24-Hour Intraocular Pressure of Young Healthy Humans in Supine Position: Rhythm and Reproducibility

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Purpose. We evaluated the supine 24-hour IOP rhythm reproducibility over 6 weeks in healthy humans.

Methods. Six healthy young male subjects underwent six 24-hour sessions of IOP measurements over a 6-week period. Subjects were housed in a sleep laboratory in a constant controlled supine position and in a strictly controlled environment. IOP was measured hourly using a pneumatonometer. A nonlinear least-squares dual harmonic regression analysis was used to model the 24-hour IOP rhythm. The intra- and intersubject variability of acrophase, bathyphase, amplitude, and IOP values were evaluated.

Results. A significant nyctohemeral IOP rhythm was noted in 30 of 36 (83%) sessions. Mean nocturnal IOP was significantly higher than diurnal IOP (20.1 ± 0.2 mm Hg [SD] vs. 18.8 ± 0.1 mm Hg, $P < 0.001$) in all subjects. Amplitudes were not statistically different among subjects ($P = 0.52$). In contrast, acrophase and bathyphase were statistically different ($P < 0.05$). Intrasubject homogeneity of distribution over time of the acrophase and bathyphase was significant in 3 of 6 and 4 of 6 subjects, respectively. Intraclass correlation coefficients of midline estimating statistic of rhythm (MESOR) and IOP values at 2:00, 3:00, 4:00, 10:00, and 11:00 AM, and 2:00 PM showed fair to good agreement among sessions.

Conclusions. In a constant supine position, all subjects exhibited a nyctohemeral IOP rhythm present at an average rate of 80% of all sessions. With the currently available methods of tonometry, intrasubject reproducibility of rhythmic parameters and IOP values is limited. IOP values in the morning and IOP MESOR were the most reproducible parameters among the six visits. (*Invest Ophthalmol Vis Sci.* 2012;53:8186–8191) DOI:10.1167/iovs.12-10877

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IOP is known to vary throughout the 24-hour period of a day, defined as a nyctohemeral rhythm in humans.[1–9] The 24-hour IOP changes have been defined as circadian in animals, using appropriate methodology, such as rhythmic synchronization by the environmental light-dark cycle and persistence in constant darkness.[10–13] Many factors influence the IOP's nyctohemeral variations (e.g., age, myopia, stage of sleep, posture),[2,5,6,14] the most important factor being posture.[2,4,7,14] IOP is higher in the supine position than in the sitting position due to elevation of episcleral venous pressure[15,16] and this may participate in IOP elevation during the night. However, IOP remains higher during the night than the day even during the 24-hour constant supine position.[2,4–7,9,17,18] The existence of circadian control suggests that IOP rhythm could be constant and repeatable.

To our knowledge, reproducibility of the IOP measurements has been evaluated previously only on a temporal range of 12 hours by comparing two hour-by-hour measurements 1 week apart on sitting subjects with a Goldmann tonometer.[19,20] These studies showed fair to good agreement for IOP values at any given time on different days, but essentially no agreement for IOP fluctuations.[20] In a recent study,[21] a novel contact lens device was used in glaucoma patients, and the investigators measured the association of 24-hour IOP changes (in arbitrary units) across two sessions 1 week apart. The results of this study suggest fair to good agreement between pairs of intervals across sessions using this device.

The goal of the present study was to characterize IOP rhythm variability during six separate 24-hour sessions of continuous bedrest in healthy subjects over a 6-week period.

Methods

Patients

Our 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 (#5921, CPP SUD-EST V, 2010–39). All healthy subjects provided verbal and written informed consent.

Inclusion criteria were healthy subjects who were free of sleep disturbance, endocrine illness, or ocular disease (spherical equivalent between −2 and +1 diopter), with regular life habits and a habitual total sleep time of approximately 8 hours. Exclusion criteria were shift workers, experience of a transmeridian flight less than 2 months before the beginning of the study, any medical treatment, and tobacco smokers.

All study participants underwent a complete ophthalmic examination, including refraction, slit-lamp biomicroscopy, IOP measurement (Goldmann tonometer), gonioscopy, and fundus examination. The ophthalmologic examination was completed by visual field tests (Humphrey 24/2 Sita-Standard visual field) and a color vision test

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(Ishihara test and Farnsworth-Munsell 100 Hue test). All study participants also filled out a general health questionnaire and underwent a complete physical examination.

Experimental Sessions

The six subjects were studied during six 24-hour sessions over a period of 6 weeks. The sessions were strictly 1 week apart and took place on weekdays (Monday, Wednesday, or Friday) in November and December. One week before the onset of the experimental sessions, subjects were studied for 1 day in ambulatory conditions (while receiving explanations and undergoing tonometer tests). The subjects maintained a self-selected constant sleep-wake schedule (onset between 10:00 PM and 12:00 AM, and waking between 7:00 and 8:00 AM) 1 week before and during the study (verified by sleep-wake diaries). During the experimental sessions, they were requested not to drink alcohol and caffeine-containing beverages.

For each experimental session, subjects were housed in a sleep laboratory for 24 hours in a strictly controlled environment (light cycle, temperature, fluid intake, meals) and maintained continuous bed rest with continuous monitoring of sleep at night. The subjects were not allowed to sleep during the day. Hourly IOP measurements of the right eye started at 9:00 AM and were performed over 24 hours in the supine position with a pneumatonometer (Modular One; Digilab, Cambridge, MA). The IOP measurements were taken after the instillation of a contact anesthetic (oxybuprocaine; Théa, Clermont-Ferrand, France), in one series of 120 consecutive measurements (40 measurements/s) until the SE of the measurements was less than 0.05 mm Hg. At night the subjects were awakened hourly for IOP measurement, remaining recumbent in bed.

Statistical Analysis

A nonlinear least-squares, dual-harmonic regression analysis[22,23] was used to model the 24-hour rhythms of IOP:

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

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 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 (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. All values shown are the mean ± SD. Student's *t*-test was used for statistical comparison between diurnal IOP (9:00 AM–11:00 PM) and nocturnal IOP (11:00 PM–9:00 AM). The subjects' mean amplitudes were tested with an ANOVA between subjects. The distribution over time of the acrophase and bathyphase were analyzed using the Rayleigh test and the Watson-Williams test.[24] The intrasubject relationship between IOP curves was quantified using cross correlation analysis.[25] The homogeneity of lags between curves to obtain the maximum correlation coefficients was analyzed using the χ^2 test.

The intraclass correlation coefficient (ICC) was used to assess the IOP agreement at the six visits; the analyses included: IOP assessment at each time point of the 24-hour IOP curve (e.g., IOP at 9:00 AM compared over the six visits), and assessment of calculated amplitude, acrophase, bathyphase, and MESOR of the modeled rhythm. The following interpretation scheme for ICC has been described: <0.4 represents poor agreement beyond chance, 0.4 to 0.75 represents fair to good agreement beyond chance, and >0.75 represents excellent agreement beyond chance.[26] Data analyses were performed using SPSS (version 17.0, Statistical Package for the Social Sciences; SPSS Inc., Chicago, Illinois) and R software (version 2.14; R Foundation for Statistical Computing, Vienna, Austria).[27] Differences reaching a P value less than 0.05 were considered statistically significant.

Results

Six healthy male Caucasian subjects aged 24.7 ± 1.4 years (body mass index 22.6 ± 1.8 kg/m^2) participated in the study. The mean ± SD, maximum and minimum IOP characteristics by subject, and 24-hour IOP measurements are described in Table 1.

Characterization of IOP Rhythm within the Group Of Healthy Subjects

After modeling the 24-hour IOP curves, a significant IOP rhythm was identified in 30 of the 36 sessions (83%, Table 1). Throughout the six sessions, mean IOP amplitude of all subjects was 2.1 ± 0.9 mm Hg. Amplitude means were not statistically different among the six subjects ($P = 0.52$). Mean nocturnal IOP was significantly higher than diurnal IOP (20.1 ± 0.2 mm Hg [SD] vs. 18.8 ± 0.1 mm Hg, $P < 0.001$) in all subjects. The average acrophase of the population was 7:35 AM ± 5 hours 02 minutes. The average bathyphase of the population was 9:32 PM ± 2 hours 08 minutes. Among these six subjects, the homogeneity of mean acrophases and mean bathyphases was rejected ($P < 0.05$, Watson-Williams test), meaning that acrophases and bathyphases were significantly different from one subject to another. Figure 1 illustrates, for one subject, the raw IOP curves over 24 hours and the corresponding modeled curves. Figure 2 displays graphically the characteristics of IOP rhythms for each subject.

Study of Repeatability of IOP Measurements and Rhythms

For each subject, the distribution of the acrophase and bathyphase over 24 hours is summarized in Table 2. A unimodal distribution of acrophase (meaning that acrophases were not significantly different from one session to another) was found with a specified mean direction in three of the six subjects (50%) and a unimodal distribution of bathyphase with a specified mean direction in four of the six subjects (67%).

For each subject, the correlations of the six individual modeled IOP curves are shown in Table 3. The cross-correlation of the individual modeled 24-hour curves showed a correlation coefficient between 0.67 and 0.93 in five of the six subjects. The homogeneity test showed a significant lag between the modeled curves for each subject.

In the population, the ICCs of each hour's IOP measurement over the 24-hour cycle (raw data) ranged from −0.27 to 0.9. The ICCs (95% confidence interval [CI], P value) were 0.82 (0.43–0.97, $P = 0.04$) for 2:00 AM, 0.89 (0.66–0.98, $P = 0.004$) for 3:00 AM, 0.82 (0.46–0.97, $P = 0.04$) for 4:00 AM, 0.86 (0.56–0.98, $P = 0.02$) for 10:00 AM, 0.90 (0.68–0.98, $P = 0.003$) for 11:00 AM, and 0.81 (0.46–0.97, $P = 0.03$) for 2:00 PM, which showed fair to good agreement. Analyzing the parameters of rhythm, the ICC of the MESOR was significant (0.81 [0.46–0.97], $P = 0.03$) with fair to good agreement. There was a trend for the significance of ICC of the amplitude (0.76 [0.33–0.96], $P = 0.08$) and the bathyphase (0.76 [0.34–0.96], $P = 0.08$). The ICCs of the acrophase (0.30 [–0.84 to 0.88], $P = 0.63$) were not significant.

Table 1. Descriptive Data of IOP Measurements of the Six Healthy Subjects

		Raw IOP		24-Hour IOP Descriptive Statistics				
				Nonlinear Least-Squares, Dual-Harmonic Modeling of IOP Rhythm				
Subjects	Days	Min, mm Hg	Max, mm Hg	Amplitude, mm Hg	Mean Amplitude, mm Hg ± SD	MESOR IOP, mm Hg	Bathyphase, h	Acrophase, h
Subject 1	Day1	16	26	1.9	1.5 ± 0.3	19.5	12:00 AM	6:30 AM
	Day2	14	24	1.8		19.6	3:36 AM	11:00 AM
	Day3	14	21	1.1		18	NA	NA
	Day4	16	21	1.1		18.4	10:06 PM	3:30 PM
	Day5	16	21	1.4		18.6	1:06 AM	8:06 AM
	Day6	16	22	1.5		18.5	1:36 AM	8:30 AM
Subject 2	Day1	14	25	4.5	3.1 ± 1.2	19.5	7:00 PM	3:18 AM
	Day2	15	24	1.8		19.4	NA	NA
	Day3	15	22	1.9		18.2	6:54 PM	2:24 AM
	Day4	13	22	3		17.1	12:00 PM	4:30 AM
	Day5	16	24	3		18.4	11:36 AM	4:24 AM
	Day6	14	27	4.6		18.4	6:36 PM	2:48 AM
Subject 3	Day1	16	26	1.3	2.5 ± 0.8	20.7	NA	NA
	Day2	15	25	2.1		19.6	8:54 PM	6:18 AM
	Day3	15	26	2.9		19.4	2:36 PM	6:18 AM
	Day4	17	24	2.3		20.5	6:54 PM	3:24 AM
	Day5	16	26	3.7		20.7	5:24 PM	2:00 AM
	Day6	16	23	2.5		18.6	6:18 PM	2:36 AM
Subject 4	Day1	17	24	1.1	1.7 ± 0.4	20.8	10:42 PM	12:48 PM
	Day2	15	23	1.4		18.7	NA	NA
	Day3	16	26	2.1		21.4	9:48 PM	5:06 AM
	Day4	16	22	1.6		19.5	12:00 AM	4:36 PM
	Day5	17	27	1.3		20.7	NA	NA
	Day6	15	23	2.2		19.6	12:00 AM	6:48 AM
Subject 5	Day1	16	24	1.6	1.8 ± 0.9	18.9	6:18 AM	1:24 PM
	Day2	14	22	1.2		18.5	NA	NA
	Day3	14	21	1.6		18.2	4:48 AM	12:00 PM
	Day4	15	21	1.5		18.6	4:54 AM	12:06 PM
	Day5	16	24	1.5		19.7	10:54 PM	7:00 AM
	Day6	14	24	3.6		18.5	3:30 AM	11:06 AM
Subject 6	Day1	16	26	1.6	2 ± 0.6	20.8	12:54 AM	5:06 PM
	Day2	16	26	1.3		20.5	8:18 PM	4:24 AM
	Day3	13	26	2.5		19.1	4:48 PM	12:24 AM
	Day4	17	24	2.1		19.7	9:36 PM	4:54 AM
	Day5	16	25	1.8		19.6	3:54 PM	7:48 AM
	Day6	15	23	2.8		19.3	3:30 PM	7:48 AM

Data from significant dual-harmonic modeling of rhythm are highlighted in gray. NA, Non applicable (nonsignificant modeling).

Discussion

In our study, we evaluated the intraocular pressure rhythm reproducibility over six separate 24-hour sessions of continuous bedrest over a 6-week period in healthy humans. We found that most healthy subjects exhibited a nyctohemeral rhythm of IOP in a constant position, with a higher nocturnal IOP. Among the subjects, the parameters of the 24-hour IOP patterns (acrophases and bathyphases) usually were significantly different. The most robust parameter among sessions for each subject was the MESOR, and the most reproducible IOP measurements were taken between 2:00 and 11:00 AM.

To our knowledge, this is the first study to evaluate the reproducibility over 6 weeks of 24-hour IOP patterns in healthy subjects. The methodology of the study is complementary to previous clinical experiments in healthy humans, usually studying diurnal variations (12 hours) in the sitting position, in real-life conditions. We took IOP measurements every hour in continuous bed rest conditions and in controlled environmental conditions specifically to avoid the stimuli that may influence IOP so as to unmask its endogenous rhythm. IOP data then were modeled mathematically. Hourly measurements made modeling the rhythms significantly more precise and meaningful.[2,14] The nonlinear least-squares dual harmonic regression procedure[22,23] that was used in our study has the advantage of being applicable to all sorts of rhythms and not exclusively to monophasic rhythms, and does not assume a priori that a rhythm is sinusoidal, in contrast with the cosinor technique.

All subjects studied were male. The influence of the menstrual cycle on sleep is well known, in particular, but not only, in females with premenstrual syndrome. The endogenous circadian clock has been shown recently to tick with a slightly different intrinsic period in males and females.[28] It is known that the estrogen receptors and progesterone receptors are present in the ciliary body of the human eye in male and female subjects.[29] Some studies have shown that, in nonglaucomatous women or in women with glaucoma, IOP is different between pre- and postmenstrual phases.[30] Therefore, because menstruation or sleep and the circadian system are potential drivers of IOP rhythm, we chose to include only male subjects to avoid a potential gender effect, which would have

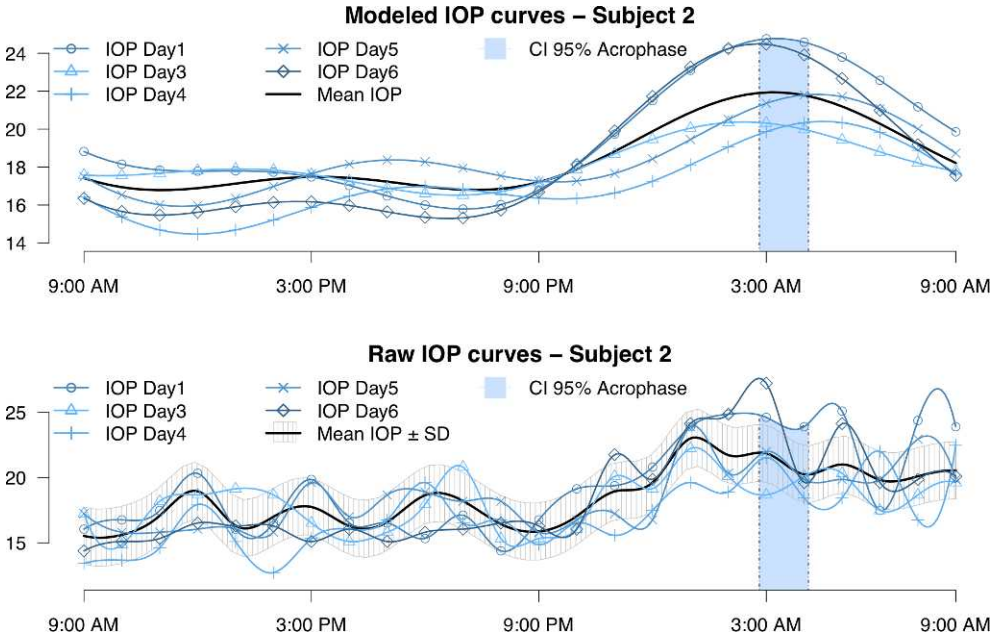

Figure 1. Modeled and raw individual IOP curves of subject #2.

increased intersubject variability and would have required a higher number of subjects to keep the same statistical power. The experimental conditions may at least explain partially that our conclusions sometimes are different from those of previous studies. Limitations of our study could be the small number of subjects, which can be explained by the complexity of the experiments (study of 36 nyctohemeral cycles) and the verification of sleep-wake schedules using self-reported diaries.

One of the characteristics of the rhythm in healthy subjects in the supine position was an average IOP at night higher than the diurnal IOP, as described previously.[2,4,7,9,14,18] Further, the average acrophases in healthy subjects was at 7:35 AM ± 5 hours 02 minutes, which was comparable to previously reported values (7:43 AM ± 6 hours 15 minutes, right eye).[9] In our study, 50% of the mean subject acrophases were reported during the nighttime (before 9:00 AM), similar to the range found by Liu et al.[4] and 50% during the morning phase (before 12:00 PM). Among different healthy subjects, acrophases and bathyphases varied, and usually were not comparable between subjects. The larger distribution of the acrophases in the constant supine position may be explained by the effect of posture with an estimated IOP difference between night (supine position) and day (sitting position) of about 4 mm Hg.[6] We found no additional data in the literature comparing the

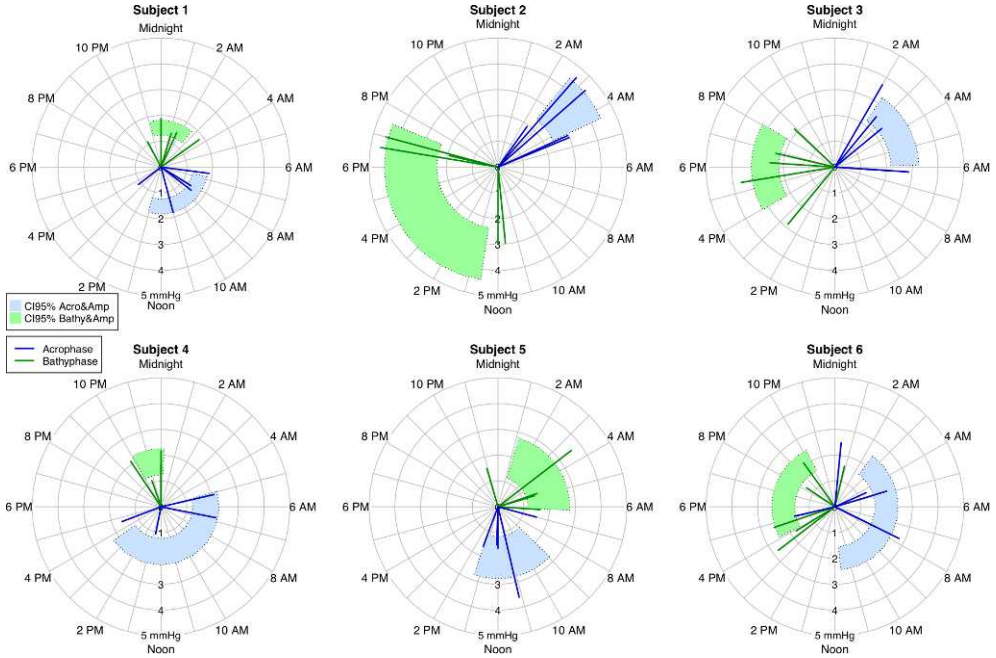

Figure 2. Polar graphs of the distribution over the six sessions of the acrophase and bathyphase for six subjects. *Acro&Amp*: Acrophase and its amplitude. *Bathy&Amp*: Bathyphase and its amplitude.

Table 2. Distribution of Acrophase and Bathyphase over the Six 24-Hour Measurements

	Calculated Acrophase		Calculated Bathyphase	
	Mean, h (95% CI)	Rayleigh Test	Mean, h (95% CI)	Rayleigh Test
Subject 1	9:54 AM (6:54 AM–1:00 PM)	$P = 0.07$	12:54 AM (11:06 PM–2:42 AM)	$P = 0.01$*
Subject 2	3:30 AM (2:36 AM–4:18 AM)	$P = 0.002$*	4:00 PM (12:42 PM–7:24 PM)	$P = 0.1$
Subject 3	4:06 AM (2:18 AM–5:54 AM)	$P = 0.01$*	6:00 PM (4:00 PM–8:00 PM)	$P = 0.01$*
Subject 4	10:18 AM (5:06 AM–3:30 PM)	$P = 0.6$	11:06 PM (10:00 PM–12:12 AM)	$P = 0.01$*
Subject 5	11:06 AM (9:00 AM–1:18 PM)	$P = 0.01$*	3:42 AM (1:12 AM–6:12 AM)	$P = 0.03$*
Subject 6	7:00 AM (2:30 AM–11:36 AM)	$P = 0.3$	7:06 PM (4:12 PM–10:12 PM)	$P = 0.08$

Acrophases and bathyphases were calculated after modeling.
* Significant mean hour direction ($P < 0.05$).

distribution of acrophases for the same subjects versus the sitting/supine position.

Regarding the reproducibility of the 24-hour IOP values, based on ICC calculations, we found a limited number of IOP measurements with fair to good agreement, mainly in the morning, as reported previously.[31] One recent study highlighted the limits of a single clinical assessment of IOP in 1 day, since ICC values were low in 40 healthy subjects studied at two visits 1 week apart.[19,20] After modeling IOP, we also evaluated the reproducibility of rhythmic parameters. Interestingly, the MESOR appeared to be most reproducible in a subject in the supine position. The limited reproducibility of the other parameters, such as amplitude, acrophase, and bathyphase, may stem from several causes, including the limited number of values (24 measurements/cycle, making this modeling method sensitive to aberrant or extreme values), and the lower amplitude of IOP in the constant supine position. These factors could limit the ability of the modeling methods available, cosinor or nonlinear least-squares dual harmonic regression.

Our results showed that the range of distribution of acrophases among subjects is greater, between 2 and 10 hours, than the intrasubject range if distribution of acrophases is unimodal, between 2 and 4 hours. This intersubject variability in rhythmic parameters suggests strongly that comparisons of IOP rhythm among different sessions in healthy subjects should involve intrasubject analysis (the subject is his own control).

Preliminary data in our laboratory (Study of nyctohemeral IOP changes using a noninvasive continuous monitoring, free oral communication, French Society of Ophthalmology, Paris, 2012) suggest that continuous monitoring of IOP using noninvasive contact lens telemetry provided more accurate modeling (signal-to-noise ratio) of 24-hour IOP values. Therefore, similar studies evaluating the reproducibility of IOP rhythmic parameters should be conducted using this method.

Table 3. Average Correlation of the Individual Models of the Six Subjects

	6 Modeled IOP Curves	
	Average Correlation Coefficient	χ^2 Test for Homogeneity of Lags
Subject 1	0.67	$P < 0.001$
Subject 2	0.93	$P < 0.001$
Subject 3	0.92	$P < 0.001$
Subject 4	0.66	$P < 0.001$
Subject 5	0.80	$P < 0.001$
Subject 6	0.36	$P < 0.001$

Conclusion

In a constant supine position, all subjects exhibited a nyctohemeral IOP rhythm present at an average rate of 80% of all sessions. With the currently available tonometry methods, intra- and intersubject variability of rhythmic parameters and IOP values is relatively high. The IOPs in the morning and the MESOR were the most reproducible values among the visits.

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