Effect of 24-Hour Corneal Biomechanical Changes on Intraocular Pressure Measurement

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PURPOSE. To study 24-hour changes of corneal biomechanical properties and their influences on measurement of intraocular pressure (IOP).

METHODS. Fifteen healthy young volunteers (age range, 20–25 years) were housed for 1 day in a sleep laboratory. Sitting and supine central corneal thickness (CCT) were measured every 2 hours with an ultrasonic pachymeter. Sitting IOP and corneal hysteresis, an indicator of viscoelasticity, were measured with a noncontact tonometer.

RESULTS. There were consistent 24-hour variations of CCT and IOP for the group. Nocturnal mean CCT and nocturnal mean IOP were significantly higher than the diurnal mean CCT and diurnal mean IOP, respectively. The peak CCT occurred at 1:30 to 5:30 AM and the trough CCT at 1:30 PM. The peak IOP occurred at 5:30 AM and the trough IOP at 9:30 PM. Cosine fits of each subject’s 24-hour CCT and IOP data showed synchronized rhythms. The phase timing of 24-hour CCT rhythm was significantly earlier than the phase timing of 24-hour IOP rhythm. Twenty-four-hour variation of corneal hysteresis was inconsistent and cosine fits of 24-hour data of corneal hysteresis did not display a 24-hour rhythm.

CONCLUSIONS. In healthy young adults, CCT was thicker, and IOP was higher during the nocturnal period than during the diurnal period. Nocturnal peak CCT occurred a few hours earlier than did nocturnal peak IOP. The twenty-four-hour change in corneal viscoelasticity was not significant. There was no evidence that the 24-hour change in IOP was due to the change in corneal biomechanical properties. (Invest Ophtalmol Vis Sci. 2006;47:4422–4426) DOI:10.1167/ios.06-0507

Diurnal variation of intraocular pressure (IOP) is an important consideration in the diagnosis and treatment of glaucoma. We have described 24-hour variations of IOP in various groups of experimental subjects housed in a sleep laboratory. Most noninvasive methods of IOP measurement, including the pneumotonometry used in our previous studies, can be influenced by corneal biomechanical properties that may not remain constant throughout 24 hours. One example is the swelling of the cornea at night due to a higher hydration state. Previous in vitro studies have indicated that tonometric readings can be negatively correlated with central corneal thickness (CCT) when the corneal hydration increases in individual eyes. However, a thicker CCT is usually associated with a higher IOP in cross-sectional comparisons of different eyes. It is not clear whether a daily time-dependent change in corneal thickness affects the 24-hour IOP measurement in vivo in an individual eye. Effects of other in vivo corneal biomechanical changes on the 24-hour IOP measurement are not known due to the inability to measure corneal biomechanical properties during tonometry.

The noncontact tonometer is reliable for measuring IOP within the normal range. A recent advance of noncontact tonometry showed that an indicator of corneal viscoelasticity, corneal hysteresis, can be monitored during the IOP measurement. Corneal viscoelasticity varies in different eyes; there is a positive correlation between CCT and corneal hysteresis. Although the clinical implication of corneal hysteresis is not clear, corneal hysteresis represents at least a portion of the biomechanical influence on IOP when using the noncontact tonometer. Conversely, an instant elevation of IOP using an ophthalmodynamometer did not alter corneal hysteresis. This indicated no secondary influence of IOP on this indicator of corneal viscoelasticity. In the present study, we collected 24-hour data of CCT, IOP, and corneal hysteresis from a group of healthy young adults to study time-dependent changes in corneal biomechanical properties and their influences on the 24-hour measurement of IOP as an unwanted artifact.

METHODS

The study adhered to the tenets of the Declaration of Helsinki and was approved by our Institutional Review Board. Fifteen healthy, nonsmoking, young volunteers (6 men and 9 women) were recruited from university students and local residents. They were selected for having a regular daily sleep cycle close to 11 PM to 7 AM. Informed consent was obtained after explanation of the nature and possible risks of the study. These were six Hispanic, five white, and four Asian participants. The mean age was 22.1 ± 1.9 years (mean ± SD); range, 20–25 years. Each candidate had a complete ophthalmologic examination during office hours demonstrating absence of any eye disease and remarkable refractive disorder. The mean CCT, IOP, refractive state, and axial length were 551.0 ± 37.9 μm, 14.7 ± 2.9 mm Hg, −0.70 ± 1.14 D, and 23.45 ± 0.84 mm, respectively.

Participants were instructed to maintain a daily 8-hour sleep period for 7 days before the laboratory recordings. This assigned sleep period was similar to the individual’s regular sleep cycle. Each subject wore a wrist monitor (Activwatch; Mini Mitter, Sunriver, OR) for light exposure and physical activity and kept a wake–sleep log. The week of wake–sleep synchronization was confirmed by these data. The subjects were instructed to abstain from alcohol and caffeine for 3 days before the laboratory study.

The subjects arrived at the laboratory at approximately 2 PM and stayed in individual studio apartments for 24 hours. Light intensity in the laboratory was held constant during the 16-hour diurnal/wake period at 500 to 1000 lux at eye level when standing. The 8-hour period of darkness in the subject’s apartment was adjusted to correspond to each individual’s sleep period. Times for measurements were individualized to coordinate with this sleep period. For presentations, the corresponding clock times were aligned as if each subject had an assigned sleep period from 11 PM to 7 AM.

Measurements of CCT, IOP, corneal hysteresis, blood pressure, and heart rate were taken every 2 hours by experienced researchers. Blood
pressure and heart rate were measured in both sitting and supine body positions with an automated wrist blood pressure monitor (Model HEM-608; Omron Vernon Hills, IL) before the ocular measurements. For bilateral ocular measurements, 1 or 2 drops of 0.5% proparacaine were applied as a local anesthetic. CCT was measured in the sitting and supine body positions with an ultrasonic pachymeter (model 550; DGH Technology, Exton, PA). The recorded CCT was the average of three consecutive measurements. IOP and corneal hysteresis were measured with a noncontact tonometer (Ocular Response Analyzer; Reichert Ophthalmic, Depew, NY) that can take measurements only in subjects in the sitting position. IOP and corneal hysteresis were determined by the tonometer. During the measurement, the instrument was automatically aligned. A rapid air impulse was applied to the cornea, and the deformation of the 3-mm central cornea was monitored electro-optically. The air impulse caused the cornea to move inward, past the first applanation stage, and into a slight concavity. When the air impulse recessed, the cornea moved outward, past the second applanation stage, and returned to its convex curvature. This process required approximately 20 ms. The viscous damping in the cornea caused difference delays in the inward and outward applanation events, producing two applanation pressure estimates. IOP was calculated as the average of the inward and outward applanation pressures. The difference between the inward and the outward applanation pressures was calculated as corneal hysteresis.21–23

Before the assigned sleep period, measurements were taken at 3:30, 5:30, 7:30, and 9:30 PM. The subjects were instructed to lie in bed for 5 minutes before the supine measurements of blood pressure, heart rate, and CCT. They then sat for 5 minutes before the measurements of blood pressure, heart rate, IOP, corneal hysteresis, and CCT. They were encouraged to continue their normal indoor activities. Food and water were freely available, and meal times were not regulated. Lights in individual sleep rooms were turned off at 11 PM. Nocturnal measurements were taken at 11:30 PM and 1:30, 3:30, and 5:30 AM. Dim room lights were turned on to assist in obtaining the measurements at night.5–7 The subjects were awakened if necessary, and the supine measurements were taken immediately. They then sat for 5 minutes before the sitting measurements. Lights were turned off after the measurements. Room activities were continuously videotaped with infrared cameras. When the assigned sleep period ended at 7 AM, room lights were turned back on to daytime level, and the subjects were awakened if necessary. Measurements were continued at 7:30, 9:30, and 11:30 AM, and 1:30 PM, as described earlier.

Data analyses were similar to those in previous studies.5–7 Mean blood pressure was calculated as the diastolic blood pressure plus one third of the difference between the systolic and the diastolic blood pressures. Calculations of CCT, IOP, and corneal hysteresis were performed separately for the right and left eyes. Means of each parameter (CCT, IOP, corneal hysteresis, mean blood pressure, and heart rate) in the group of subjects were calculated for each time point. The peaks and the troughs of the group means were determined. Statistical comparisons of the means were made between the peaks and the troughs and between the diurnal and the nocturnal periods, using paired t-tests. The criterion for statistical significance was P < 0.05.

Mathematical estimation of the 24-hour rhythm was performed for each parameter of CCT, IOP, and corneal hysteresis. Assuming that the 24-hour rhythm resembled a cosine profile, the best-fitting cosine curve was estimated by using data collected from each individual at the 12 time points. Each cosine curve had a fitted peak, the acrophase. The clock time of the acrophase represented the phase timing of the rhythm. The null hypothesis of a random distribution of 15 acrophases around the 24 hours was evaluated by using the Rayleigh statistical test.24 Lack of statistical significance indicated no synchronized 24-hour rhythm in this group of 15 subjects, whereas the alternative indication showed synchronized rhythm in the group. The amplitude (half the distance between the cosine-fit maximum and minimum) represented a parameter estimate of the variation for the 24-hour period. The acrophases for the 24-hour rhythm of sitting CCT and for

**Figure 1.** The 24-hour variations in CCT, IOP, and corneal hysteresis in healthy young adults. Measurements of CCT were obtained with an ultrasonic pachymeter and measurements of IOP and corneal hysteresis with a noncontact tonometer. Error bars, SEM (N = 15).

The 24-hour rhythm of IOP were compared by using the Wilcoxon signed-rank test for paired data. Linear regression was used to examine the association of CCT and corneal hysteresis. One kind of analysis was performed on the 15 pairs of CCT mean and corneal hysteresis mean collected from the individual subjects during the diurnal period, the nocturnal period, or the 24-hour period.21,22 The other kind of linear regression was performed for 12 pairs of time-dependent CCT and corneal hysteresis data collected from each subject.

**RESULTS**

There were consistent 24-hour change patterns in CCT and IOP in this group of 15 experimental subjects. The 24-hour profiles of right-eye CCT, IOP, and corneal hysteresis in the sitting position are presented in Figure 1. In the right eye, the average CCT was 553.0 ± 47.6 μm (mean ± SD) with the thinnest individual CCT being 477 μm and the thickest CCT 685 μm. The peak CCT of 564.5 μm was observed at both 1:30 and 5:30 AM, and the mean trough CCT of 544.8 μm was observed at 1:30 PM. The sitting peak and trough CCT in the left eye and the supine peak and trough CCT in either eye occurred at approximately the same clock times (data not shown). The fluctuations of CCT (peak minus trough) in individual right eyes ranged from 9 μm to 84 μm. The nocturnal mean CCT was significantly higher than the diurnal mean CCT in both the right and left eyes in either body position. For example, the diurnal mean CCT was 548.3 ± 45.9 μm and the nocturnal mean CCT was 562.6 ± 52.2 μm in the right eye in the sitting position (P < 0.01).

During the diurnal period, sitting IOP was higher in the morning and decreased progressively. There was a continuous
IOP increase during the nocturnal period. The lowest right-eye IOP was 6.2 mm Hg and the highest 29.1 mm Hg among all subjects. The mean sitting right-eye peak IOP was 16.8 ± 4.6 mm Hg at 5:30 AM, and the mean trough IOP was 12.2 ± 3.1 mm Hg at 9:30 PM (Fig. 1). The nocturnal mean IOP of 15.3 ± 2.9 mm Hg was significantly higher than the diurnal mean IOP of 13.4 ± 2.7 mm Hg (P < 0.01). Corneal hysteresis remained relatively constant for 24 hours in either eye (Fig. 1; right eye). The diurnal mean corneal hysteresis in the right eye was 11.9 ± 1.5 mm Hg, not statistically different from the nocturnal mean corneal hysteresis of 11.7 ± 1.9 mm Hg. Based on the SD of 1.0 mm Hg for the difference in mean corneal hysteresis between the diurnal and nocturnal periods, the statistical power was 0.82 for detecting a 0.8-mm Hg change in corneal hysteresis, when using the paired t-test and accepting a type I error of 0.05.

Cosine fits of CCT, IOP, and corneal hysteresis data were computed for each subject, and the acrophases and amplitudes were determined. The Rayleigh test detected synchronized group acrophases for 24-hour sitting and supine CCT (P < 0.001) and for the 24-hour sitting IOP (P < 0.01), but not for corneal hysteresis. The null hypothesis of a random distribution of phase timings for 24-hour change in CCT or IOP was rejected. The null hypothesis of a random distribution of phase timings for 24-hour corneal hysteresis was accepted, suggesting a lack of 24-hour rhythm. Acrophases and amplitudes for the 24-hour rhythms of sitting CCT and IOP in the right eye are presented in Figure 2. The mean acrophase for CCT was 2:10 AM ± 158 minutes and the mean amplitude was 10.6 ± 8.2 μm. The mean acrophase for IOP was 5:50 AM ± 254 minutes and the mean amplitude was 2.0 ± 1.0 mm Hg. When acrophases of sitting CCT and IOP were compared, the difference was statistically significant (P < 0.01). This result indicated that 24-hour rhythms of CCT and IOP in the sitting position had different phase timings.

Corneal hysteresis varied among different eyes. Linear regression analysis showed a positive correlation between 15 paired sitting mean CCTs and mean corneal hystereses in the right eye during the diurnal period (r = 0.760, P < 0.01), the nocturnal period (r = 0.717, P < 0.01), and the 24-hour period (r = 0.769, P < 0.001; Fig. 3). When linear regression was performed between the 12 paired time-dependent, sitting CCT and corneal hysteresis collected from the same individual, there was a significant correlation in only 1 of 15 individual right eyes (Table 1).

The nocturnal mean blood pressure and heart rate in the supine position were lower than the diurnal levels in the sitting position (P < 0.05), as observed previously in healthy young adults.7

**Discussion**

We collected 24-hour IOP data from a group of 15 healthy young adults by using a noncontact tonometer (Ocular Response Analyzer; Reichert Ophthalmic). The measurements showed a change pattern of 24-hour sitting IOP similar to that previously observed in healthy young adults.7 The peak IOP occurred at the end of the nocturnal period, and the trough IOP occurred at the end of diurnal period. During the nocturnal period, IOP continuously increased. The nocturnal mean IOP was significantly higher than the diurnal mean IOP. With the available 24-hour data of CCT and corneal hysteresis from the same subjects in the sitting position, the influence of these two corneal biomechanical parameters on the 24-hour profile of IOP could be examined.

As expected, CCT was found to be thicker during the nocturnal–sleep period than during the diurnal–wake peri-

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**Figure 2.** Estimated 24-hour rhythms of (A) central corneal thickness and (B) IOP in the sitting position. The clock time of the acrophase (phase timing) is shown with the amplitude in the radial scale (N = 15).

**Figure 3.** Linear regression showing a correlation (r = 0.769, P < 0.001) between the 24-hour means of CCT and corneal hysteresis in healthy young adults (N = 15).
Figure 1 shows that the 24-hour pattern of CCT was different from the 24-hour pattern of IOP in this group of experimental subjects. The troughs occurred at different diurnal time points. An increase of CCT occurred more rapidly in the early nocturnal hours. The peak CCT appeared a few hours earlier than the peak IOP when the CCT and IOP profiles were examined during the nocturnal period. In Figure 2, mathematical approximation shows different phase timings for the 24-hour rhythms of CCT and IOP. Thus, the time-dependent elevation of IOP cannot be explained by the time-dependent increase of CCT during the nocturnal period.

Compared with the Goldmann tonometer and the pneumatometer, the noncontact tonometer is more affected by CCT in cross-sectional population studies. One may assume that the potential effect of time-dependent CCT change on IOP can be larger when using the noncontact tonometer. In a previous study, it was estimated that, for a 10-μm difference in CCT, the IOP difference was 0.28 mm Hg with the Goldmann tonometer, 0.38 mm Hg with the pneumatometer, and 0.46 mm Hg with the noncontact tonometer. Based on these estimations and the assumption that corneal hydration at night had no damping effect on IOP, the diurnal-to-nocturnal CCT difference of 14.3 μm in the present study (Fig. 1) may be converted to an estimated difference in IOP of 0.66 mm Hg. We observed a much larger difference in IOP of 1.9 mm Hg between the diurnal and nocturnal period. Therefore, the contribution of increased CCT to the nocturnal elevation of IOP can be regarded as weak at most. In a previous study involving treated patients with glaucoma, the magnitudes of 24-hour fluctuations in CCT and IOP were examined. It was found that a small 24-hour CCT fluctuation could not account for the 24-hour IOP fluctuation.

Corneal hysteresis derives from characteristics in central corneal movement during the noncontact IOP measurement. This new indicator of corneal viscoelasticity may be related to the overall effect of corneal biomechanical properties on the IOP reading. We confirmed that there was a positive correlation between CCT and corneal hysteresis when considering paired data collected from different subjects (Fig. 3). However, no correlation between time-dependent data of CCT and corneal hysteresis was found in 14 of 15 individual subjects (Table 1). Despite an increase in CCT at night, individual corneal viscoelasticity did not change significantly, probably because the major change was only the corneal hydration state. Therefore, the 24-hour IOP pattern obtained using the noncontact tonometer was not associated with a change in corneal viscoelasticity and possibly other corneal biomechanical properties.

We conclude that there is no evidence that a 24-hour pattern of change in IOP in healthy young adults is significantly associated with a 24-hour change in known corneal biomechanical parameters. Although both CCT and IOP are higher during the nocturnal period than during the diurnal period, the nocturnal IOP elevation cannot be explained by the nocturnal increase in CCT when examining both the timing and the magnitude of the change. No significant 24-hour change in corneal viscoelasticity related to IOP measurement was detected with the noncontact tonometer (Ocular Response Analyzer; Reichert). Twenty-four-hour patterns of change in IOP observed in healthy young adults measured with the noninvasive tonometers in the present study and in our previous reports most likely represent true change patterns inside the globe. Whether this conclusion can be extended to 24-hour patterns of change in IOP in healthy older adults and in patients with glaucoma with a higher IOP should be investigated.

Acknowledgments

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References


Table 1. Strength of the Association between CCT and Corneal Hysteresis in Each Subject

<table>
<thead>
<tr>
<th>Subject</th>
<th>CCT Range (μm)</th>
<th>Corneal Hysteresis Range (mm Hg)</th>
<th>Regression Coefficient (Slope)</th>
<th>Correlation Coefficient (r)</th>
<th>P</th>
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<tbody>
<tr>
<td>1</td>
<td>477–507</td>
<td>6.1–9.4</td>
<td>−0.008</td>
<td>−0.070</td>
<td>0.850</td>
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<td>2</td>
<td>490–533</td>
<td>8.6–12.7</td>
<td>0.007</td>
<td>0.097</td>
<td>0.764</td>
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<tr>
<td>3</td>
<td>493–515</td>
<td>11.2–14.3</td>
<td>0.033</td>
<td>0.188</td>
<td>0.558</td>
</tr>
<tr>
<td>4</td>
<td>535–565</td>
<td>9.4–13.6</td>
<td>0.043</td>
<td>0.341</td>
<td>0.278</td>
</tr>
<tr>
<td>5</td>
<td>504–519</td>
<td>9.1–13.5</td>
<td>−0.142</td>
<td>−0.475</td>
<td>0.119</td>
</tr>
<tr>
<td>6</td>
<td>532–541</td>
<td>9.1–21.7</td>
<td>−0.050</td>
<td>−0.044</td>
<td>0.892</td>
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<tr>
<td>7*</td>
<td>566–600</td>
<td>10.4–15.2</td>
<td>0.020</td>
<td>0.160</td>
<td>0.618</td>
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<tr>
<td>8</td>
<td>511–544</td>
<td>6.0–14.2</td>
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<td>−0.234</td>
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<td>0.401</td>
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<tr>
<td>12</td>
<td>524–563</td>
<td>9.5–12.1</td>
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<td>0.252</td>
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<tr>
<td>14*</td>
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<td>12.9–18.4</td>
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* A significant correlation between 12 paired CCTs and corneal hystereses in this subject.


