).

Results

The mean ± standard deviation (SD) age of the subjects was 23.0 ± 1.0 years (range from 21 to 25 years) and the mean spherical equivalent refractive error was -2.53 ± 2.21 D (-6.38 D to +0.88 D). Table 1 summarizes the mean values for all parameters from the sessions, revealing significant reductions in CCT ($F(4, 96) = 15.772$, $p < 0.001$) and IOP ($F(4, 96) = 2.913$, $p = 0.025$). The maximum CCT, which was observed at 09:00, was significantly higher than the CCT at all subsequent visits (paired t-tests, $p < 0.001$) (Figure 1). Although IOP showed a decreasing trend during the day, the readings between the early morning and other sessions were not significant ($p > 0.05$) (Figure 2). A stable meanK was maintained ($F(4, 96) = 1.369$, $p = 0.251$) (Figure 2). Two corneal biomechanical parameters, corneal stiffness ($F(4, 96) = 0.819$, $p = 0.516$) and corneal tangent modulus ($F(4, 96) = 0.803$, $p = 0.526$), did not demonstrate significant diurnal patterns (Figures 3) during the day. IOP was not significantly correlated with CCT, meanK and corneal tangent modulus across all measurement sessions ($-0.160 < r < 0.344$, all $p > 0.05$).

Upon the observed sample effect size of 0.18 and correlation of 0.8 among repeated measures on corneal tangent modulus, 96% power was achieved with alpha at 0.05 when sphericity was assumed.

Discussion

Corneal stiffness is dependent on corneal geometry and IOP. The diurnal changes of CCT during matched time period agreed with those reported in previous studies.[1,4] The meanK remained stable consistently.[1,20] Although CCT varied by a mean of 10 µm throughout the study, such negligible changes did not lead to significant variations in corneal stiffness. Diurnal IOP variations have been extensively reviewed using various types of tonometers.[1-4,20] It was reported that the magnitude of IOP changes between 09:00 and 21:00 was negligible (within 2 mmHg). Likewise, we found insignificant reduction of GAT-IOP from a mean value of 13.1 mmHg at 09:00 to 11.9 mmHg at 21:00, which warranted a stable corneal stiffness.

We confirmed no significant diurnal rhythm in corneal tangent modulus during wake time, which indicated that the cornea exhibits stable elastic properties. Mean corneal tangent modulus for all measurements across all sessions was 0.474 ± 0.085 MPa under a mean IOP of 12.3 mmHg, and the daily variation was between 0.469 and 0.485 MPa. Leung and coworkers[32] measured corneal tangent modulus in glaucoma patients and obtained a higher reading of 0.63 ± 0.11 MPa (range between 0.41 and 0.89 MPa). Their glaucoma patients were expected to have higher modulus values because of a higher mean IOP (18.5 mmHg). Corneal tangent modulus is positively associated with IOP.[29] When the IOP increased, the measured corneal tangent modulus increased. To facilitate between-group comparison, corneal tangent modulus should be normalized to a common IOP reference value. In our previous repeatability study, corneal tangent modulus in each subject was normalized to 15.5 mmHg (the mean IOP of healthy human eyes).[30] In the current study, the IOP of subjects decreased during the day, with a range of variation of 2 mmHg. We did not normalize the CID results by using a single IOP value. Doing so would have been inappropriate because our subjects' IOP varied throughout the study diurnally. We attempted to normalize corneal tangent modulus by using a mean IOP of 15.5 mmHg and diurnal variation of 2 mmHg; the magnitudes still remained stable from 09:00 to 21:00 (Appendix). Corneal biomechanics could vary in elderly and in subjects with highly myopic eyes.[33-36] The subject group in the current study was homogeneous in terms of narrow ranges of age and refractive error.

The commonly used corneal biomechanical parameters, CH and CRF, did not show significant diurnal variation when the measurement time was matched with the current study.[14-19] However, CH and CRF represent different mechanical meanings than the corneal tangent modulus. They are viscoelastic parameters with a combined effect of elasticity and viscosity.[11] A theoretical model illustrated that a high CH could be associated with low or high corneal elasticity, depending on the viscosity.[13] Therefore a higher CH does not necessarily represent a stiff cornea (i.e. higher elastic modulus), which renders interpretation difficult. Furthermore, significant correlations of CH and CRF with CCT have been reported.[35,37,38] Thus, corneal geometry confounds these viscoelastic measurements. The CID was designed to measure the elastic regimen of human cornea. Experimentally, the cornea behaved as if it were purely elastic when the rate of corneal indentation was manipulated above the threshold value.[29] Therefore, the cornea is considered stiffer when a higher corneal tangent modulus is obtained. Notably, calculation of corneal tangent modulus incorporates individual variations of corneal thickness and radius. Hence, the influence of corneal geometry is compensated and corneal tangent modulus is solely affected by IOP.

Because of the complexity of corneal microstructure, the generalized equations assume that the cornea is spherical and of uniform thickness. Individual IOP was estimated by GAT, which is known to deviate from the true IOP and depends on corneal properties.[7] The GAT-IOP did not associate with CCT, meanK or corneal tangent modulus in our group of subjects. Diurnal variation of the true IOP is believed to exist and vary in the same manner as in GAT-IOP, which has been observed in studies involving tonometers that are less sensitive to corneal properties.[2-4] Thus, the normalization process does not provide absolute modulus values unless the true IOP is known. Our investigation was limited to wake time assessment and to the corneas of healthy young adults. However, on the basis of previous studies on CH,[15,19] we do not anticipate any significant change in corneal tangent modulus over 24 hours. To explore the clinical usefulness of the CID, further studies ought to involve groups with different corneal and ocular conditions.

The fundamental corneal deformation parameters in the Corvis ST may be better than CH and CRF in delineating corneal biomechanics.[39] Some studies found that keratoconus,[40,41] corneas of glaucomatous eyes,[42] or corneas after different types of refractive surgery[27,43] showed different deformation patterns. One limitation of the Corvis ST is the lack of information about the conventional stress and strain measurement, in which the CID is measuring.

To conclude, the elastic properties of the cornea in healthy Chinese subjects were stable during wake time. Corneal tangent modulus measures the intrinsic material stiffness of human cornea at a specific IOP value. Our group is currently investigating the change of corneal tangent modulus in eyes undergoing corneal reshaping therapy. Other studies such as change of corneal tangent modulus in corneal refractive surgeries are also important.

Disclosure

The corneal indentation device is patented by The Hong Kong University of Science and Technology. The authors report no conflicts of interest in any devices used in the study.

Appendix

Corneal tangent modulus was normalized using a mean IOP of 15.5 mmHg[30] and an IOP variation of 2 mmHg between 09:00 and 21:00 (Table 2).[2-4] Normalized corneal tangent modulus (E_n) was calculated using the following equation,

$$E_n = \frac{\mathrm{E}|_{\mathrm{IOP}}}{GAT-IOP} \times mean\ IOP\ ,$$

where $E|_{IOP}$ was determined by the CID at a specific GAT IOP. Table 2 shows the normalized data across all sessions. No significant difference was observed ($F(4, 96) = 1.284$, $p = 0.282$) and the mean value throughout the day was 0.619 ± 0.166 MPa (Figure 4).

Supplemental Digital Content

Graph 1. Definition of mechanical terms. *Left:* A constant stress-strain relationship in material like metals. Elastic modulus is defined as the slope on the stress-strain curve. *Right:* Biological tissues exhibit nonlinear stress-strain relationship. Tangent modulus is defined as an instantaneous slope on the stress-strain curve.

Photo 1. View of the corneal indentation device (CID). *Left:* Positioning the CID on a slit-lamp unit. Right: Positioning the indenter prior to corneal stiffness measurement.

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Figure Legends

Figure 1. Mean and standard deviation of central corneal thickness (CCT) over time. ★Indicates significant difference in post-hoc test. Each error bar indicates 1 standard deviation.

Figure 2. Mean and standard deviation of intraocular pressure (IOP) and central corneal radius over time. Each error bar indicates 1 standard deviation.

Figure 3. Mean and standard deviation of corneal stiffness and corneal tangent modulus (*E*) over time. Each error bar indicates 1 standard deviation.

Figure 4. Mean and standard deviation of normalized corneal tangent modulus (E_n) over time. Each error bar indicates 1 standard deviation.

Tables

Table 1. Mean and standard deviation of ocular parameters measured throughout the study period.

Time	CCT/μm (SD)	meanK/mm (SD)	IOP/mmHg (SD)	S/Nmm^{-1} (SD)	E/MPa (SD)
9:00	564 (30)	7.89 (0.30)	13.1 (2.0)	0.063 (0.010)	0.475 (0.094)
12:00	556 (30)	7.90 (0.30)	12.3 (2.5)	0.062 (0.008)	0.472 (0.074)
15:00	556 (31)	7.89 (0.31)	11.9 (2.2)	0.061 (0.007)	0.471 (0.079)
18:00	555 (32)	7.90 (0.31)	12.2 (2.2)	0.061 (0.008)	0.469 (0.091)
21:00	554 (30)	7.90 (0.30)	11.9 (2.3)	0.063 (0.007)	0.485 (0.086)
Mean	557	7.89	12.3	0.062	0.474
SD	31	0.30	2.2	0.008	0.085
***P*[a]**	<0.001[b]	0.251	0.025[b]	0.516	0.526

CCT = central corneal thickness; meanK = mean central corneal radius; IOP = intraocular pressure; S = corneal stiffness; E = corneal tangent modulus; SD = standard deviation

[a]Significance of the F statistic from repeated-measures ANOVA.

[b]Significant effect within sessions.

Table 2. Mean and standard deviation of normalized corneal tangent modulus at various IOP values.

Time	IOP/mmHg	Normalized E/MPa (SD)
9:00	16.5	0.612 (0.153)
12:00	16.0	0.633 (0.141)
15:00	15.5	0.635 (0.177)
18:00	15.0	0.594 (0.153)
21:00	14.5	0.622 (0.206)
Mean	/	0.619
SD	/	0.166
P^a	/	0.282

IOP = intraocular pressure; E = corneal tangent modulus; SD = standard deviation

[a]Significance of the F statistic from repeated-measures ANOVA.

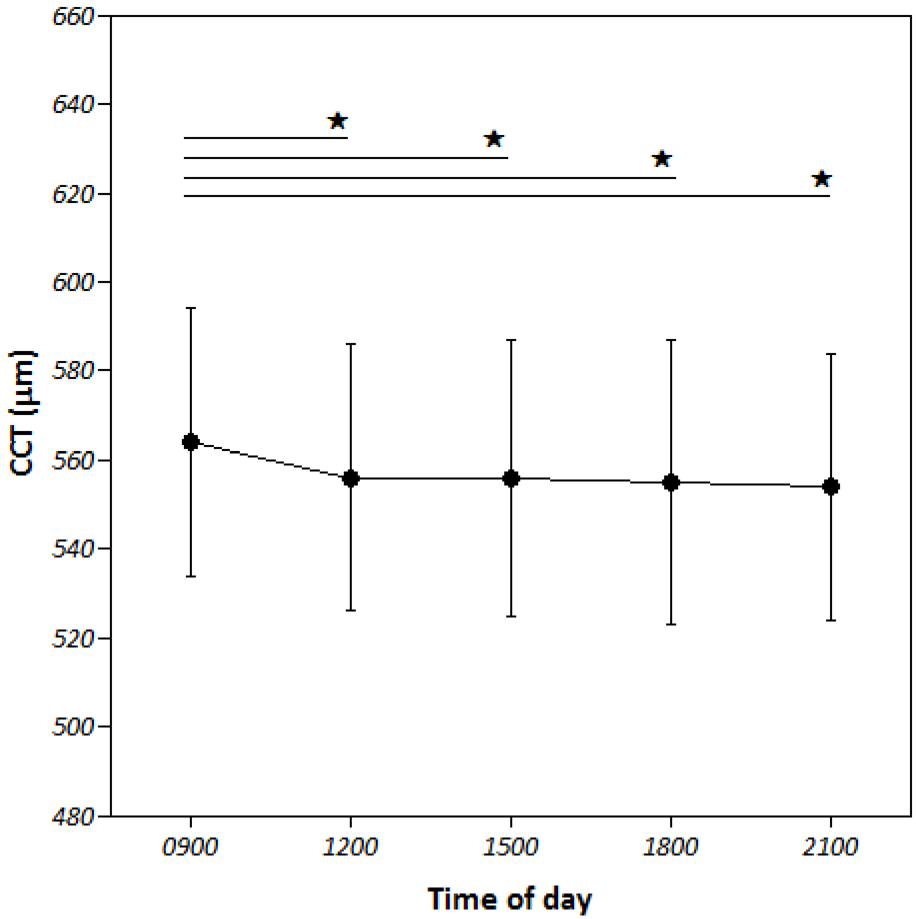

660
640
620
600
580
560
540
520
500
480
CCT (µm)
0900
1200
1500
1800
2100
Time of day

Figure 1

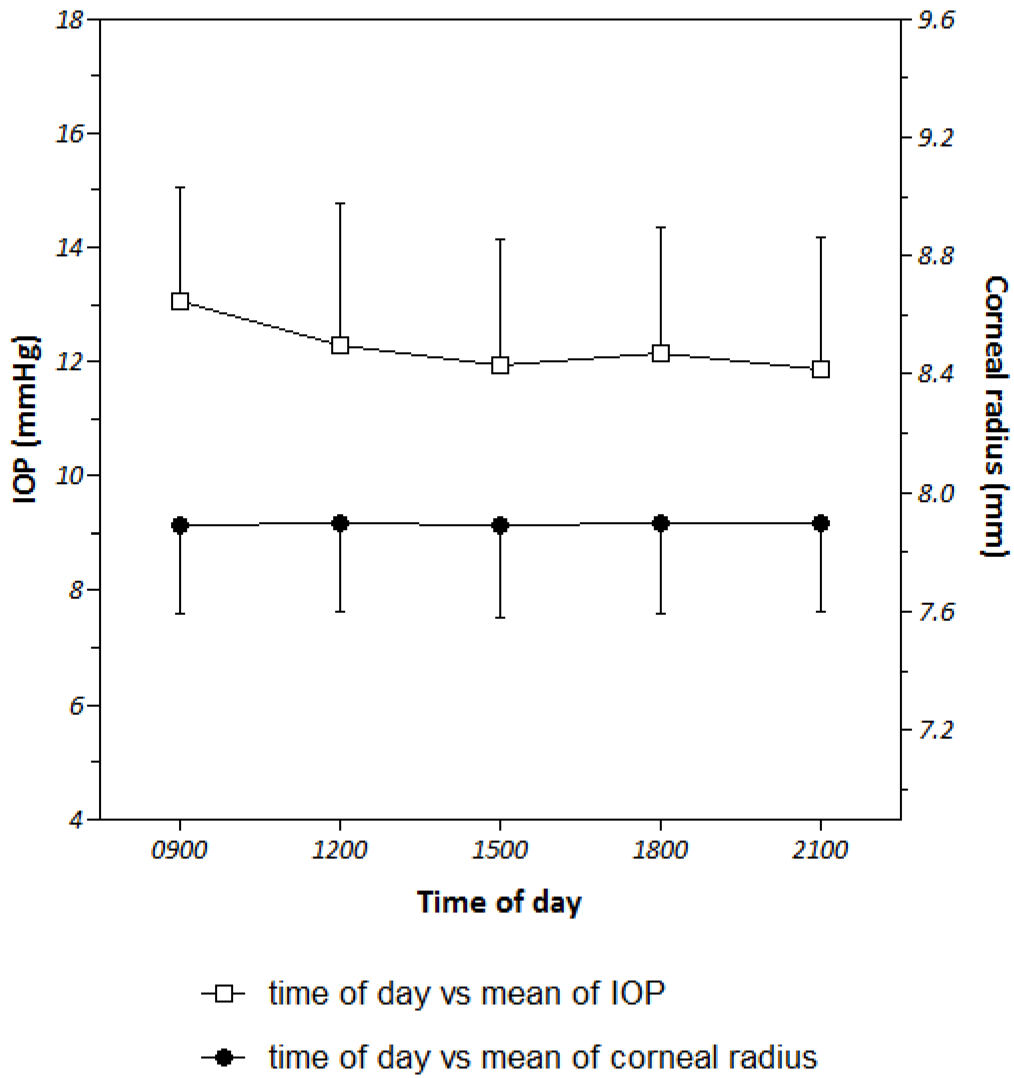
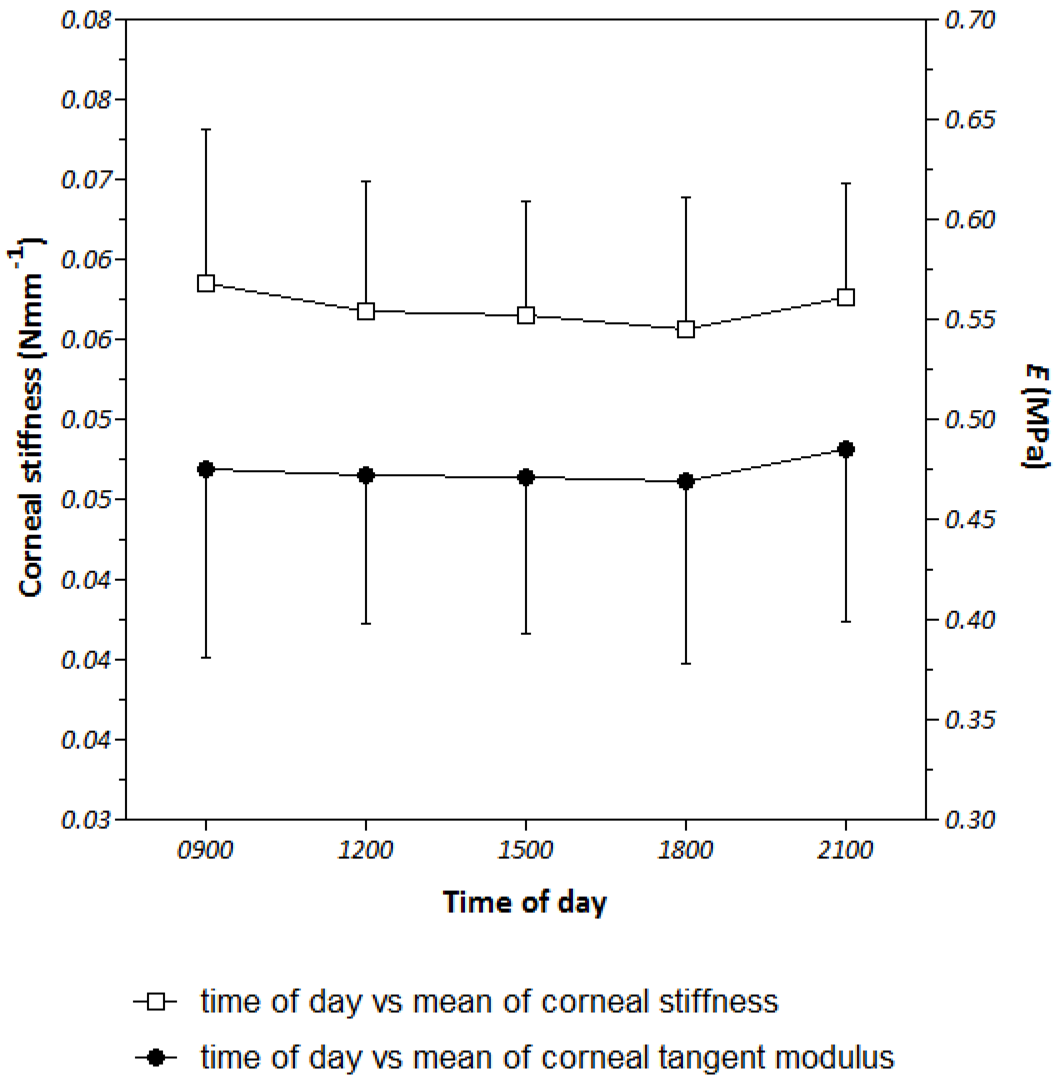

18
16
14
12
10
8
6
4
IOP (mmHg)
9.6
9.2
8.8
8.4
8.0
7.6
7.2
Corneal radius (mm)
0900
1200
1500
1800
2100
Time of day
time of day vs mean of IOP
time of day vs mean of corneal radius

Figure 2



0.08
0.08
0.07
0.06
0.06
0.05
0.05
0.04
0.04
0.04
0.03
Corneal stiffness (Nmm^{-1})
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
E (MPa)
0900
1200
1500
1800
2100
Time of day
time of day vs mean of corneal stiffness
time of day vs mean of corneal tangent modulus

Figure 3

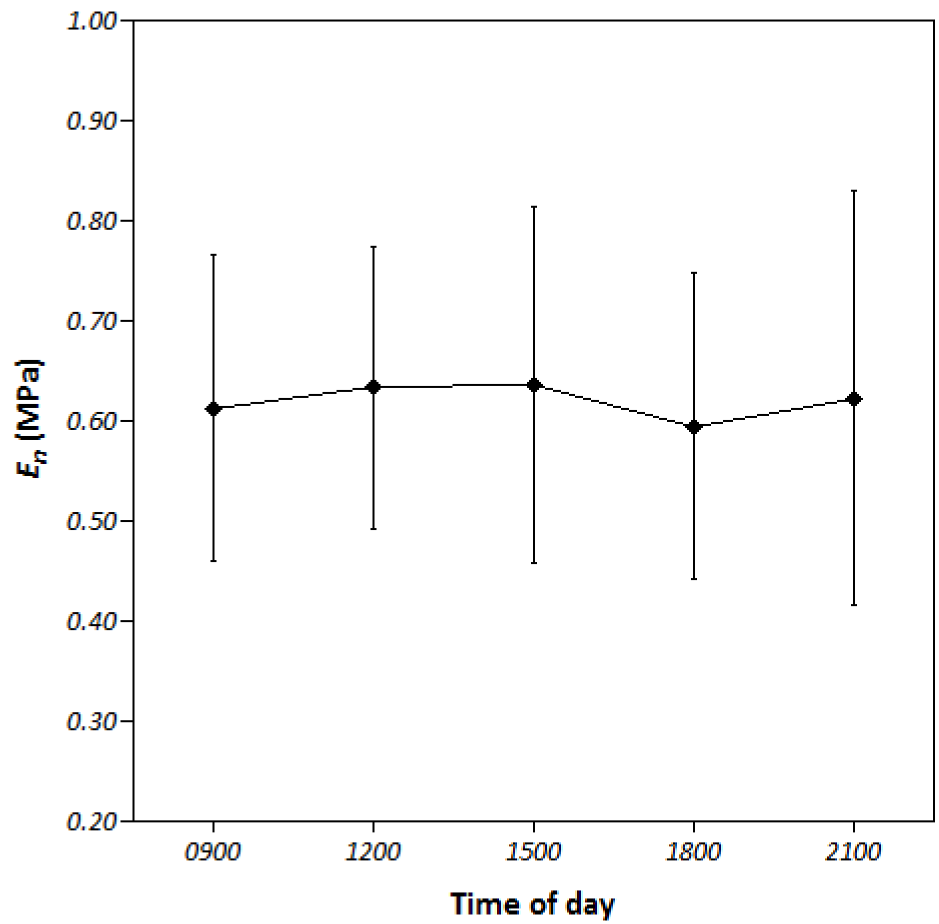

1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
E_n (MPa)
0900
1200
1500
1800
2100
Time of day

Figure 4