24-Hour Intraocular Pressure Rhythm in Young Healthy Subjects Evaluated With Continuous Monitoring Using a Contact Lens Sensor

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IMPORTANCE This study evaluates a new device that has been proposed to continuously monitor intraocular pressure (IOP) over 24 hours.

OBJECTIVE To evaluate 24-hour IOP rhythm reproducibility during repeated continuous 24-hour IOP monitoring with noncontact tonometry (NCT) and a contact lens sensor (CLS) in healthy participants.

DESIGN, SETTING, AND PARTICIPANTS Cross-sectional study of 12 young healthy volunteers at a referral center of chronobiology.

INTERVENTIONS Participants were housed in a sleep laboratory and underwent four 24-hour sessions of IOP measurements over a 6-month period. After initial randomized attribution, the IOP of the first eye was continuously monitored using a CLS and the IOP of the fellow eye was measured hourly using NCT. Two sessions with NCT measurements in 1 eye and CLS measurements in the fellow eye, 1 session with CLS measurements in only 1 eye, and 1 session with NCT measurements in both eyes were performed.

MAIN OUTCOMES AND MEASURES A nonlinear least squares, dual-harmonic regression analysis was used to model the 24-hour IOP rhythm. Comparison of acrophase, bathyphase, amplitude, midline estimating statistic of rhythm, IOP values, IOP changes, and agreement were evaluated in the 3 tonometry methods.

RESULTS A significant nyctohemeral IOP rhythm was found in 31 of 36 sessions (86%) using NCT and in all sessions (100%) using CLS. Hourly awakening during NCT IOP measurements did not significantly change the mean phases of the 24-hour IOP pattern evaluated using CLS in the contralateral eye. Throughout the sessions, intraclass correlation coefficients of the CLS acrophase (0.6 [95% CI, 0.0 to 0.9]; \(P = .03\)), CLS bathyphase (0.7 [95% CI, 0.1 to 0.9]; \(P = .01\)), NCT amplitude (0.7 [95% CI, 0.1 to 0.9]; \(P = .01\)), and NCT midline estimating statistic of rhythm (0.9 [95% CI, 0.9 to 1.0]; \(P < .01\)) were significant. When performing NCT measurements in 1 eye and CLS measurements in the contralateral eye, the IOP change at each point normalized from the first measurement (9 AM) was not symmetric individually or within the population.

CONCLUSIONS AND RELEVANCE The CLS is an accurate and reproducible method to characterize the nyctohemeral IOP rhythm in healthy participants but does not allow for estimating the IOP value in millimeters of mercury corresponding to the relative variation of the electrical signal measured.

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ntraocular pressure (IOP) is known to vary throughout the 24-hour period of a day, defined as a nyctohemeral rhythm in healthy humans and patients with glaucoma.1–3 Currently, the only way used to study 24-hour IOP rhythm is to perform repeated IOP measurements with portable tonometers. They only allow episodic and noncontinuous IOP measurements, up to 1 measurement per hour in the best cases. They are far from physiologic conditions, as they require awakening patients during the nocturnal/sleep period, potentially introducing stress-related artifacts and disturbing sleep organization. They are performed in a fixed position, thus ignoring dynamic changes related to daily-life physical activities. A contact lens sensor (CLS) (SENSIMED Triggerfish; SENSIMED AG) was recently developed to continuously monitor IOP over 24 hours in an ambulatory setting. This novel method is based on the assumption that a correlation exists between IOP and corneal curvature.5 Studies have shown that an IOP variation of 1 mm Hg produces a change of central corneal curvature radius of approximately 3 μm.6,7 This new approach was validated in vitro on cannulated enucleated eyes.6 In a small number of studies,8–11 this new device was used in humans with glaucoma.

In healthy humans, this new device has not yet been validated and not yet been used to characterize the 24-hour IOP rhythm during repeated continuous 24-hour IOP monitoring sessions. We conducted a prospective study to evaluate the 24-hour IOP rhythm reproducibility during repeated continuous 24-hour IOP monitoring with noncontact tonometry (NCT) and the Triggerfish CLS in healthy participants. The study was designed to evaluate rhythm reproducibility in a given eye over several sessions and the rhythm symmetry between 2 eyes in a given session and compare the 2 tonometry methods’ variations in measurements.

Methods

This prospective investigation was conducted in a university-affiliated sleep laboratory following the tenets of the Declaration of Helsinki and was approved by the local institutional review board (8881, 2010-39). All participants provided both verbal and written informed consent.

Study Population

The eyes of healthy participants were studied in four 24-hour study sessions over a 6-month period. Inclusion criteria were participants free of sleep disturbance, endocrine illness, or ocular disease (spherical equivalent between −1 and +1 diopter), with regular lifestyle habits and a habitual total sleep time of approximately 8 hours. Exclusion criteria were shift workers, having taken a transmeridian flight less than 2 months before the beginning of the study, any medical treatment, and tobacco smokers. At the inclusion visit, all study participants underwent a complete ophthalmic examination (including refraction, biomicroscopy, Goldmann applanation tonometry [GAT], gonioscopy, fundus examination, and ultrasound pachymetry [Pocket II pachymeter; Quantel Medical]). All participants also filled out a general health questionnaire and underwent a complete physical examination. For each participant, 1 eye was randomized to the eyes 1 group and the fellow eye was included in the eyes 2 group.

Instruments

The SENSIMED Triggerfish consists of a highly oxygen-permeable soft CLS, whose key elements are 2 sensing-resistive strain gauges that are capable of recording circumferential changes in the area of the corneoscleral junction. The contact lens (diameter, 14.1 mm; thickness, 585 μm at the center and 260 μm at the border) exists in 3 different base curves: steep, medium, and flat, with, respectively, an 8.4-, 8.7-, and 9-mm curvature radius. Ten data points/s are acquired during a 30-second measurement period, repeated every 5 minutes. The output of the sensor is expressed in electric arbitrary units (eqVm).

Pulsair intelliPuff (Keeler) is an NCT that measures IOP in patients in the sitting or supine position. An average of 3 readings were recorded hourly over the 24-hour session.12 Goldmann applanation tonometry was performed according to standard protocol, using a slitlamp (BQ900; Haag-Streit).

Experimental Sessions

The protocol, summarized in Table 1, was designed to compare the 2 tonometry methods, evaluate intersession reproducibility using each method, and assess the symmetry of IOP pattern in both eyes. The participants maintained a self-selected constant sleep-wake schedule (onset between 10 PM and 12 AM and wake up between 7 AM and 8 AM) 2 weeks before and during the study, checked by sleep-wake diaries and ambulatory actigraphy monitoring using a wrist accelerometer (Actiwatch; CamNtech). During the experimental sessions, they were requested not to drink alcohol and caffeine-containing beverages.

For each visit, immediately before inserting and removing the CLS, eyes in groups eyes 1 and eyes 2 were measured using NCT and GAT. Although the patients were housed in the hospital, they were allowed to have free activities between the NCT hourly IOP measurements at the first visit (M0), third visit (4-month) (M4), and fourth visit (6-month) (M6) and every time at the second visit (2-month) (M2) because there were no NCT hourly IOP measurements. At each visit, participants were...
asked to go to bed after the IOP measurement at 10 PM and were asked to get up after the IOP measurement at 8 AM.

**Statistical Analysis**

**IOP Rhythm Over a 24-Hour Session**

From raw IOP data over 24 hours (Figure 1), a nonlinear least squares, dual-harmonic regression analysis was used to model the 24-hour IOP rhythms as:

\[
IOP_t = M + A_1 \cos \left( \frac{2\pi}{\tau} t + \phi_1 \right) + A_2 \cos \left( 2 \frac{2\pi}{\tau} t + \phi_2 \right)
\]

where \(A_1\) is the amplitude of the fundamental cosine fit, \(A_2\) is the amplitude of the first harmonic cosine fit, \(\phi_1\) is the acrophase of the fundamental cosine fit, \(\phi_2\) is the acrophase of the first harmonic cosine fit, \(\tau\) is the endogenous circadian period (set at 24 hours because of entrained conditions), \(M\) is the midline estimating statistic of rhythm (MESOR), and \(t\) is time. Unbiased estimates and confidence limits of amplitude (half the difference between the highest and lowest IOP values in a 24-hour cycle), MESOR (average IOP values in a 24-hour cycle), acrophase (time of the highest IOP value in a 24-hour cycle), and bathyphase (time of the lowest IOP value in a 24-hour cycle) were obtained from modeling each IOP curve. The distribution of the acrophase and bathyphase over time was analyzed using the Rayleigh test of uniformity and Watson-Williams test for homogeneity of means. The averaged acrophase and bathyphase for visits M0 and M4 (awakening sessions) were calculated for each participant and compared with night sleep session acrophase and bathyphase (visit M2).

**IOP Reproducibility Over 24-Hour Sessions Using the Same Tonometry Method**

The 2-way random average agreement intraclass correlation coefficient (ICC) from Shrout and Fleiss was used to assess the agreement of IOP at the 3 visits; the analyses included (1) assessment of the IOP value at each point of the 24-hour IOP curve (eg, IOP at 10 AM compared for 3 visits), (2) assessment of IOP changes at each point of the 24-hour IOP curve (IOP values were normalized according to the first IOP value at 9 AM), and (3) assessment of calculated amplitude, acrophase, bathyphase, and MESOR of the rhythm modeled. The following interpretation scheme for ICC has been described: less than 0.4 represents poor agreement beyond chance; 0.4 to 0.75 represents fair to good agreement beyond chance; and more than 0.75 represents excellent agreement beyond chance.

**IOP Symmetry Within the Same 24-Hour Session**

The coefficient of determination \(R^2\) in linear regression was used to assess the correlation of the simultaneous IOP changes in the eyes 1 group and IOP changes in the eyes 2 group at the same visit. \(R^2\) represents the proportion of response explained by the model (ie, \(R^2 = 1\) indicates that all variability was explained by linear regression).

**IOP Agreement Across Methods in the Same Eye**

Bland-Altman graphs were used to plot general agreement of the same IOP changes in the eyes 1 group measured with the different tonometry methods. The better of either linear re-
A significant nyctohemeral IOP rhythm was found in 31 of thirty-six 24-hour sessions (86%) using NCT and in all 24-hour sessions (100%) using CLS. In all participants and throughout the sessions, mean (SD) nocturnal IOP was significantly higher than diurnal IOP using NCT in the eyes 2 group (15.6 [0.5] mm Hg vs 13.9 [0.5] mm Hg; P < .01) or CLS in the eyes 1 group (14.0 [4.2] eqVm vs −0.2 [4.8] eqVm; P < .01). Minimum, maximum, and mean IOP values and amplitude, acrophase, and bathyphase characteristics of the population are summarized in Table 2.

In all visits in which CLS and NCT were simultaneously used, mean (SD) acrophases (3:05 AM [37 minutes] vs 5:28 AM [41 minutes]; P < .01) and bathyphases (3:14 PM [55 minutes] vs 7:32 PM [57 minutes]; P < .01) were significantly earlier in the eyes 1 group measured with CLS than in the eyes 2 group measured with NCT (Table 2). Using the same tonometry method (NCT), mean (SD) acrophases (5:21 AM [51 minutes] vs 7:32 PM [57 minutes]; P < .01) were significantly earlier in the eyes 1 group than in the eyes 2 group. The mean (SD) value of the acrophase of visit M2 (without awakening) was significantly different from the acrophase of visit M2 (without awakening): 3:05 AM (37 minutes) vs 7:32 PM (57 minutes); P < .01). Minimum, maximum, and mean IOP values and amplitude, acrophase, and bathyphase characteristics of the population are summarized in Table 2.

**Table 2. Characteristics of 24-Hour IOP Rhythms Calculated Using NCT and CLS**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Mean IOP (eqVm)</th>
<th>Max IOP (eqVm)</th>
<th>Min IOP (eqVm)</th>
<th>Amplitude (eqVm)</th>
<th>Acrophase (AM)</th>
<th>Bathyphase (PM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>5.8 (1.9)</td>
<td>6.2 (2.4)</td>
<td>4.9 (1.3)</td>
<td>1.2 (0.6)</td>
<td>5:30 AM</td>
<td>5:24 PM</td>
</tr>
<tr>
<td>M2</td>
<td>5.7 (1.8)</td>
<td>6.0 (2.3)</td>
<td>4.8 (1.2)</td>
<td>1.1 (0.5)</td>
<td>5:29 AM</td>
<td>5:18 PM</td>
</tr>
<tr>
<td>M4</td>
<td>5.6 (1.7)</td>
<td>6.0 (2.2)</td>
<td>4.7 (1.1)</td>
<td>1.0 (0.4)</td>
<td>5:28 AM</td>
<td>5:17 PM</td>
</tr>
<tr>
<td>M6</td>
<td>5.5 (1.6)</td>
<td>5.9 (2.1)</td>
<td>4.6 (1.0)</td>
<td>0.9 (0.3)</td>
<td>5:27 AM</td>
<td>5:16 PM</td>
</tr>
</tbody>
</table>

Abbreviations: CLS, contact lens sensor; eqVm, electric arbitrary unit; IOP, intraocular pressure; M0, first visit; M2, second visit (2-month); M4, third visit (4-month); M6, fourth visit (6-month); Max, maximum; Min, minimum; NCT, noncontact tonometry.

**Results**

**Population**

Twelve healthy white participants (24 eyes) were included (8 female and 4 male; mean [SD] age, 22.3 [2.3] years; mean [SD] body mass index [calculated as weight in kilograms divided by height in meters squared], 20.8 [2.0]). Ten of 12 individuals (83%) received a medium CLS and the others received a steep CLS. At inclusion, mean (SD) IOP values using GAT were 13.8 (2.1) mm Hg in the right eye and 13.7 (1.9) mm Hg in the left eye (P = .90). Mean (SD) central corneal thickness was 550 (20) μm in the right eye and 554 (20) μm in the left eye (P = .61). The mean (SD) corneal power was 43.6 (1.1) diopters in both eyes.

**Characterization of IOP Rhythm**

A significant nyctohemeral IOP rhythm was found in the different tonometry methods.

Data analyses were performed using SPSS (version 17.0; SPSS Inc) and R software. Statistical significance was set at P < .05.

**Reproducibility of IOP Measurements Over 24-Hour Sessions**

Reproducibility of CLS IOP Measurements

Nine hourly IOP values of 25 (Table 3) and 9 points of 24 for IOP changes (Table 4) presented significant ICCs, indicating generally good agreement (ie, 95% CI) (Figure 2A and B).

Reproducibility of NCT IOP Measurements

Eighteen points of 25 presented significant ICCs, indicating generally fair to good agreement (ie, 95% CI) (Table 3). For IOP
changes, 1 point of 24 presented a significant ICC (Table 4) (Figure 2C and D).

Table 3. Reproducibility of 24-Hour IOP Absolute Valuesa

<table>
<thead>
<tr>
<th>Time</th>
<th>Visit M0</th>
<th>Visit M4</th>
<th>Visit M6</th>
<th>ICC (95% CI)</th>
<th>Visit M0</th>
<th>Visit M2</th>
<th>Visit M4</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 AM</td>
<td>15.2 (1.9)</td>
<td>14.7 (2.7)</td>
<td>14.2 (1.6)</td>
<td>0.8 (0.5 to 0.9)a</td>
<td>NA</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>10 AM</td>
<td>15.6 (2.7)</td>
<td>15.1 (2.2)</td>
<td>13.6 (1.9)</td>
<td>0.7 (0.3 to 0.9)a</td>
<td>0.3 (-0.2 to 0.6)</td>
<td>4.2 (6.9)</td>
<td>0.6 (8.1)</td>
</tr>
<tr>
<td>11 AM</td>
<td>15.2 (1.3)</td>
<td>14.5 (1.9)</td>
<td>14.2 (1.7)</td>
<td>0.6 (0.1 to 0.9)a</td>
<td>0.6 (0.0 to 0.9)a</td>
<td>1.1 (8.4)</td>
<td>-3.1 (10.6)</td>
</tr>
<tr>
<td>12 AM</td>
<td>15.0 (2.3)</td>
<td>14.4 (1.7)</td>
<td>13.9 (1.6)</td>
<td>0.7 (0.2 to 0.9)a</td>
<td>0.6 (0.1 to 0.9)a</td>
<td>0.4 (9.9)</td>
<td>-5.8 (15.8)</td>
</tr>
<tr>
<td>1 PM</td>
<td>14.1 (1.9)</td>
<td>13.7 (1.9)</td>
<td>14.3 (2.0)</td>
<td>0.9 (0.7 to 1.0)a</td>
<td>0.3 (-0.2 to 0.7)</td>
<td>-7.2 (13.4)</td>
<td>-9.9 (21.4)</td>
</tr>
<tr>
<td>2 PM</td>
<td>14.2 (1.6)</td>
<td>13.7 (1.7)</td>
<td>13.3 (1.6)</td>
<td>0.8 (0.5 to 0.9)a</td>
<td>0.6 (0.1 to 0.9)a</td>
<td>-1.0 (12.5)</td>
<td>-9.9 (21.9)</td>
</tr>
<tr>
<td>3 PM</td>
<td>14.1 (1.9)</td>
<td>13.7 (1.9)</td>
<td>14.3 (2.0)</td>
<td>0.9 (0.7 to 1.0)a</td>
<td>0.3 (-0.2 to 0.7)</td>
<td>-7.2 (13.4)</td>
<td>-9.9 (21.4)</td>
</tr>
<tr>
<td>4 PM</td>
<td>13.6 (1.7)</td>
<td>13.6 (1.4)</td>
<td>13.8 (1.2)</td>
<td>0.8 (0.3 to 0.9)a</td>
<td>0.6 (0.1 to 0.9)a</td>
<td>-6.5 (16.5)</td>
<td>-7.4 (20.6)</td>
</tr>
<tr>
<td>5 PM</td>
<td>13.6 (1.7)</td>
<td>13.4 (2.0)</td>
<td>13.3 (1.7)</td>
<td>0.9 (0.6 to 1.0)a</td>
<td>0.6 (0.0 to 0.8)</td>
<td>-2.6 (11.4)</td>
<td>-10.9 (21.2)</td>
</tr>
<tr>
<td>6 PM</td>
<td>14.4 (1.9)</td>
<td>13.7 (1.7)</td>
<td>13.6 (1.6)</td>
<td>0.8 (0.4 to 0.9)a</td>
<td>0.7 (0.2 to 0.9)a</td>
<td>-3.5 (16.0)</td>
<td>-2.7 (18.8)</td>
</tr>
<tr>
<td>7 PM</td>
<td>14.2 (1.2)</td>
<td>13.6 (2.0)</td>
<td>14.3 (2.1)</td>
<td>0.8 (0.6 to 1.0)a</td>
<td>0.6 (0.1 to 0.9)a</td>
<td>-3.8 (14.9)</td>
<td>-2.1 (16.9)</td>
</tr>
<tr>
<td>8 PM</td>
<td>13.9 (1.5)</td>
<td>14.1 (1.4)</td>
<td>14.4 (1.9)</td>
<td>0.7 (0.1 to 0.9)a</td>
<td>0.7 (0.3 to 0.9)a</td>
<td>-0.6 (16.4)</td>
<td>-2.6 (17.1)</td>
</tr>
<tr>
<td>9 PM</td>
<td>13.0 (1.8)</td>
<td>13.2 (2.0)</td>
<td>12.8 (1.6)</td>
<td>0.8 (0.4 to 0.9)a</td>
<td>0.5 (-0.1 to 0.7)</td>
<td>-0.7 (16.3)</td>
<td>2.1 (16.5)</td>
</tr>
<tr>
<td>10 PM</td>
<td>13.4 (1.8)</td>
<td>13.8 (1.5)</td>
<td>13.1 (1.6)</td>
<td>0.8 (0.4 to 0.9)a</td>
<td>0.3 (-0.3 to 0.5)</td>
<td>0.9 (19.3)</td>
<td>5.6 (17.0)</td>
</tr>
<tr>
<td>11 PM</td>
<td>12.8 (1.9)</td>
<td>14.3 (2.4)</td>
<td>13.3 (2.3)</td>
<td>0.4 (-0.1 to 0.7)</td>
<td>0.4 (-0.2 to 0.5)</td>
<td>7.4 (15.5)</td>
<td>9.2 (16.5)</td>
</tr>
<tr>
<td>12 PM</td>
<td>14.6 (2.7)</td>
<td>15.3 (2.7)</td>
<td>13.9 (2.7)</td>
<td>-0.2 (-0.6 to 0.3)</td>
<td>-1.0 (-1.0 to 0.0)</td>
<td>11.8 (14.4)</td>
<td>12.5 (15.5)</td>
</tr>
<tr>
<td>1 AM</td>
<td>14.4 (2.6)</td>
<td>16.8 (4.5)</td>
<td>15.5 (2.7)</td>
<td>0.0 (-0.4 to 0.4)</td>
<td>0.3 (-0.3 to 0.5)</td>
<td>14.6 (12.5)</td>
<td>14.2 (15.0)</td>
</tr>
<tr>
<td>2 AM</td>
<td>16.0 (2.1)</td>
<td>16.8 (3.7)</td>
<td>14.7 (2.2)</td>
<td>0.7 (0.2 to 0.9)a</td>
<td>0.1 (-0.4 to 0.5)</td>
<td>11.9 (11.2)</td>
<td>13.5 (14.2)</td>
</tr>
<tr>
<td>3 AM</td>
<td>16.3 (2.2)</td>
<td>15.2 (2.9)</td>
<td>15.3 (1.6)</td>
<td>0.7 (0.2 to 0.9)a</td>
<td>0.4 (-0.1 to 0.6)</td>
<td>13.6 (12.8)</td>
<td>13.9 (15.7)</td>
</tr>
<tr>
<td>4 AM</td>
<td>16.1 (2.2)</td>
<td>16.7 (3.7)</td>
<td>15.1 (1.8)</td>
<td>0.4 (-0.1 to 0.6)</td>
<td>0.4 (-0.2 to 0.7)</td>
<td>12.7 (13.1)</td>
<td>13.5 (14.8)</td>
</tr>
<tr>
<td>5 AM</td>
<td>15.4 (2.8)</td>
<td>17.1 (3.0)</td>
<td>14.5 (1.3)</td>
<td>0.3 (-0.2 to 0.6)</td>
<td>0.4 (-0.1 to 0.6)</td>
<td>11.6 (11.5)</td>
<td>14.4 (15.2)</td>
</tr>
<tr>
<td>6 AM</td>
<td>14.7 (2.3)</td>
<td>16.8 (3.1)</td>
<td>15.0 (2.1)</td>
<td>0.8 (0.4 to 0.9)a</td>
<td>0.7 (0.1 to 0.9)a</td>
<td>12.9 (11.5)</td>
<td>13.9 (16.7)</td>
</tr>
<tr>
<td>7 AM</td>
<td>16.4 (2.0)</td>
<td>16.4 (2.6)</td>
<td>16.0 (2.8)</td>
<td>0.4 (-0.1 to 0.7)</td>
<td>0.5 (-0.1 to 0.8)</td>
<td>14.3 (11.9)</td>
<td>11.6 (20.7)</td>
</tr>
<tr>
<td>8 AM</td>
<td>16.1 (1.9)</td>
<td>16.0 (1.8)</td>
<td>16.1 (2.1)</td>
<td>0.8 (0.4 to 0.9)a</td>
<td>0.7 (0.1 to 0.9)a</td>
<td>7.7 (15.7)</td>
<td>10.6 (19.3)</td>
</tr>
<tr>
<td>9 AM</td>
<td>14.7 (1.3)</td>
<td>14.8 (1.8)</td>
<td>15.0 (2.3)</td>
<td>0.6 (0.0 to 0.9)</td>
<td>0.6 (0.0 to 0.8)</td>
<td>-2.0 (18.2)</td>
<td>-0.7 (17.4)</td>
</tr>
</tbody>
</table>

Abbreviations: CLS, contact lens sensor; eqVm, electric arbitrary unit; ICC, intraclass correlation coefficient; IOP, intraocular pressure; M0, first visit; M2, second visit (2-month); M4, third visit (4-month); M6, fourth visit (6-month); NA, not applicable; NCT, noncontact tonometry.

a For each individual, 1 eye was randomized to the eyes 1 group and the fellow eye was included in the eyes 2 group.

b Significant at P < .05.

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Table 4. Reproducibility of 24-Hour IOP Relative Changesa

<table>
<thead>
<tr>
<th>Time</th>
<th>ΔIOP, %, in Eyes 2 Group Using NCT</th>
<th>Mean (SD)</th>
<th>ΔIOP, eqVm, in Eyes 1 Group Using CLS</th>
<th>ICC (95% CI)</th>
<th>ICC (95% CI)</th>
<th>ICC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit M0</td>
<td>-1.8 (12.7)</td>
<td>0.5 (0.0 to 0.9)</td>
<td>0.3 (0.0 to 0.9)</td>
<td>1.1 (8.4)</td>
<td>0.6 (0.0 to 0.9)</td>
<td></td>
</tr>
<tr>
<td>Visit M4</td>
<td>1.9 (14.7)</td>
<td>0.2 (0.0 to 0.8)</td>
<td>0.7 (0.1 to 0.9)</td>
<td>12.9 (11.5)</td>
<td>0.6 (0.0 to 0.9)</td>
<td></td>
</tr>
<tr>
<td>Visit M6</td>
<td>3.6 (14.9)</td>
<td>0.8 (0.0 to 0.8)</td>
<td>0.7 (0.1 to 0.9)</td>
<td>14.3 (11.9)</td>
<td>0.6 (0.0 to 0.9)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CLS, contact lens sensor; D+1, the first IOP measurement 24 hours later; eqVm, electric arbitrary unit; ICC, intraclass correlation coefficient; IOP, intraocular pressure; ΔIOP, change in IOP; M0, first visit; M2, second visit (2-month); M4, third visit (4-month); M6, fourth visit (6-month); NCT, noncontact tonometry.

Discussion

In the present study, we evaluated the 24-hour IOP rhythm reproducibility in healthy participants during repeated sessions, both with NCT and a new CLS. We combined sessions with NCT measurements in 1 eye and CLS measurements in the fellow eye, a session with CLS measurements alone (1 eye), and a session with NCT measurements in both eyes to evaluate the rhythm reproducibility in a given eye over sessions, the rhythm symmetry between 2 eyes in a given session, and 2 tonometry methods’ variations in measurements.

With the 2 tonometry methods, we found that all healthy participants exhibited a nyctohemeral IOP rhythm. As previously described12-15 with the currently available tonometry methods, the IOP nyctohemeral rhythm was characterized by an acrophase in the late night/early morning period. Interestingly, sessions performed with CLS measurements alone confirmed these previous results, thus demonstrating that the IOP rhythm previously described in healthy participants with the available tonometry methods is not an artifact due to awakening and related sleep disorganization. In a given session, the acrophases and bathyphases of 1 eye evaluated with 1 tonometry technique and of the fellow eye evaluated with the other technique were usually significantly different. In a given session, the acrophases and bathyphases of the 2 eyes evaluated with the same tonometry technique (NCT) were usually comparable. This cannot be evaluated with the CLS because simultaneous measurements are not possible for technical reasons. These latter results suggest that the differences obtained between 2 different techniques are related to technical methods (number of IOP measurements) and not biological variability.

Among the sessions, the 24-hour rhythm parameters found with the same tonometry technique (NCT or CLS) in a given participant and in a given eye were usually comparable. The most robust parameters among sessions were the MESOR and amplitude for NCT and the acrophase and bathyphase for CLS. The most reproducible IOP values were taken during the day (8 AM to 10 PM) with NCT; the most reproducible IOP changes were taken between 11 AM and 1 PM and between 6 PM and 8 PM with CLS. The discrepancy between agreement of absolute IOP and agreement of IOP change is consistent with the findings of Reali and al17,20 using GAT: agreement of diurnal IOP values was fair to good and agreement of diurnal IOP
changes was poor. Interestingly, we found higher agreement of relative IOP changes among sessions during the first diurnal 12 hours using CLS measurements than using NCT measurements.

A few studies have been conducted in humans with this new CLS and focused on patients with glaucoma. These studies evaluated the 24-hour hypotensive drug activity in patients with normotensive glaucoma, corneal thickness after overnight
wear in patients with ocular hypertension or established glaucoma, or the reproducibility of the 24-hour IOP pattern in patients with suspected and confirmed glaucoma. To our knowledge, the present study is the first to assess the reproducibility over several months of 24-hour IOP patterns in healthy participants both with the CLS and NCT. We found that the CLS is a more sensitive method than the NCT in detecting and characterizing the 24-hour IOP rhythm. The CLS allowed better online dual-harmonic modeling of the 24-hour IOP rhythm. Thus, the CLS usually detects acrophases and bathyphases significantly earlier (about 2 hours) than NCT. The NCT acrophases were similar to those found by Mansouri and Al in the sitting or supine position in young participants. One reason explaining the greater ability of the CLS to detect and characterize the 24-hour IOP rhythm is likely the higher frequency of data acquisition, strongly reducing the potential influence of outliers.

Noncontact tonometry and CLS are different and complementary for the study of the 24-hour IOP rhythm. Regarding the reproducibility of the 24-hour IOP rhythms assessed with NCT among visits, amplitude showed significant fair to good agreement and MESOR showed excellent agreement. In contrast, reproducibility of NCT acrophases and bathyphases was limited and not significant. In contrast, CLS can define temporal phases that contribute to nyctohemeral rhythm (acrophases and bathyphases) with greater confidence than NCT. The new CLS measures an electrical signal expressed in millivolts. Measurements are normalized to the first measurement of the session (in electric arbitrary units). Therefore, it is therefore arbitrarily set at 0 eqVm. The subsequent measurements are the relative signal change. The unresolved question about this new device is whether these signal variations can be used to estimate the variations in IOP expressed in millimeters of mercury reached at each point using the IOP measured just before contact lens equipment with NCT or GAT. Our results, summarized in Figure 2 and Table 4, clearly show that the CLS cannot estimate the absolute value of IOP in millimeters of mercury when using the pre- and post-CLS GAT measurements or pre- and post-CLS NCT measurements. When performing NCT measurements in both eyes (visit M6), IOP changes at each point compared with the first measurement (9 AM) are usually symmetric in a given participant or in the population. When performing NCT measurements in one eye and CLS measurements in the fellow eye (visits M0 and M4), IOP changes at each point compared with the first measurement (9 AM) are not symmetric in a given participant or in the population. It is therefore not possible to use the relative change in CLS signal multiplied by the IOP measured before CLS equipment to estimate the absolute IOP at each point of the 24-hour session. Regarding the presession and postsession measurements with GAT and NCT, the agreement on the change
in IOP in the CLS and NCT or GAT was also poor. Bland-Altman analyses suggest that CLS overestimates the large IOP changes in comparison of NCT.

This study could have some limitations. Other factors related to sleep such as the impact of the eyelid during the sleep phase could have influenced the CLS measurements and thus the difference between the tonometry methods. We are currently conducting complimentary studies in our laboratory using overnight polysomnography measurements. Regarding inter-eye symmetry, an earlier study found asymmetric spontaneous IOP changes in fellow eyes regardless of the tonometry method used. Realini et al\(^3\) showed that asymmetric spontaneous IOP changes commonly occur between fellow eyes in normal participants: 50% exhibited an asymmetric IOP change between 2 consecutive visits and overall asymmetric IOP changes were observed in 13.7% of follow-up visits. In the present study, the NCT-CLS comparisons were based on the finding that the 24-hour IOP value changes of the 2 fellow eyes are symmetric with the same tonometry method but cannot be checked directly in humans because the contact lens completely covered the cornea. Because of technical limitations, it is currently not possible to use the CLS simultaneously in both eyes. Finally, the artifacts of electrical signal measurement of the CLS method could have an impact regarding the results.

In conclusion, the CLS is an accurate and reproducible method to model IOP rhythm and characterize acrophases and bathyphases in healthy participants but does not estimate the absolute value and IOP changes in millimeters of mercury corresponding to the relative variation of the electrical signal measured.

Changes were calculated between day 0 at 9 AM and day 1 at 9 AM. A, Agreement between the contact lens sensor (CLS) and noncontact tonometry (NCT). B, Agreement between CLS and Goldmann applanation tonometry (GAT). C, Agreement between NCT and GAT. For each individual, 1 eye was randomized to the eyes 1 group. 95% CI, 95% modeling confidence interval; LCB, global lower 95% confidence bound; M0, first visit; M2, second visit (2-month); M4, third visit (4-month); UCB, global upper 95% confidence bound; and Δ, change in.

Figure 4. Bland-Altman Graphs of Intraocular Pressure Changes Agreement in the Eyes 1 Group

A

B

C

Changes were calculated between day 0 at 9 AM and day 1 at 9 AM.
A, Agreement between the contact lens sensor (CLS) and noncontact tonometry (NCT). B, Agreement between CLS and Goldmann applanation tonometry (GAT). C, Agreement between NCT and GAT. For each individual, 1 eye was randomized to the eyes 1 group. 95% CI, 95% modeling confidence interval; LCB, global lower 95% confidence bound; M0, first visit; M2, second visit (2-month); M4, third visit (4-month); UCB, global upper 95% confidence bound; and Δ, change in.
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