Hourly Awakening vs Continuous Contact Lens Sensor Measurements of 24-Hour Intraocular Pressure Effect on Sleep Macrostructure and Intraocular Pressure Rhythm

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IMPORTANCE All studies of 24-hour intraocular pressure (IOP) rhythm conducted to date have used repeated IOP measurements requiring nocturnal awakenings, potentially disturbing sleep macrostructure.

OBJECTIVE To evaluate the effects on sleep architecture and IOP rhythm of hourly awakening vs a contact lens sensor (CLS) to continuously monitor IOP without awakening.

DESIGN, SETTING, AND PARTICIPANTS Cross-sectional study at a referral center of chronobiology among 12 young healthy volunteers, with a mean (SD) age of 22.3 (2.3) years.

INTERVENTIONS Volunteers underwent two 24-hour IOP measurement sessions during a 2-month period. The eye order and session order were randomized. During one session, the IOP of the first eye was continuously monitored using a CLS, and the IOP of the fellow eye was measured hourly using a portable noncontact tonometer (session with nocturnal hourly awakening). During the other session, the IOP of the first eye was continuously monitored using a CLS, and the IOP of the fellow eye was not measured (session without nocturnal awakening). Overnight polysomnography was performed during the 2 sessions.

MAIN OUTCOMES AND MEASURES A nonlinear least squares, dual-harmonic regression analysis was used to model the 24-hour IOP rhythm from the CLS data. Comparisons of acrophase, bathyphase, amplitude, and the midline estimating statistic of rhythm were used to evaluate the effect of hourly awakening on IOP rhythm. To evaluate the effects of hourly awakening on sleep architecture, comparisons of sleep structure were used, including total sleep period, rapid eye movement, wake after sleep onset, absolute and relative total sleep time, and non-rapid eye movement sleep (N1, N2, and N3).

RESULTS A 24-hour IOP rhythm was found in all individuals for the sessions with and without awakening (P < .05). Hourly awakening for nocturnal IOP measurements increased wake after sleep onset (P = .04) but did not seem to change total sleep time, total sleep period, sleep efficiency, or slow-wave and rapid eye movement sleep stage duration (P > .30). Hourly awakening during noncontact tonometer IOP measurements did not seem to alter the mean variables of the 24-hour IOP pattern evaluated using CLS, including signal, maximum signal, minimum signal, acrophase, and bathyphase (P > .15).

CONCLUSION AND RELEVANCE The 24-hour IOP rhythms seem to be unaffected by hourly nocturnal awakening for IOP measurements in young healthy individuals.
To date, all intraocular pressure (IOP) measurement methods (whether portable or nonportable) require individuals to be awakened for nocturnal measurements. To our knowledge, all studies of 24-hour IOP rhythm have used repeated IOP measurements requiring nocturnal awakenings, potentially disturbing sleep macrostructure. This process may have biased previous descriptions of physiological IOP rhythm. The effects of awakening for IOP measurements on sleep macrostructure and IOP rhythm are unknown.

A contact lens sensor (CLS) (Triggerfish; SENSIMED AG) was recently developed to continuously monitor IOP noninvasively during 24 hours in an ambulatory setting. This innovative method is based on the assumption that a correlation exists between IOP and corneal curvature. Animal studies have shown that an IOP variation of 1 mm Hg produces a change in the central corneal curvature radius of approximately 3 μm. The device has been approved by European regulatory authorities (class IIa device CE-mark) since 2009 and has been evaluated in healthy individuals and in patients with glaucoma in a few studies. It has recently been demonstrated that this new device represents an accurate and reproducible method to characterize the 24-hour nyctohemeral IOP rhythm in young healthy individuals.

In the present study, we evaluated the effects of hourly awakening for IOP measurements on sleep using polysomnography and the effects of hourly awakening on IOP rhythm using a CLS that allowed us to continuously monitor IOP during 24 hours. The underlying issue was the validity of the data provided by the previous studies conducted with awakening after having found that IOP follows a nyctohemeral rhythm in healthy humans and in patients with glaucoma.

Methods

Study Population

The study protocol has been recently described in detail. This prospective investigation was conducted in the Laboratory of Ocular Chronobiology, Université Grenoble Alpes, Grenoble, France, in accord with the tenets of the Declaration of Helsinki and was approved by the Comité de Protection des Personnes Sud Est V. All participating individuals provided both verbal and written informed consent. Participants were paid for their time and effort.

Twenty-four eyes of 12 healthy volunteers were studied in two 24-hour IOP measurement sessions during a 2-month period. The inclusion criteria were individuals free of sleep disorders, with regular lifestyle habits, with usual sleep duration lasting approximately 8 hours, and without endocrine illness or ocular disease (spherical equivalent between −1 and +1 diopter). The exclusion criteria were shift workers, tobacco smokers, individuals with any medical treatment, and persons who had taken a transmeridian flight less than 2 months before the beginning of the study.

At the study inclusion visit, all individuals underwent a complete ophthalmic examination, including refraction, gonioscopy, biomicroscopy, fundus examination, Goldmann applanation tonometry, and ultrasonographic pachymetry (Pocket II; Quantel Medical). All individuals also filled out a general health questionnaire and underwent a complete physical examination. The eye order and session order (session with nocturnal hourly awakening and session without nocturnal awakening) were randomized.

IOP Measurements

The CLS is an oxygen-permeable soft contact lens 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 (with a diameter of 14.1 mm and thicknesses of 585 μm at the center and 260 μm at the edge) is available in 3 different base curves (steep, medium, and flat) with an 8.4-mm, 8.7-mm, and 9-mm curvature radius, respectively. Ten data points per second are acquired during a 30-second measurement period, repeated every 5 minutes. The output of the sensor is expressed in electric arbitrary units (eqVm).

The noncontact tonometer (NCT) used herein (Pulsair intelliPuff; Keeler) measures the IOP in patients in the sitting or supine position. A mean of 3 readings was recorded hourly during a 24-hour session (every hour from 9 AM to 9 AM). It was previously found that the use of this NCT agrees well with Goldmann applanation tonometry in normotensive and hypertensive individuals in the sitting position.

Polysomnography

Continuous recordings were obtained with the electrode positions C3/A2-C4/A1-Cz/01 of the International 10-20 System of Electrode Placement measuring eye movements, a chin electromyogram, and an electrocardiogram with a modified V2 lead. Sleep was scored manually according to standard criteria. Airflow was measured by nasal pressure associated with the sum of buccal and nasal thermistor signals. Respiratory effort was monitored with abdominal and thoracic bands. Pulse transit time, an additional indicator of respiratory effort, was recorded concurrently. Oxygen saturation was measured using a pulse oximeter (Biox-Ohmeda 3700; Ohmeda).

Experimental Sessions

Participants maintained a self-selected constant sleep-wake schedule (sleep onset between 10 PM and 12 midnight and wake-up between 7 AM and 8 AM) 2 weeks before and during the study, checked by sleep-wake diaries and by ambulatory actigraphy monitoring using a wrist accelerometer (Actiwatch; CamNtech). During the experimental sessions, they were requested not to drink alcohol-containing or caffeine-containing beverages. Although the participants were housed in a hospital, they were allowed to have free activities between the NCT hourly IOP measurements. At each session, 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. The protocol is summarized in eTable 1 in the Supplement.
Research  Original Investigation

Statistical Analysis
From raw IOP data during 24 hours, a nonlinear least squares, dual-harmonic regression analysis was used to model the 24-hour IOP rhythm with the following equation:

\[ IOP_t = M + A_1 \cos \left( \frac{2\pi}{\tau} t + \phi_1 \right) + A_2 \cos \left( \frac{4\pi}{\tau} t + \phi_2 \right) \]

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, and \( t \) is the time. Variables obtained from the modeling of each IOP curve included acrophase (time of the highest IOP value in a 24-hour cycle), bathyphase (time of the lowest IOP value in a 24-hour cycle), the midline estimating statistic of rhythm (mean IOP values in a 24-hour cycle), and unbiased estimates and confidence limits of amplitude (half the difference between the highest and lowest IOP values in a 24-hour cycle). \(^{18,19}\) The distribution of the acrophase and bathyphase over time was analyzed using the Rayleigh test of uniformity and the Watson-Williams test for homogeneity of means. \(^{20}\)

The skewness-kurtosis normality test was used to assess the normality of the measurements. The paired \( t \) test and analysis of variance were used to compare the means and percentages. McNemar \( \chi^2 \) test was used for the analysis of dichotomous variables. Within-patient across-session relationships were obtained by correlating parallel recording time points using each of the 5-minute recordings with Pearson product moment correlations. To take into account a potential time lag or delay between the 2 measurement series, we also studied the within-patient across-session relationships using the cross-correlation function. The cross-correlation function of 2 time series is the product moment correlation as a function of lag (or time offset) between the series. The cross-correlation function identifies the lag that leads to the stronger correlation between the 2 time series.

The 2-way random mean agreement intraclass correlation coefficient from the conversion by Shrout and Fleiss \(^{21}\) was used to assess the IOP agreement at the 2 sessions and at each time point during the nocturnal period (10 PM to 8 AM) (eg, IOP at 11 PM compared for 2 sessions). The following interpretation scheme for the intraclass correlation coefficient has been described: less than 0.40 represents poor agreement beyond chance, 0.40 to 0.75 represents fair to good agreement beyond chance, and greater than 0.75 represents excellent agreement beyond chance. \(^{22}\)

Data analyses were performed using statistical software. These included SPSS (version 17.0; SPSS Inc) and R software (version 2.14; R Foundation for Statistical Computing). \(^{23}\)

Results
Participant Characteristics
Twelve young healthy volunteers (24 eyes) of white race/ethnicity were included in the study (8 women and 4 men), with a mean (SD) age of 22.3 (2.3) years and a mean (SD) body mass index (calculated as weight in kilograms divided by height in meters squared) of 20.8 (2.0). All participants were easily fitted with the CLS (9 medium lenses, 2 steep lenses, and 1 flat lens depending on previous keratometry) on one randomly selected eye (6 left eyes and 6 right eyes). Six participants had the session with nocturnal hourly awakening first, and 6 participants had the session without nocturnal awakening first. At study inclusion, the mean (SD) IOP values using Goldmann applanation tonometry were 13.8 (2.1) mm Hg in the right eye and 13.7 (1.9) mm Hg in the left eye (\( P = .86 \)). The 24-hour and nocturnal NCT IOP measurements of the contralateral eye at session 1 are summarized in eTable 2 in the Supplement.

Effects of Hourly Awakening for IOP Measurements on Sleep
Table 1 lists the Microarousal Index, \(^{17}\) the number of cycles per night, rapid eye movement (REM) and non-REM (N1, N2, and N3) sleep, sleep efficiency (total sleep time divided by total sleep period), total sleep period (period measured from sleep onset to final awakening), sleep architecture with absolute and percentage wake after sleep onset time, and total sleep time (total of REM and non-REM sleep in a period). Hourly awakening for nocturnal IOP measurements increased wake after sleep onset (\( P = .04 \)) but did not seem to alter sleep macrostructure, with no differences in total sleep time (\( P = .53 \)), sleep efficiency (\( P = .92 \)), the proportions of slow-wave and REM sleep stages in

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) [95% CI] (% of Total Sleep Time)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time, min</td>
<td>381.5 (74.5) [339.3-423.7]</td>
<td>.53</td>
</tr>
<tr>
<td>Total sleep period, min</td>
<td>481.0 (65.9) [443.7-518.3]</td>
<td>.31</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>79.1 (14.3) [70.8-87.3]</td>
<td>.92</td>
</tr>
<tr>
<td>Sleep stage, min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W</td>
<td>151.4 (56.7) [119.3-183.5]</td>
<td>.04*</td>
</tr>
<tr>
<td>N1</td>
<td>36.8 (8.3) [32.1-41.5] (10.0%)</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>195.3 (55.4) [163.9-226.7] (50.6%)</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>66.7 (26.0) [52.0-81.4] (17.3%)</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>83.5 (19.6) [72.4-94.6] (22.0%)</td>
<td>.09</td>
</tr>
<tr>
<td>Cycles per night, No.</td>
<td>5.1 (0.6) [4.8-5.4]</td>
<td></td>
</tr>
<tr>
<td>Microarousal Index</td>
<td>7.7 (4.4) [5.2-10.2]</td>
<td>.42</td>
</tr>
</tbody>
</table>

Table 1. Sleep Duration, Sleep Quality Variables, and Sleep Architecture

Abbreviations: N, non–rapid eye movement; R, rapid eye movement; W, wake after sleep onset. *By Wilcoxon signed rank test. All other P values are by paired \( t \) test.

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relation to total sleep time \((P = .38)\), and the number of cycles per night \((P = .09)\). Sleep fragmentation also remained unchanged, with no difference in the Microarousal Index \((P = .42)\).

**Figure 1** shows the polysomnographs from the 2 sessions for 1 participant. It illustrates how participants seemed to compensate for the multiple awakenings imposed and maintained unchanged total sleep time, sleep efficiency, and the duration of each sleep stage \((N_1, N_2, N_3, \text{REM})\), and absolute or percentage relative to total sleep time.

**Effects of Hourly Awakening for IOP Measurements on 24-Hour IOP Rhythm**

The CLS signal showed a significant nyctohemeral rhythm for all 12 participants at sessions 1 and 2 \((P < .05)\). The 24-hour minimum, maximum, and mean signal values and amplitude, acrophase, and bathyphase characteristics of the population are summarized in **Table 2**. The amplitude of the 95% CIs and residuals (root-mean-square errors) of the nonlinear least squares, dual-harmonic regression analyses of the 24 sessions are summarized in eTable 3 in the Supplement. Nocturnal \((10 \text{ PM} \text{ to} 8 \text{ AM})\) minimum, maximum, and mean signal values and amplitude of the population are summarized in eTable 4 in the Supplement. In all participants and for both sessions, the mean nocturnal IOP was higher than the mean diurnal IOP: the mean (SD) values at session 1 were 22.1 (15.6) vs −0.4 (8.9) \((P = .004)\), and the mean (SD) values at session 2 were 12.9 (15.5) vs −5.1 (6.7) \((P = .008)\).

Hourly awakening during NCT IOP measurements did not seem to alter the mean variables of the 24-hour IOP pattern evaluated using CLS, including signal, maximum signal, minimum signal, acrophase, and bathyphase \((P > .15)\).

Correlations and cross-correlations of the 24-hour CLS measurements at sessions 1 and 2 are summarized in eTable 5 in the Supplement. Six of 12 participants exhibited a strong correlation \((r > 0.7)\), and 6 of 12 participants exhibited a strong cross-correlation \((r > 0.7)\), with a mean \((SD)\) time lag of 11.7 (9.0) minutes between the 2 sessions.

The IOP agreement at the 2 sessions and at each time point during the nocturnal period \((10 \text{ PM} \text{ to} 8 \text{ AM})\) is summarized in eTable 6 in the Supplement and shown in **Figure 2**. None of 11 nocturnal hourly IOP values had intraclass correlation coefficients with \(P < .05\), demonstrating poor agreement between the 2 nocturnal period IOP measurements. From Table 2, Figure 2, and **Figure 3**, it can be seen that the variability of IOP measurements was much greater during the session with nocturnal hourly awakening.

**Discussion**

All previous studies\(^4\)–\(^7\) of the 24-hour IOP conducted to date have found a significant nyctohemeral rhythm in healthy participants and in patients with glaucoma, including those in a constant sitting or supine position, with higher IOP levels usu-
ally occurring during the nocturnal period and lower IOP levels usually occurring during the diurnal period. However, when studying the circadian rhythm of a biological variable, a crucial point is to avoid using a method that could disrupt the normal sleep-wake cycle. Studies have demonstrated that many biological endogenous circadian rhythms may be perturbed by forced interruption of the sleep-wake cycle, including melatonin secretion, body temperature, plasma cortisol level, blood pressure, heart rate, and others. Until recently, all IOP measurement methods (portable or nonportable) required individuals to be awakened for nocturnal measurements. Therefore, we speculate that the results of several studies conducted with hourly or punctual awakening may have been biased or falsely induced by stress-related artifacts or sleep-wake cycle disorganization. The present study identified few sleep changes related to hourly nocturnal awakening for IOP measurements. Participants seemed to compensate for the multiple awakenings imposed by increasing the total sleep period, so that total sleep time and the proportions of slow-wave and REM sleep stages in relation to total sleep time seemed unchanged. Sleep quality or fragmentation was also not altered by nocturnal IOP measurements, with sleep efficiency and the Microarousal Index remaining unchanged. We also found comparable 24-hour IOP rhythms and nocturnal IOP patterns evaluated using the CLS with and without hourly nocturnal awakening for IOP measurements. Nevertheless, an increase in CLS signal value variability throughout the night was observed when individuals were awakened.

Few studies have evaluated the effects of hourly forced awakening on sleep architecture in young healthy individuals. They have evaluated the effects of a few forced awakenings encountered in conditions such as Ramadan fasting or awakenings related to noise disturbances in young healthy individuals, and the results are balanced. In agreement with the
results of our study, these studies found no major disturbances in the different sleep stages, particularly in the number of REM cycles and the proportions of slow-wave and non-REM sleep stages in relation to total sleep time.

Forced awakening may have different effects in older individuals according to studies demonstrating that sleep architecture differs in the elderly, who are also more susceptible to environmental disturbances. No studies to date have evaluated the effects of forced experimental awakening on sleep architecture in the elderly. In older individuals with diseases, such as sleep apnea, that lead to multiple awakenings throughout the night, several sleep architecture disturbances have been demonstrated, including sleep fragmentation, an increase in microarousal, and a decrease in sleep efficiency, slow-wave sleep, and REM sleep. Further studies should evaluate the effects of hourly awakening for IOP measurements on sleep architecture and IOP rhythm in patients with glaucoma (most of whom are older than 50 years) in a similar manner as done in the present study. In some sleep disorders such as insomnia and restless legs syndrome that are associated with difficulty in initiating or maintaining sleep, the effect of hourly awakening might be greater. This underscores the value of new IOP measurement methods because insomnia and restless legs syndrome affect 20% and 8% of the general population, respectively.39,40

We found good correlation and cross-correlation of the 24-hour CLS measurements at sessions 1 and 2. Previous studies conducted with a noncontact or Goldmann applanation tonometer during a range of 12 to 24 hours have demonstrated poor intradividual reproducibility of IOP values and IOP rhythm variables. In contrast, previous investigations in patients with glaucoma using the same CLS have found good correlation between two 24-hour measurement sessions at a 1-week interval conducted without nocturnal awakening. In that study, the greater frequency of data acquisition with the CLS compared with noncontact or Goldmann applanation tonometry could explain the higher correlation between the 2 measurement sessions (24 time points with hourly noncontact or Goldmann applanation tonometry vs 288 time points with the CLS). The good correlation between the 2 sessions in our study also reinforces the finding that hourly awakening for IOP measurements does not seem to alter the 24-hour IOP pattern.

We found an increase in CLS signal value variability throughout the night when participants were awakened. Because sleep architecture is not disorganized by awakening, a technical reason may explain this finding. The CLS provides 10 data acquisitions per second during a 30-second measurement period, repeated every 5 minutes during 24 hours. The device does not indicate when acquisitions are made. Therefore, it is likely that some NCT IOP measurements of the fellow eye were obtained during CLS acquisitions of the first eye. Stress related to awakening, lid opening or contraction, or changes in body position could cause a sudden and unsustainable increase in the CLS signal that leads to greater variability throughout the night. Another limitation of our study may be the few participants, increasing the risk of type I error, which can be explained by the complexity of the experiments (two 24-hour sessions in a sleep laboratory with overnight polysomnography for each individual).

Conclusions

We found that sleep organization and 24-hour IOP rhythm seem to be unaffected by hourly nocturnal awakening for IOP measurements in young healthy individuals. This finding supports the results of previous studies conducted with IOP measurement methods requiring participants to be awakened and demonstrating a nyctohemeral rhythm of IOP in humans.