Relationship Between Nocturnal Intraocular Pressure Variations and Sleep Macrostructure

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Purpose. The purpose of this study was to characterize the relationships between nocturnal intraocular pressure (IOP) variations and sleep macrostructure in healthy subjects.

Methods. This was a cross-sectional study conducted in a center with shared expertise in chronobiology. Twelve healthy volunteers (22.3 ± 2.3 years) underwent a 24-hour IOP measurement session. The IOP variations of one eye were continuously estimated using a contact lens sensor (CLS) measuring the changes in corneal curvature related to the IOP and not requiring nocturnal awakening for measurements. The CLS measurement characteristics (mean, maximum, minimum, and amplitude) were evaluated across sleep stages (non–rapid eye movement [NREM] sleep [N1, N2, N3], REM) and assessed using polysomnography. The CLS signal measurement changes during sleep stage changes were calculated to evaluate the effects of sleep on IOP.

Results. A 24-hour IOP nyctohemeral rhythm was found in all subjects. During the nocturnal period, IOP signal values were significantly lower during wake stages than during REM and NREM N1, N2, and N3 sleep stages ($P \leq 0.04$). The IOP signal values were significantly higher during the REM stage than during the NREM stages ($P \leq 0.03$) and progressively decreased as NREM sleep deepened ($P \leq 0.04$). We found a positive relationship between the micro-arousal index and the nocturnal period CLS signal SD ($r = 0.76$; $P = 0.024$) and a negative relationship between sleep efficiency and the nocturnal period CLS signal SD ($r = -0.69$; $P = 0.041$).

Conclusions. Sleep micro- and macrostructure and nocturnal IOP variations are closely related in young subjects without sleep disorders. Across sleep stages, IOP is highest during REM sleep and progressively decreases as NREM sleep deepens.

Keywords: intraocular pressure, sleep, polysomnography, contact lens sensor, rhythm

Many physiologic parameters known to have an impact on intraocular pressure (IOP) levels and fluctuations vary across the different sleep stages: blood pressure, central venous pressure, heart and respiratory rate, body temperature, and sympathetic and parasympathetic nerve activity.[1–6] All studies on sleep and related 24-hour or nocturnal IOP rhythms conducted to date have used repeated IOP measurements (hourly or less frequent IOP measurements) requiring nocturnal awakenings, thus potentially disturbing sleep structure, blood pressure dipping status,[7] and sympathetic activity. These repetitive arousals actually prevented a continuously valid evaluation of the relationship between IOP variations and sleep micro- and macrostructure.[8–12]

A contact lens sensor (CLS; SENSIMED Triggerfish; SENSIMED AG, Lausanne, Switzerland) was recently developed to continuously monitor IOP noninvasively over 24 hours in an ambulatory setting.[13–16] The measurement using this device is based on the assumption that a correlation exists between IOP and corneal curvature.[5] We previously demonstrated that this new device is an accurate and reproducible method to characterize the 24-hour nyctohemeral IOP rhythm in young healthy subjects, although the CLS signal cannot be translated in absolute IOP expressed in millimeters of mercury at each point of the 24-hour session.[17–19]

The present study takes advantage of this new noninvasive method monitoring IOP fluctuations without induced arousals to evaluate the physiologic relationships between nocturnal IOP level variations and sleep micro- and macrostructure in healthy young subjects free of sleep disorders.

Methods

Study Population

The protocol has been previously described in detail.[17–19] This prospective investigation was conducted in a university-affiliated hospital sleep laboratory, followed the tenets of the Declaration of Helsinki, and was approved by the local institutional review board (#8881). All participating subjects provided both verbal and written informed consent. Participants were paid for their time and effort.

Twenty-four eyes of 12 healthy subjects were studied. Inclusion criteria were as follows: subjects free of sleep disorders, without endocrine illness or ocular disease (spherical

equivalent between −1 and +1 diopter), with regular lifestyle habits and usual sleep duration lasting approximately 8 hours. The exclusion criteria were as follows: 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, gonioscopy, fundus examination, and ultrasound pachymetry [Pocket II pachymeter; Quantel Medical, Clermont-Ferrand, France]). All subjects also filled out a general health questionnaire and underwent a complete physical examination. The eyes studied were randomized when both were eligible.

IOP Measurements

The CLS (Triggerfish; SENSIMED AG) is a highly oxygen-permeable soft contact lens whose key elements are two 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 edge) exists in three 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).

Polysomnography

Continuous recordings were taken 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 ECG with a modified V2 lead. Sleep was scored manually according to standard criteria.[20] Air flow was measured with nasal pressure associated with the sum of buccal and nasal thermistor signals. Respiratory effort was monitored with abdominal and thoracic bands. Oxygen saturation was measured using a pulse oximeter.

Experimental Sessions

Subjects 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 by ambulatory actigraphy monitoring using a wrist accelerometer Actiwatch (CamNtech, Cambridge, UK). During the experimental sessions, they were requested not to drink alcohol- and caffeine-containing beverages. Although the patients were housed in the hospital, they were allowed to have free activities during the diurnal period of the 24-hour session (9 AM to 10 PM). Subjects were asked to go to bed at 10 PM and were asked to get up at 8 AM.

Statistical Analysis

From raw IOP data over 24 hours, a nonlinear least-square, 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, Φ_1 is the acrophase of the fundamental cosine fit, Φ_2 is the acrophase of the first harmonic cosine fit, τ is the endogenous circadian period (set at 24 hours due to entrained conditions), M is 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 (M; 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.[21,22]

The CLS measurement characteristics (mean signal, maximum signal, minimum signal, and amplitude) were evaluated across sleep stages (non–rapid eye movement [NREM] sleep [N1, N2, N3] and REM). The CLS signal measurement changes during sleep stage changes were calculated to evaluate the effects of sleeping or awakening on IOP. The relationship between the micro-arousal index, sleep efficiency (total sleep time per sleep period), and the nocturnal period CLS signal SD was examined to evaluate the influence of sleep quality and fragmentation on nocturnal IOP fluctuations.

The skewness-kurtosis normality test was used to assess the normality of the measurements. The paired Student's t-test and ANOVA were used to compare means and percentages. McNemar χ^2 tests were used for the analysis of dichotomous variables. Correlations were evaluated using the Pearson correlation coefficient. Data analyses were performed using SPSS (Statistical Package for the Social Sciences, version 17.0; SPSS, Inc., Chicago, IL, USA) and R software (version 2.14; R Foundation for Statistical Computing, Vienna, Austria).

Results

Subject Characteristics

Twelve healthy Caucasian subjects (24 eyes) were included (eight women and four men; 22.3 ± 2.3 years old; body mass index, 20.8 ± 2.0 kg/m^2). All subjects were easily fitted with the Triggerfish CLS (nine medium lenses, two steep, and one flat, depending on keratometry) on one randomly selected eye (six left eyes and six right eyes). At inclusion, mean IOP values using Goldmann applanation tonometry were 13.8 ± 2.1 mm Hg on the right eye and 13.7 ± 1.9 mm Hg on the left eye (P = 0.9). Total sleep time (TST, total of NREM [N1, N2, N3] and REM sleep in a period), total sleep period (TSP, period of time measured from sleep onset to final awakening), sleep efficiency (TST/TSP), sleep architecture with absolute and percentage of time spent awake after sleep onset (WASO), NREM (N1, N2, and N3) and REM sleep, number of cycles per night, and the micro-arousal index are displayed in Table 1.

Intraocular Pressure and Sleep Stages

The minimum, maximum, amplitude, and mean signal values of the population during the 24-hour and the diurnal periods and during each sleep stage of the sleep period (wake NREM N1, N2, N3, and REM) are summarized in Table 2. All subjects had a nocturnal acrophase (3:51 AM ± 43 minutes; range, 3:26 AM to 4:12 AM) and a diurnal bathyphase (2:30 PM ± 34 minutes; range, 2:12 PM to 2:48 PM).

The relationship between the sleep stages and the IOP signal values was evaluated using ANOVA. We found a significant relationship between the sleep stages and the IOP signal values (P = 0.02). Follow-up multiple post hoc pairwise comparisons were then performed to compare the different groups. The significance level was not adjusted for those post hoc comparisons, given that an ANOVA test was performed first and showed a significant relationship. We compared the IOP values during awakening and during various sleep stages. The IOP signal values were significantly lower during

Table 1. Sleep Duration, Quality, and Architecture With Absolute and Relative NREM (N1, N2, and N3) and REM Sleep Stage Duration and Percentages of Total Sleep Time

Sleep Parameters	Mean ± SD [95% CI]
Total sleep time, min	365.3 ± 48.6 [337.8; 392.8]
Total sleep period time, min	459.9 ± 29.4 [443.2; 476.5]
Sleep efficiency, total sleep time/sleep period	79.4 ± 11.5% [72.8; 86.1]
Wake after sleep onset, min	110.1 ± 36.1 [92.2; 128.0]
Stage N1, min and (% of total sleep time)	40.7 ± 20.1 [29.3; 52.1] (11.1)
Stage N2, min and (% of total sleep time)	179.0 ± 35.4 [158.9; 199] (49.3)
Stage N3, min and (% of total sleep time)	66.1 ± 17.1 [56.7; 76.1] (18.1)
REM sleep, min and (% of total sleep time)	79.6 ± 27.8 [63.8; 95.3] (21.5)
Number of cycles per night	5.5 ± 0.5 [5.2; 5.8]
Micro-arousal index, number/h of sleep	6.4 ± 3.2 [4.6; 8.2]

Data are presented as mean ± SD [95% confidence interval].

awakening than during REM and NREM N1, N2, and N3 stages ($P = 0.04$, 0.02, 0.01, and 0.01, respectively). We compared the IOP values during the REM stage and the NREM stages. The IOP signal values were significantly higher during the REM stage than during the NREM N1, N2, and N3 stages ($P = 0.03$, 0.02, and 0.018, respectively). Finally, the IOP values were compared during the slow-wave N3 stage to the N1 and N2 NREM stages. The IOP signal values were significantly higher during NREM N1 and N2 stages than during the NREM N3 stages ($P = 0.04$ and 0.02, respectively). Figure 1 shows the 24-hour raw and modeled individual IOP curves of two subjects and illustrates that IOP follows a nyctohemeral rhythm in young healthy subjects and was lower during the diurnal period and higher during the nocturnal period.

Intraocular Pressure Changes Across Sleep Stages

The CLS signal measurement changes from one sleep stage to another are summarized in Table 3. The CLS signal significantly increased when moving from wake to REM and NREM N1 and N2 stages ($P = 0.004$, 0.03, and 0.04, respectively). The CLS signal significantly increased when going from NREM N2 and N3 stages to REM stages ($P = 0.018$ and 0.028, respectively). The CLS signal significantly decreased when going from REM to wake ($P = 0.027$) and from NREM N1, N2, and N3 stages to wake ($P = 0.04$, 0.038, and 0.021, respectively).

The CLS signal measurement changes during the night are summarized in Table 2. We found a significant negative relationship between changes in sleep stages and changes in CLS values, indicating that CLS values increase during sleeping (i.e., negative changes in sleep stages) and decrease during awakening (i.e., positive changes in sleep stages; $P = 0.026$).

Intraocular Variability and Sleep Quality

We found a significant positive relationship between the micro-arousal index and the nocturnal period CLS signal SD ($r = 0.76$, $P = 0.024$) and a significant negative relationship between sleep efficiency (total sleep time per sleep period) and the nocturnal period CLS signal standard deviation ($r = -0.69$, $P = 0.041$).

Table 2. Contact Lens Sensor Signal Measurement Characteristics: Minimum, Maximum, and Mean Signal Values and Amplitude

Signal Measurements	24-h	Nocturnal Period, 10 PM to 8 AM	Nocturnal Period W Stage	Nocturnal Period REM Stage	Nocturnal Period N1 Stage	Nocturnal Period N2 Stage	Nocturnal Period N3 Stage
Mean signal, eqVm	3.4 ± 10.9 [−2.8; 9.6]	12.9 ± 15.5 [4.1; 21.7]	10.02 ± 4.22 [3.2; 16.9]	15.75 ± 2.40 [5.6; 25.9]	13.50 ± 3.52 [4.9; 22.1]	13.31 ± 2.77 [5.0; 21.5]	12.24 ± 2.78 [4.1; 20.3]
Maximum signal, eqVm	28.0 ± 10.2 [22.2; 33.8]	22.6 ± 16.5 [13.2; 31.9]	18.8 ± 5.21 [12.1; 25.6]	22.4 ± 3.1 [13.2; 31.6]	21.0 ± 4.1 [11.7; 30.3]	21.4 ± 2.9 [10.9; 31.9]	19.2 ± 2.6 [10.7; 27.7]
Minimum signal, eqVm	−20.7 ± 21.1 [−32.7; −8.7]	−0.5 ± 18.1 [−10.7; 9.7]	−0.5 ± 7.84 [−10.1; 9.5]	2.4 ± 5.64 [−7.8; 10.2]	1.9 ± 4.79 [−8.3; 10.2]	1.1 ± 4.44 [−8.8; 10.0]	0.2 ± 4.08 [−8.1; 8.4]
Amplitude, eqVm	48.1 ± 23.3 [34.9; 61.3]	22.8 ± 6.1 [19.3; 26.2]	19.3 ± 9.45 [17.4; 21.4]	24.8 ± 7.63 [20.7; 28.9]	23.0 ± 7.10 [20.1; 26.0]	22.5 ± 6.78 [19.8; 25.3]	19.4 ± 6.45 [17.0; 22.2]

Data are presented as mean ± SD [95% CI]. W, wake.

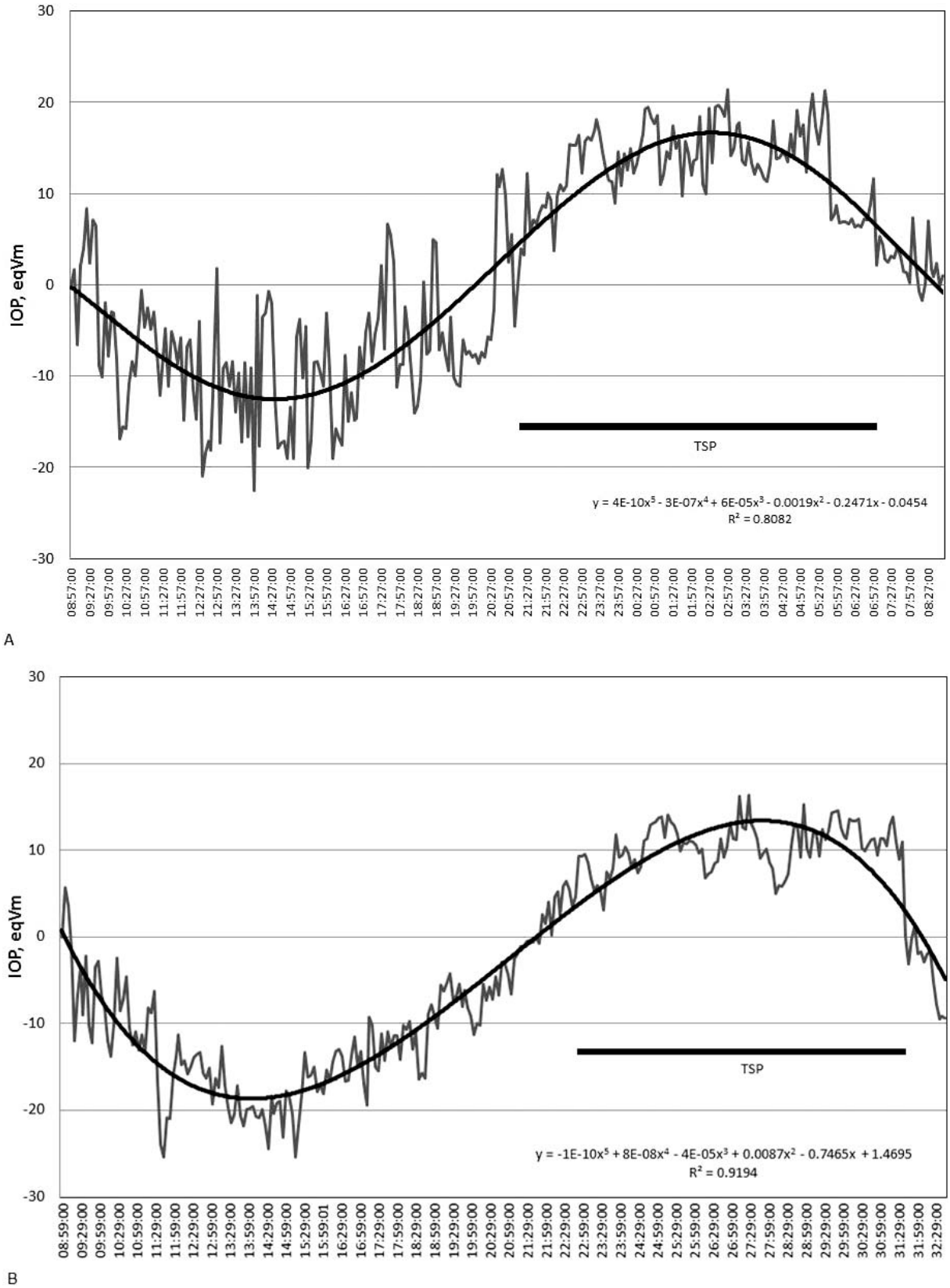

Figure. (**A**, **B**) Examples of 24-hour raw and modeled individual IOP curves of two subjects. The IOP is expressed in eqVm.

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Table 3. Contact Lens Sensor Signal Measurement Changes During Sleep Stage Changes

Sleep Stage Changes	W	REM	N1	N2	N3
From W to		+2.16 ± 0.94*	+2.58 ± 1.02*	+1.89 ± 0.76*	NA
From REM to	−4.56 ± 1.44*		−1.95 ± 0.97	−2.06 ± 0.81*	NA
From N1 to	−1.74 ± 0.88	NA		−0.31 ± 0.27	−1.09 ± 0.41
From N2 to	−2.07 ± 0.72*	+3.24 ± 1.11*	NA		−0.51 ± 0.37
From N3 to	−1.49 ± 0.56*	+2.47 ± 0.84*	NA	−0.08 ± 0.67	

Data are presented as mean ± SD. The mean change in CLS signal when going from REM to wake could be found in the third line, second column (–4.56 ± 1.44).

* Significant change ($P < 0.05$).

Discussion

Using an innovative continuous IOP measurement that does not disturb sleep, we evaluated the physiologic relationships between nocturnal IOP levels and variations and sleep quality and structure in healthy subjects. We found that during the nocturnal period, the IOP was lower during awakening than during REM and NREM N1, N2, and N3 sleep stages. Among the sleep stages, IOP was higher during the REM stage and progressively decreased with deepening of NREM sleep. We found a higher variability in nocturnal IOP in subjects with the highest micro-arousal index and the lowest sleep efficiency.

Only two previous studies have assessed the relationships between sleep macrostructure and IOP levels and fluctuations.[8,10]

The first one was conducted in 12 young and 12 older healthy subjects.[8] During a 24-hour period, IOP was measured hourly with a Tono-Pen electronic tonometer (Oculab, Glendale, CA, USA). Nocturnal polysomnography was performed. The IOP was lower during wakefulness (14.9 ± 0.1 mm Hg) than during light sleep (16.6 ± 0.3 mm Hg), slow-wave sleep (17.0 ± 0.4 mm Hg), and REM sleep (16.0 ± 0.3 mm Hg). The difference in IOP between slow-wave and REM sleep was significant ($P = 0.03$). However, it should be noted that subjects were awakened hourly for IOP measurements. Oxybuprocaine eye drops were administered before IOP measurements, and series of three to six measurements were repeated until the intermeasure variability was less than 5%. For these reasons, the authors reported a duration of IOP measurement longer than 1 minute (81.4 ± 2.1 and 85.3 ± 3.6 seconds in young and older subjects, respectively). The mean delay for returning to sleep after IOP measurements was rather long: 198.5 ± 15.2 and 521.0 ± 85.4 seconds in young and older subjects, respectively. Moreover, in this study, IOP was not strictly speaking measured during sleep, but immediately after awakening. Another reason that could explain the differences with our study is that only six to nine nocturnal IOP measurements were taken for each subject depending on sleep duration (hourly measurements). Because this was not sufficient to obtain several IOP values during each of the sleep stages for each subject, the data from all subjects were pooled before comparing IOP values among sleep stages. In one individual subject, it was not possible to compare the IOP levels or variations among sleep stages, nor to evaluate the IOP changes when going from one sleep stage to another. By

Table 4. CLS Signal Measurement Changes During Sleeping/Awakening

Number of Sleep Stage Changes		
+ 4 (awakening)	W (stage 5)	−0.72 ± 0.66*
+ 3 (awakening)	REM (stage 4)	−1.79 ± 0.47*
+ 2 (awakening)	N1 (stage 3)	−3.79 ± 0.81*
+1 (awakening)	N2 (stage 2)	−3.45 ± 0.94*
−1 (sleeping)	N3 (stage 1)	+1.15 ± 0.51*
−2 (sleeping)	Sleeping: negative change	+1.08 ± 0.33*
−3 (sleeping)	Awakening: positive change	+0.08 ± 0.56*
−4 (sleeping)		NA

Data are presented as mean ± SD. Sleep occurs in repetitive cycles of approximately 90 minutes, usually four or five of them per night, which include an increasing proportion of REM sleep as they repeat. The whole cycle normally proceeds in the following order: N1 → N2 → N3 → REM or N1 → N2 → N3 → N2 → REM.

* Significant change ($P < 0.05$).

contrast, in our study, 3600 data points were acquired every hour, making it possible to obtain thousands of IOP values for each of the subjects' sleep stages and to make intraindividual paired comparisons.

The second study conducted by the same team using a similar design assessed 16 healthy young African volunteers and 11 young African open-angle glaucoma patients.[10] During a 24-hour period, IOP was measured hourly with a Modular One pneumatonometer (Modular One; Digilab, Cambridge, MA, USA). Nocturnal polysomnography was performed. The IOP was also lower during wakefulness than during light sleep, slow-wave sleep, and REM sleep. The variations in IOP were lowest during REM sleep and highest during slow-wave sleep. This study, however, has the same limitations as the above-mentioned study, which we believe could explain that the IOP and IOP variations were found lower during the REM sleep than during the slow-wave sleep, whereas we found the opposite.

Many ocular or systemic factors involved during the sleep stages could explain the higher IOP levels during REM sleep and the wake state than during NREM stages.

Local Factors

Studies have shown that blinking and eye movements could increase IOP.[23,24] Blinking and eye movements are frequent during the REM sleep stages and micro-arousals and by contrast much less frequent during the NREM sleep stages, particularly during the deep slow-wave NREM sleep stages.

Systemic Factors

Studies have found that compared with wake and REM sleep, NREM sleep is characterized by a predominance of vagal parasympathetic activity, with a decline in sympathetic activity that is most pronounced in slow-wave sleep.[7,25] Consequently, blood pressure, central venous pressure, and the heart and respiratory rates decrease throughout NREM sleep, particularly during slow-wave sleep. This physiologic context could explain that we found that IOP continuously decreases with the progressive deepening of NREM sleep. By contrast, studies have demonstrated that in REM sleep, sympathetic activity increases significantly and is highly variable.[7,25,26] Consequently, blood pressure and heart rate are higher and highly changeable. This could also explain that we found a significantly higher IOP during the REM sleep compared with the NREM sleep.

The findings of the present study have important implications for physiologic knowledge and clinical relevance.

Given that the NREM sleep is prominent at the beginning of the night, whereas the duration of the REM sleep increases during the last sleep cycles, the findings of the present study could explain that the acrophase of the IOP 24-hour variation occurs in the second part of the night or in the early morning just before awakening in a vast majority of healthy subjects.[8–10,12,17,19]

The finding that the nocturnal regulation of IOP is related to sleep characteristics could suggest that sleep disorders affect the nyctohemeral and nocturnal rhythms of IOP and increase the nocturnal variability of IOP. Numerous studies have evaluated the relationships between glaucoma and sleep apnea, and the association between glaucoma and sleep apnea is still debated.[27] Further studies should also evaluate the impact of other disturbances in sleep quality and quantity on 24-hour and nocturnal IOP and, in turn, ocular diseases.

In a recent study, a customized algorithm developed by the manufacturer of the device allowing to detect and quantify eye blinks and to identify wake and sleep periods (REM and NREM) from the signal recorded was presented.[28] Because the algorithm used in this study was a customized algorithm but is not yet commercially available, we did not detect eye blinks and identify wake and sleep periods from the CLS signal in the present study. As taking a measurement only with the CLS is much more convenient for the patient than undergoing a complete polysomnography, it would be interesting to compare the results of sleep studies and the results of sleep evaluation provided by this new algorithm in future studies.

In conclusion, we found that sleep micro- and macrostructure and nocturnal regulation of IOP are related in young healthy humans. During the nocturnal period, IOP is lower during the wake stages than during the REM and NREM N1, N2, and N3 stages. Among sleep stages, IOP is higher during the REM stage and continuously decreases with the progressive deepening of NREM sleep. Intraocular pressure is highly variable in subjects with poor sleep quality. These data open new avenues in research and prompt to evaluate sleep quality and quantity in clinical studies in patients with ocular hypertension or glaucoma.

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