Nocturnal Elevation of Intraocular Pressure Is Detectable in the Sitting Position

John H. K. Liu,[1] *Randy P. Bouligny,*[1] *Daniel F. Kripke,*[2] *and Robert N. Weinreb*[1]

Purpose. When intraocular pressure (IOP) was monitored in supine healthy young adults throughout a 24-hour period, a diurnal-to-nocturnal elevation of IOP was observed. This study was undertaken to investigate whether a similar elevation of IOP can be detected when experimental subjects are in the sitting position.

Methods. Experimental subjects were 16 nonsmoking, healthy young volunteers (ages, 18–25 years). Subjects with myopia of more than 3 D were excluded. They were housed in a sleep laboratory for 24 hours in a strictly controlled environment. An 8-hour nocturnal/sleep period was assigned to each volunteer according to the individual's accustomed sleep cycle. IOP was measured every 2 hours with a pneumatonometer with the volunteers in both sitting and supine positions. Mean diurnal-to-nocturnal IOP change and the cosine-fit 24-hour IOP rhythm were compared between the sitting and the supine IOP data.

Results. Mean IOP was significantly higher in the nocturnal period than in the diurnal/wake period for both the sitting and the supine IOPs. The 24-hour IOP troughs appeared at the end of the diurnal period, and the peaks appeared at the end of the nocturnal period. The difference between the trough and the peak was 3.8 ± 0.6 mm Hg (mean ± SEM) in the sitting position and 3.4 ± 0.6 mm Hg in the supine position. Cosine-fitting of 24-hour IOP data showed a synchronized 24-hour rhythm of the sitting and the supine IOPs for the group. There was no difference in the phase timing or the magnitude of variation between these two 24-hour rhythms of sitting and supine IOPs.

Conclusions. A nocturnal elevation of IOP can be detected in healthy young adults in both the sitting and the supine positions. There is a 24-hour rhythm of sitting IOP that is not different from the 24-hour rhythm of supine IOP. (*Invest Ophthalmol Vis Sci.* 2003;44:4439–4442) DOI:10.1167/iovs.03-0349

Human intraocular pressure (IOP) varies significantly during the wake–sleep cycle.[1] It is known that a simple postural change from upright to recumbent elevates IOP, because of the hydrostatic responses in the episcleral venous pressure and the distribution of body fluid.[2] Thus, the recumbent body position in the nocturnal/sleep period sets IOP at a different level compared with the upright body position in the diurnal/wake period. Besides the postural influence, certain physiological factors also affect IOP at night. When IOP was monitored in the supine position throughout a 24-hour period, a diurnal-to-nocturnal elevation of IOP appeared in healthy young adults.[3–5] We have reported that a moderate light exposure at night has little effect on this IOP elevation.[6]

Important questions remain about the nocturnal elevation of IOP. It has been unclear whether a nocturnal elevation of IOP can be detected in the sitting position. When IOP in the sitting position was monitored for a full wake-sleep cycle, one report showed a nocturnal IOP elevation[7] and two other reports indicated that the nocturnal IOP was lower than the daytime IOP.[8,9] There was a speculation that at night the altering of natural body position from recumbent to sitting for the IOP measurement may hinder the natural IOP pattern.[10,11] Even if a nocturnal IOP elevation was detected in the sitting position, a question would arise whether this elevation of sitting IOP is related to the nocturnal elevation of IOP in the supine position.

To answer these questions, we collected 24-hour IOP data from a group of healthy young adults in both the sitting and supine positions. The diurnal-to-nocturnal changes of IOP in the two positions were compared. We used the cosine-fitting technique to determine the 24-hour rhythms of the sitting IOP and supine IOPs. The phase timings (acrophases) and the magnitudes of variation (amplitudes), essential parameters of the 24-hour rhythms,[12] were compared.

Methods

The study adhered to the tenets of the Declaration of Helsinki and was approved by our Institutional Review Board. Sixteen paid volunteers (ages, 18–25 years) were recruited from university students and employees. Candidates with myopia over 3 D were excluded, because their 24-hour IOP patterns are likely to be different.[13] We selected nonsmoking, healthy individuals who had a regular daily sleep cycle close to 11 PM to 7 AM. Informed consents were obtained after explanation of the nature and possible consequences of the study. There were eight men and eight women with an age of 21.5 ± 2.1 (mean ± SD), including eight whites, five Asians, two African Americans, and one Hispanic. Each subject had an ophthalmic examination demonstrating absence of any eye disease or a narrow iridocorneal angle. Office IOP readings measured by the Goldmann tonometer with the volunteers in the sitting position were in the range of 9 to 21 mm Hg (15.4 ± 3.9, mean ± SD). Central corneal thickness was not measured.

Subjects were instructed to maintain their accustomed wake–sleep cycles for 7 days before the laboratory study. They wore a wrist device to monitor light exposure and physical activity (Actiwatch; Mini Mitter, Sunriver, OR). Subjects were told to abstain from alcohol and caffeine for 3 days. They reported to the laboratory at approximately 2 PM and stayed indoors for the next 24 hours. Laboratory conditions were strictly controlled as in our previous study.[13] Onset of darkness in each sleep room was adjusted according to the individual's sleep cycle, and the clock times for the IOP measurements were individualized correspondingly. For data presentation, clock times were normalized as if each subject had a sleep period from 11 PM to 7 AM. Subjects were encouraged to continue their normal indoor activities. Food and water were always available and meal times were not regulated. Room activities were continuously videotaped using infrared cameras.

From the [1]Hamilton Glaucoma Center and Department of Ophthalmology and the [2]Department of Psychiatry, University of California, San Diego, La Jolla, California.

Supported by National Eye Institute Grant EY07544.

Submitted for publication April 5, 2003; revised May 19, 2003; accepted May 30, 2003.

Disclosure: **J.H.K. Liu**, None; **R.P. Bouligny**, None; **D.F. Kripke**, None; **R.N. Weinreb**, None

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: John H. K. Liu, Department of Ophthalmology, University of California, San Diego, La Jolla, CA 92093-0946; joliu@ucsd.edu.

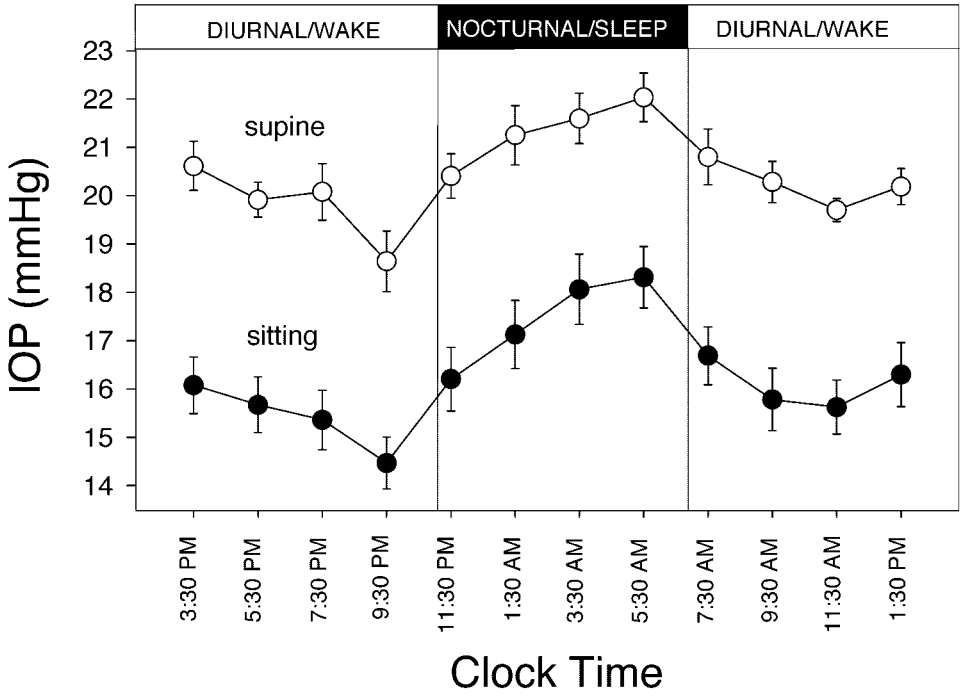

FIGURE 1. Twenty-four-hour patterns of mean IOP in healthy young adults in the sitting (●) and supine (○) positions (n = 16). Error bars, SEM. Data were obtained from the same subjects with a pneumatonometer.

IOP was measured in both eyes every 2 hours in the sitting and supine positions with a pneumatonometer (Model 30 Classic; Mentor O&O, Norwell, MA). It was verified that different measurement angles using this device produce the same IOP reading. Before the nocturnal-sleep period, measurements of IOP were taken at 3:30, 5:30, 7:30, and 9:30 PM. Subjects were instructed to lie down on the bed for 5 minutes before the supine IOP measurements, and they then sat for 5 minutes before the sitting IOP measurements. Proparacaine 0.5% was applied to the eye as local anesthetic. A hard-copy record was evaluated for every IOP measurement.[3] Immediately before the supine and sitting IOP measurements, systolic and diastolic blood pressures and heart rate were determined using an automated wrist blood pressure monitor (model HEM-608; Omron, Vernon Hills, IL) positioned at heart level.

Subjects went to bed just before the scheduled lights-off at 11 PM. Their sleep positions were not controlled. Measurements of blood pressure, heart rate, and IOP were taken during the 8-hour nocturnal period at 11:30 PM and at 1:30, 3:30, and 5:30 AM. Subjects were awakened, if necessary, and the measurements were taken in dim red light (<10 lux) in the supine position and 5 minutes later in the sitting position. The dim red lights were turned off after the measurements. When the assigned nocturnal period ended at 7 AM, room lights were turned on and subjects were awakened, if necessary. Measurements were taken again at 7:30, 9:30, and 11:30 AM and 1:30 PM.

IOPs from both eyes were averaged and used for data analyses. Mean arterial blood pressure was calculated as the diastolic blood pressure plus one third of the difference between the systolic and diastolic blood pressures. The mean sitting and supine IOPs at each time point for the 16 subjects were calculated. The trough and peak IOPs were selected, and the differences between the trough and the peak for the sitting and the supine IOPs were compared using the paired t-test. $P < 0.05$ was regarded as statistically significant. For each body position, means of IOP, blood pressure, and heart rate were calculated for the diurnal period and for the nocturnal period. Diurnal-to-nocturnal changes of these parameters were compared between the sitting and the supine positions using the paired t-test.

Using the best-fitting cosine curve,[12] we estimated the 24-hour rhythms of IOP in the sitting position and supine positions. With the IOP data, a cosine-fit curve was generated for each experimental subject, either sitting or supine, obtained from the 12 time points. The acrophase (peak of the fitted curve) represents the phase timing. The null hypothesis of a random distribution of the 16 acrophases within 24 hours was evaluated statistically using the Rayleigh test.[14] Lack of statistical significance indicates no 24-hour IOP rhythm for the group, whereas the alternative indicates a synchronized rhythm. The amplitude (half distance between the cosine-fit maximum and minimum) represents a mathematical approximation of the IOP variation for the 24-hour period. The acrophases and amplitudes for the 24-hour rhythm of sitting IOP and the 24-hour rhythm of supine IOP were compared using the Wilcoxon signed-rank test for paired data.

RESULTS

Figure 1 presents the 24-hour profiles of IOP in both the sitting and the supine positions. Both IOP profiles indicated a gradual decrease of IOP during the diurnal/wake period and a gradual increase of IOP during the nocturnal/sleep period. The troughs of IOP appeared at 9:30 PM, the last measurement in the diurnal period, and the peaks at 5:30 AM, the last measurement in the nocturnal period. The IOP difference between the trough and peak in the sitting position was 3.8 ± 0.6 mm Hg (mean ± SEM); not statistically different from that in the supine position, 3.4 ± 0.6 mm Hg.

Table 1 lists the diurnal and nocturnal IOP, blood pressure, and heart rate in the two body positions. The nocturnal sitting IOP was significantly higher than the diurnal sitting IOP. The magnitude of this diurnal-to-nocturnal elevation of sitting IOP was not statistically different from that of supine IOP. The nocturnal blood pressure and heart rate were lower than the diurnal levels in the sitting position as well as in the supine position. The diurnal-to-nocturnal reductions in these cardiovascular parameters were not different between the sitting position and the supine position.

The Rayleigh test detected synchronized phase timings (acrophases) for the sitting and the supine IOPs ($P < 0.01$). Acrophases and amplitudes for the two 24-hour IOP rhythms are presented in Figure 2. For the 24-hour rhythm of sitting IOPs, the acrophase was at 6:35 AM ± 1.7 hour and the amplitude was 1.4 ± 0.4 mm Hg. For the 24-hour rhythm of

TABLE 1. Diurnal and Nocturnal IOP, Blood Pressure, and Heart Rate in Two Body Positions

	Body Position	Diurnal Period (7 AM–11 PM)	Nocturnal Period (11 PM–7 AM)	Δ Change
IOP (mm Hg)	Sitting	15.7 ± 0.5	17.4 ± 0.6	1.7 ± 0.5*
	Supine	20.0 ± 0.3	21.3 ± 0.4	1.3 ± 0.3*
Blood pressure (mm Hg)	Sitting	92.9 ± 2.2	87.7 ± 2.1	−5.2 ± 1.7*
	Supine	89.5 ± 2.2	84.3 ± 1.6	−5.2 ± 1.1*
Heart rate (beats/min)	Sitting	72.7 ± 2.4	68.5 ± 2.4	−4.2 ± 1.4*
	Supine	70.2 ± 2.2	65.3 ± 2.1	−5.0 ± 1.3*

Data are the mean ± SEM ($N = 16$).
* $P < 0.01$; paired *t*-test between the diurnal and nocturnal periods.

supine IOP, the acrophase was at 5:31 AM ± 1.8 hour and the amplitude was 1.2 ± 0.4 mm Hg. The Wilcoxon signed-rank test determined that the acrophase and the amplitude were not statistically different between these two 24-hour IOP rhythms.

DISCUSSION

In this group of nonsmoking, healthy young adults with no moderate or severe myopia, a nocturnal IOP elevation was observed in both the sitting and the supine positions. Comparing the two body positions, magnitudes of the IOP elevation from trough to peak and the mean diurnal-to-nocturnal IOP elevation were not different. These magnitudes were very close to the values reported previously.[3,6]

In our previous studies involving IOP monitoring for 24 hours,[3,13,15] nighttime IOP in the sitting position was not determined because of the concern that a change of sitting IOP may not be detectable a few minutes after arousal.[10] In the present study, an IOP elevation was detectable in the sitting position at more than 5 minutes after awakening for tonometry. Although the change of body position at night from supine to sitting reset IOP to a different level, it did not alter the 24-hour IOP pattern when evaluating data from the same body position. This suggests that the nocturnal IOP elevation can be detected in the sitting position using a standard clinical applanation tonometer.

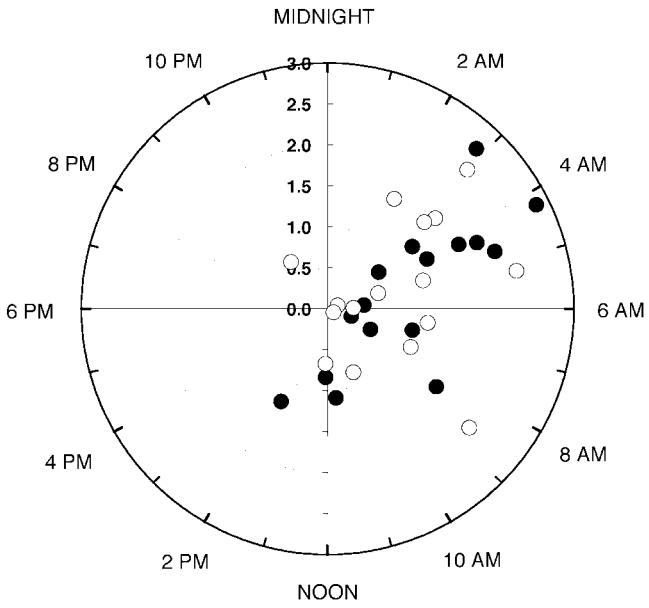

FIGURE 2. Estimated 24-hour rhythms of IOP in the sitting (●) and supine (○) positions. The clock time of the acrophase (phase timing) is shown with the amplitude in the radial scale ($n = 16$).

There were statistically indifferent 24-hour rhythms of sitting IOP and supine IOP in this group of healthy young adults. The 24-hour sitting IOP pattern and the 24-hour supine IOP pattern are probably driven by the same physiological factors. Therefore, endogenous mechanisms for the nocturnal IOP elevation can be studied in either body position as long as the control is also performed in the same body position. This should significantly expand our research opportunities in the laboratory because many ophthalmic instruments require the experimental subject to be sitting.

The physiological basis for the elevation of IOP at night remains unclear. We observed anticipated nocturnal patterns of blood pressure and heart rate immediately before the IOP data were collected at night. There were diurnal-to-nocturnal decreases of blood pressure and heart rate[16] and slight increases in these parameters after the change of body position from supine to sitting (baroreflex). Therefore, no apparent unusual cardiovascular response to the nighttime arousal was associated with the nocturnal IOP elevation in these healthy young adults. This nocturnal IOP elevation is not due to an increase of aqueous humor flow. At night, aqueous humor flow should be significantly reduced.[17] A posture-dependent change in episcleral venous pressure[2,18] per se does not explain the nocturnal elevations of IOP in both the sitting and the supine positions. It is possible that the nocturnal elevation of IOP is due to an increase of outflow resistance for aqueous humor, which has not been experimentally addressed.

No tool is yet available to measure IOP in a human asleep with the eyelids closed. Therefore, we do not know the exact nighttime IOP level in these experimental subjects before awakening. Our results only imply that an awakened young adult at night would have a higher IOP than the daytime level in a comparable body position. Can the 24-hour IOP pattern observed in the present study represent the continuous IOP pattern during a wake–sleep cycle? An observation in the laboratory rabbit might be useful in this regard. In this species, the 24-hour pattern of IOP established by hourly IOP measurements using a pneumatonometer[19] is similar to the 24-hour IOP pattern recorded by a continuous telemetry with an implanted pressure transducer connected to the anterior chamber[20] or to the vitreous.[21] Between wake and sleep, rabbits show little change of body position. A direct answer to the critical question in humans, nevertheless, would have to wait until telemetry for monitoring human IOP is available.

Acknowledgments

The authors thank Judy Nisbet, Christine Petz, Denie Cochran, and Dezirae Elkins for technical assistance.

References

1. Liu JHK. Circadian rhythm of intraocular pressure. *J Glaucoma.* 1998;7:141–147.

2. Kothe AC. The effect of posture on intraocular pressure and pulsatile ocular blood flow in normal and glaucomatous eyes. *Surv Ophthalmol*. 1994;38:S191–S197.
3. Liu JHK, Kripke DF, Hoffman RE, et al. Nocturnal elevation of intraocular pressure in young adults. *Invest Ophthalmol Vis Sci*. 1998;39:2707–2712.
4. Orzalesi N, Rossetti L, Invernizzi T, Bottoli A, Autelitano A. Effect of timolol, latanoprost, and dorzolamide on circadian IOP in glaucoma or ocular hypertension. *Invest Ophthalmol Vis Sci*. 2000;41: 2566–2573.
5. Noël C, Kabo AM, Romanet J-P, Montmayeur A, Buguet A. Twenty-four-hour time course of intraocular pressure in healthy and glaucomatous Africans: relation to sleep patterns. *Ophthalmology*. 2001;108:139–144.
6. Liu JHK, Kripke DF, Hoffman RE, et al. Elevation of human intraocular pressure at night under moderate illumination. *Invest Ophthalmol Vis Sci*. 1999;40:2439–2442.
7. Frampton P, Da Rin D, Brown B. Diurnal variation of intraocular pressure and the overriding effects of sleep. *Am J Optom Physiol Opt*. 1987;64:54–61.
8. Kitazawa Y, Horie T. Diurnal variation of intraocular pressure in primary open-angle glaucoma. *Am J Ophthalmol*. 1975;79:557–566.
9. Horie T, Kitazawa Y. The clinical significance of diurnal pressure variation in primary open-angle glaucoma. *Jpn J Ophthalmol*. 1979;23:310–333.
10. Brown B, Burton P, Mann S, Parisi A. Fluctuations in intra-ocular pressure with sleep: II. Time course of IOP decrease after waking from sleep. *Ophthalmic Physiol Opt*. 1988;8:249–252.
11. Brown B. Diurnal variation of IOP (letter). *Ophthalmology*. 1991; 98:1485–1486.
12. Nelson W, Tong YL, Lee J-K, Halberg F. Methods for cosinor-rhythmometry. *Chronobiologia*. 1979;6:305–323.
13. Liu JHK, Kripke DF, Twa MD, et al. Twenty-four-hour pattern of intraocular pressure in young adults with moderate to severe myopia. *Invest Ophthalmol Vis Sci*. 2002;43:2351–2355.
14. Zar JH. *Biostatistical Analysis.* 4th ed. Upper Saddle River, NJ: Prentice Hall; 1999:616–618.
15. Liu JHK, Kripke DF, Twa MD, et al. Twenty-four-hour pattern of intraocular pressure in the aging population. *Invest Ophthalmol Vis Sci*. 1999;40:2912–2917.
16. Mann S, Millar Craig MW, Melville DI, Balasubramanian V, Raftery EB. Physical activity and the circadian rhythm of blood pressure. *Clin Sci.* 1979;57:291S–294S.
17. Reiss GR, Lee DA, Topper JE, Brubaker RF. Aqueous humor flow during sleep. *Invest Ophthalmol Vis Sci*. 1984;25:776–778.
18. Blondeau P, Tétrault J-P, Papamarkakis C. Diurnal variation of episcleral venous pressure in healthy patients: a pilot study. *J Glaucoma*. 2001;10:18–24.
19. Liu JHK, Gallar J, Loving RT. Endogenous circadian rhythm of basal pupil size in rabbits. *Invest Ophthalmol Vis Sci*. 1996;37:2345–2349.
20. McLaren JW, Brubaker RF, FitzSimon JS. Continuous measurement of intraocular pressure in rabbits by telemetry. *Invest Ophthalmol Vis Sci*. 1996;37:966–975.
21. Schnell CR, Debon C, Percicot CL. Measurement of intraocular pressure by telemetry in conscious, unrestrained rabbits. *Invest Ophthalmol Vis Sci*. 1996;37:958–965.