Nocturnal Elevation of Intraocular Pressure in Young Adults

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PURPOSE. To distinguish 24-hour (circadian) and postural effects on intraocular pressure (IOP) in healthy young adults.

METHODS. Thirty-three volunteers were housed in a sleep laboratory for 1 day under a strictly controlled 16-hour light and 8-hour dark environment. Sleep was encouraged in the dark period. Intraocular pressure was measured in each eye every 2 hours using a pneumatoneter. Researchers used night-vision goggles to perform IOP measurements in the dark, while the subject’s light exposure was minimized. In the first group of 12 subjects, measurements were taken with subjects in the sitting position during the light-wake period and supine during the dark period. In the second group of 21 subjects, all IOP measurements were taken with the subjects supine.

RESULTS. Average IOP was significantly higher in the dark period than in the light-wake period in both groups. The lowest IOP occurred in the last light-wake measurement, and the peak IOP occurred in the last dark measurement. The trough-peak difference in IOP was 8.2 ± 1.4 mm Hg (mean ± SEM) in the first group. Intraocular pressure changed sharply at the transitions between light and dark. In the second group, the trough-peak IOP difference was 3.8 ± 0.9 mm Hg. Intraocular pressure changed gradually throughout the 24-hour period. In comparison with the sitting IOP in the first group, the supine IOP in the second group was significantly higher during the light-wake period.

CONCLUSIONS. Circadian rhythms of IOP were shown in young adults, with the peaks occurring in the late dark period. A nocturnal IOP elevation can appear independent of body position change, but change of posture from upright to recumbent may contribute to the relative nocturnal IOP elevation. (Invest Ophthalmol Vis Sci. 1998;39:2707-2712)

Intraocular pressure (IOP) is essential to maintaining eye structure and physiology. In various conditions, IOP may change rapidly. Numerous studies in the past 30 years have shown that human IOP is high in the morning and low in the afternoon and evening.1 However, IOP has been monitored beyond the light-wake period in only a handful of studies. Observations of nocturnal IOP have been inconsistent, and almost opposite 24-hour (circadian) IOP patterns have been described.

In some studies, IOP was lower in the dark-sleep period than in the light-wake period. This observation was reported in healthy subjects and in patients with glaucoma. In other studies, IOP was higher during the dark-sleep period in young subjects and older subjects including those with glaucoma. Frequently, a sharp IOP elevation was observed shortly after the change from the light-wake to the dark-sleep period. The cause of the discrepancies in the nocturnal IOP pattern among these studies is unclear. Nevertheless, a better understanding of the nocturnal variation of IOP may allow better diagnosis and management of ocular hypertension and glaucoma.

Environmental light is the primary synchronizer of many circadian rhythms. In most previous studies of human circadian IOP patterns, little attention was given to the environmental lighting conditions, particularly in the dark-sleep period. One obvious reason is that the eyes were illuminated during the measurement of IOP. In addition, subjects' body positions varied when IOP measurements were taken. Postures could be all upright, all supine, or upright during the day and supine at night. Altering body postures from supine to sitting for IOP measurements in the dark-sleep period may cause excess arousal and affect the body's autonomic and hormonal states. The influence on the natural IOP pattern is unclear. In the present study, we collected 24-hour IOP data from light-dark entrained, healthy young adults, while giving particular attention to nocturnal light exposure and body posture. The IOP patterns observed may provide an indication of what happens under normal living conditions.

METHODS

The study followed the tenets of the Declaration of Helsinki and was approved by the institutional review board. Thirty-three paid volunteers were recruited, mainly from employees...
and students of our university. Informed consent was obtained from the volunteers after explanation of the nature and possible consequences of the study. Volunteers were nonsmoking, healthy people aged 18 to 25 years (15 men and 18 women) and racially diverse (23 white, 5 Hispanic, and 5 Asian). Each volunteer underwent a complete ophthalmic examination to ensure absence of eye disease and a narrow iridocorneal angle. Individuals with myopia more than 4 diopters were excluded because of the possibility of circadian entrainment periods (lights-off) for 7 days before the laboratory study. This period (from cool white fluorescent lights) was held constant were strictly controlled. Light intensity during the light-wake period were in the range of 11 mm Hg to 23 mm Hg (15.5 ± 0.2 mm Hg; mean ± SEM; N = 33).

Subjects were selected based on their having a regular daily sleep cycle close to 11:00 PM to 7:00 AM (with a maximum deviation of 1 hour). To strengthen their circadian synchronization, subjects were asked to regulate their sleep periods (lights-off) for 7 days before the laboratory study. This assigned dark–sleep period of 8 hours matched the subject’s regular sleep cycle. Subjects wore a wrist device (Actillume; Ambulatory Monitoring, Ardsley, NY) to monitor physical activity and light exposure. They also kept a daily sleep–wake log. By these means, 7-day circadian entrainment was verified before the recording session. Subjects were instructed to abstain from alcohol and caffeine for 3 days and to avoid use of contact lenses for 24 hours before entering the laboratory.

The 24-hour IOP change was recorded in a laboratory specifically designed for studying human circadian rhythms. Subjects stayed in the laboratory for the entire recording session to avoid possible effects of bright sunlight on bodily circadian rhythms.20 Light–dark conditions in the laboratory were strictly controlled. Light intensity during the light-wake period (from cool white fluorescent lights) was held constant at 500 lux to 1000 lux at eye level when standing. During the dark–sleep period, the room was absolutely dark. The onset of darkness in each participant’s sleep room was adjusted according to the accustomed dark–sleep period for that participant. Measurements of IOP were also adjusted to each participant’s time in bed. Although bedtimes and IOP measurements were thus individualized to each subject’s accustomed pattern, the data were transformed to present results as if each subject slept from 11:00 PM to 7:00 AM.

Room activities were continuously videotaped using infrared recording systems. Intraocular pressure was measured every 2 hours in each eye (12 times in 24 hours) using a pneumatonometer (model 30 Classic; Mentor O&O, Norwell, MA). One or two drops of 0.5% proparacaine was applied as local anesthetic before tonometry. With subjects in a sitting position, the sensor probe of the pneumatonometer was applied from above at 15° from the perpendicular to the corneal surface. The probe was applied perpendicular to the corneal surface when the subjects were supine. The difference in the probe angles did not cause a difference in IOP of more than 0.5 mm Hg when calibrated against the manufacturer’s verifier.

Measurements of IOP were assigned randomly to experienced researchers working in 8-hour shifts to avoid fatigue. Before the study, variations in IOP measurements by the various researchers were confirmed to be insignificant.

In the dark period, subjects were awakened, if necessary, and IOP was measured in near-total darkness. Researchers were equipped with infrared night-vision goggles (AN/PVS-7B Dark Invader; Meyers, Redmond, WA) for these measurements. If subjects were awakened, IOP measurement was taken within 2 to 3 minutes. Subjects' light exposure during the nocturnal IOP measurement was kept to a minimum. The only light visible to subjects was a dim red light reflecting across the ceiling (<1 lux). This light, originating from the pneumatonometer and filtered through a 600-nm high-pass plastic filter (Edmund Scientific, Barrington, NJ), was necessary for the subjects to fixate during the IOP measurement. It was found in pilot studies that some volunteer’s eyes tended to track continuously in absolute darkness, which made IOP measurements difficult. During IOP measurements in the dark period, the researchers tried to disturb the subject as little as possible.

There were six men and six women in the first study group. Recording sessions were conducted with as many as three subjects in the laboratory at one time. Entry times into the laboratory for individual subjects were balanced in 4-hour intervals (at approximately 9:00 AM, 1:00 PM, 5:00 PM, and 9:00 PM; three subjects at each time point). This reduced the confounding by circadian time of the order of measurement. In the light–wake period, measurements of sitting IOP were taken in subjects seated in the same location, 30 minutes after entering the laboratory and every 2 hours thereafter. Subjects were encouraged to continue their normal activities (reading, exercising, watching TV, for example), but no naps were allowed. Food and water were always available, and meal times were not regulated. Visitors were permitted in the light–wake period. Subjects went to bed in individual sleep rooms just before the room lights were turned off (e.g., at 11:00 PM). Sleep was encouraged in the dark period. Measurements of IOP in the dark period were taken with subjects supine, first at 30 minutes after lights out and then every 2 hours: 11:30 PM, 1:30 AM, 3:30 AM, and 5:30 AM, for example. Lights were turned on after 8 hours (e.g., 7:00 AM) and subjects were awakened, if necessary. Intraocular pressure was measured in sitting subjects 30 minutes later (e.g., 7:30 AM) and every 2 hours thereafter. After the 12th IOP measurement, a debriefing interview was conducted in which the participants were asked how they slept and whether there were difficulties and symptoms.

Recent studies have indicated that a difference in individual central corneal thickness may affect the accuracy of IOP determined by the Goldmann tonometer.21 Although whether a similar artifact is associated with the pneumatonometer is uncertain, central corneal thickness was measured in six subjects by an ultrasonic pachymeter (Pachette 500, DGH Technology, Exton, PA) immediately after the IOP measurements at two time points. One was at the last IOP measurement before lights-off (e.g., 9:30 PM) and the other was at the first IOP measurement after lights-on (e.g., 7:30 AM). Three consecutive readings in individual eyes were averaged as the mean central corneal thickness.

The second group included 9 men and 12 women. Entry times to the laboratory were staggered; three subjects every 2 hours in the light–wake period (9 AM–9 PM). Procedures used for IOP measurements were similar to those used in the first group, except that all the IOP measurements were taken with subjects supine. In the light–wake period, subjects were instructed to lie down in bed for 5 minutes before the IOP measurement.

A hard-copy printout from the pneumatonometer was collected for every IOP measurement. If the printout showed an SD in IOP (calculated by the machine software) of more than 1 mm Hg, another IOP measurement was taken. However, no more than three measurements were allowed.
Among the repeated measurements, the IOP value with the least SD was selected. In most cases (>90%), one measurement was sufficient at each time point.

Values of IOP from both eyes were averaged and used as a single entry for data analyses. Statistical analyses were performed with $P < 0.05$ regarded as significant. To evaluate the circadian rhythm of IOP for each subject, the best fitting 24-hour cosine was estimated for the 12 IOP averages of both eyes. The circadian amplitude (height of the rhythm) and acrophase (timing of the fitted peak) were estimated. To compare the phase dispersion of each group of subjects, the absolute deviation of each acrophase from the group median acrophase was calculated.

**RESULTS**

All 33 subjects completed the laboratory measurements without adverse effects. Although sleep in the dark period was interrupted for the IOP measurements, 25 (76%) of 33 subjects in their debriefing interviews indicated that they had slept well between the IOP measurements, because of the quiet and darkness of the sleep rooms.

The mean 24-hour IOP was 17.1 mm Hg in subjects in the first group and 20.4 mm Hg in subjects in the second group. In the 12 subjects in the first group, the average of all IOP values in the dark period (20.8 ± 1.1 mm Hg; mean ± SEM) was significantly higher ($P < 0.001$; paired t-test) than the average IOP in the light–wake period (15.2 ± 0.7 mm Hg). The latter was close to the IOP value (16.0 ± 0.8 mm Hg) obtained with the Goldmann tonometer during the prior eye examination.

The 24-hour pattern of the mean IOP in this group is presented in Figure 1 (line with the solid circles). The lowest mean IOP occurred at the last measurement in the light–wake period (9:30 PM) and the highest IOP occurred at the last measurement in the dark period (5:30 AM). The difference in IOP between these two time points (trough–peak) was 8.2 ± 1.4 mm Hg ($n = 12$). Sharp elevations of IOP occurred between 9:30 PM and 11:30 PM and between 11:30 PM and 1:30 AM. A sharp IOP reduction occurred between 5:30 AM and 7:30 AM. Cosine fits of the individual IOP data showed the acrophases between 2 AM and 5 AM in 11 of the 12 subjects (Fig. 2; solid circles). One participant who had a nearly flat 24-hour IOP pattern had the acrophase at approximately 12 noon. There was no statistical difference (paired t-test) in the average central corneal thickness between 9:30 PM (553 ± 6 μm; $n = 12$) and 7:30 AM (558 ± 8 μm) in the six subjects studied.

In the second group, the average IOP in the dark period was 21.3 ± 0.7 mm Hg ($n = 21$), slightly higher ($P < 0.05$; Student’s t-test) than the average IOP in the light–wake period, 20.0 ± 0.4 mm Hg. The average supine IOP in the light–wake period in this group was significantly higher ($P < 0.001$, Student’s t-test) than the average sitting IOP observed in the first group (15.2 ± 0.7 mm Hg). The 24-hour IOP pattern in the second group showed gradual elevation and decrease throughout the 24 hours (Fig. 1; open circles). The trough and peak IOPs occurred at 9:30 PM and 5:30 AM, the same times as those in the first group. The trough–peak IOP difference was 3.8 ± 0.9 mm Hg. Cosine fits of IOP data from individual subjects showed that all acrophases occurred between 2:30 AM and 3:00 PM (Fig. 2; open circles).
The position of the acrophase around the circle shows its timing, and the radial distance from the center shows the amplitude of the IOP rhythm. The circumference of the circle represents an IOP amplitude of 8 mm Hg. (●) The first group of 12 subjects whose IOP measurements were taken sitting in the light-wake period (7:00 AM to 11:00 PM) and supine in the dark period (11:00 PM to 7:00 AM). (○) The second group of 21 subjects whose IOP measurements were taken while supine in both periods.

Inspection of Figure 2 showed that the acrophases in both groups occurred in a nonrandom manner. The null hypothesis of a random 360° distribution of phases was rejected with Rayleigh’s test in subjects in both groups (P < 0.001); therefore, significant 24-hour rhythms were detected. Although the mean amplitude of the circadian rhythm in the first group (3.3 ± 0.5 mm Hg) was higher than the mean amplitude in the second group (2.3 ± 0.2 mm Hg), the difference was not significant (P > 0.05; two-tailed Mann-Whitney test). The mean acrophase of subjects in the first group was at 4:22 AM, whereas the mean in the second group was at 7:30 AM (P < 0.05; two-tailed Mann-Whitney test). The deviations of acrophases from the median were far greater in subjects in the second group than in the first group (P < 0.01; two-tailed Mann-Whitney test).

**DISCUSSION**

It is unavoidable that study of human IOP during sleep is confounded by awakening the subject. When the subject is asleep, the eye positions itself under the upper lid (known as the Bell’s phenomenon). When it is time to measure the IOP, the eye and eyelids must be repositioned, which may cause an instant IOP change. Also, disturbing sleep in human subjects may change the autonomic and hormonal parameters related to IOP. Somewhat similar problems in rabbits (which, in general, sleep during the daytime) have been circumvented by surgically implanting a pressure sensor in the eye and monitoring IOP through telemetry. Results of this telemetric monitoring show a similar circadian IOP pattern to that demonstrated by the periodic IOP measurements using the pneumotonometer. However, as long as there is no technical advance to circumvent the problem with IOP measurement in sleeping humans, whether the IOP determined after awakening the human subject reflects the real nocturnal steady state IOP is uncertain. Therefore, interpretations of results in our study and in many previous studies rest on the assumption that artifacts associated with nocturnal IOP measurement are not substantial, particularly when relating the result to the state of sleep.

We observed consistent 24-hour IOP patterns in entrained healthy young adults. In both groups, IOP peaked in the late dark period, and the trough occurred in the late light-wake period. The subjects in the first group had lower IOP when awake (sitting) and approximately the same IOP in the dark period as in the second group. Therefore, subjects measured sitting in the day had a significantly lower 24-hour mean IOP and somewhat larger amplitudes in their circadian rhythms. Because of the masking effects of change of posture on the 24-hour IOP rhythms, the acrophases of subjects measured in the first group were significantly earlier and less variable, but even subjects in the second group (IOP measurements were performed in supine subjects throughout) had a nonrandom distribution of acrophases, indicating a consistent circadian rhythm.

The nocturnal IOP pattern in the present study is different from many previous observations of nocturnal human IOP. Our results did not show a nocturnal IOP reduction, as has been described in some studies. The observation of a nocturnal IOP elevation in the first group agrees in general with the report in a previous study in which IOP was measured in subjects while upright during the day and supine at night. However, IOP in our study peaked in the late dark-sleep period, not in the early dark-sleep period. Of interest, our results in the second group are similar to the observations of Duke-Elder 30 years ago.

There are several possible explanations for the differences among various studies. Enforcement of the subject’s circadian synchronization and strict control of the laboratory light-dark conditions may contribute to the consistent 24-hour IOP patterns in the present study. Studies in rabbits have shown that light exposure in the dark period suppresses nocturnal IOP elevation. Although we suspect that uncontrolled light exposure in the dark period may have interfered with nocturnal IOP elevation in some previous human studies, this issue of light suppression needs further study. It should be noted that nocturnal exposure to strong light does not affect the circadian rhythm of aqueous humor flow, which shows a nocturnal reduction. Effects of light on other parameters of aqueous humor dynamics, such as outflow resistance and episcleral venous pressure, are unknown.

A comparison of results from our two groups indicates that a significant portion of the nocturnal IOP elevation in the first group was caused by the postural change from sitting to supine in the dark period. This point of view is different from that in the previous report in which similar positioning was used for the IOP measurement as was used in our first group. An acute elevation of IOP because of postural change from sitting to supine is well known. Such postural change causes hydrostatic changes in the eye, particularly an elevation of episcleral venous pressure.
by this postural change probably occurs in daily life, because almost everybody sleeps in a near-recumbent position. This kind of nocturnal IOP elevation, however, is not driven directly by an endogenous circadian oscillator. Results from the second group showed that the postural effect on IOP did not account for all nocturnal IOP elevation. When all the IOP measurements were taken in supine subjects, a small nocturnal IOP elevation still occurred. Similar to the subjects in whom IOP measurements were taken sitting and supine, the mean IOP in the subjects measured in the supine position throughout reached the lowest value in the late light–wake period. The highest IOP occurred similarly in the late–dark period, but the magnitude of IOP elevation was smaller. What caused the elevation of nocturnal IOP that was unrelated to posture is unclear. Circadian effects on aqueous humor dynamics of systemic hormones, local hormones, local neural activities, or their combinations may all contribute to nocturnal IOP elevation. It is possible that some potential artifacts related to awakening subjects, such as instant changes of eye position, choroidal blood volume, or lid pressure, also contribute to this IOP elevation. Nocturnal IOP elevation, however, is not caused by an increase in the formation of aqueous humor. The rate of aqueous humor flow during the dark-sleep period is apparently only approximately half of that during the early light–wake period in healthy adults. A similar nocturnal reduction in aqueous flow also occurs in patients with glaucoma. Our preliminary data indicate that nocturnal IOP elevation is not an artifact caused by an increase in central corneal thickness.

The physiological significance of nocturnal IOP elevation is unknown in humans. Because the rate of nocturnal aqueous humor flow is less than the flow rate in the light–wake period, tissues in the anterior segment of the eye would not need a faster turnover of aqueous humor in the dark–sleep period for nutritional or metabolic purposes. No known function in the posterior part of the eye requires elevated IOP in the dark–sleep period. It is possible that nocturnal IOP elevation is a consequence of postural change plus physiological changes unrelated to ocular functions. This physiological IOP elevation in the dark–sleep period should cause no harm to a young healthy eye. However, the effect on an aging or diseased eye is uncertain. Usually measured in the light–wake period, high IOP has been regarded as a major risk factor in the development of glaucoma. Because part of nocturnal IOP elevation is caused by postural change, this posture-related nocturnal IOP elevation at night in patients with glaucoma (compared with their daytime values) is likely. Other factors involved in nocturnal IOP elevation may behave differently in patients with glaucoma.

The nocturnal elevation of human IOP coincides with the time when systemic blood pressure, measured at the brachial artery, is the lowest. Perfusion pressure to the optic nerve head at night, however, may change in a different direction because of the postural change from upright to supine. Further research on nocturnal ocular perfusion in the supine position is warranted. Our data (Fig. 2) indicate a large variability in the magnitude of nocturnal IOP elevation. It is unclear whether an abnormally high IOP elevation in the dark period may further interfere with ocular physiology in patients with glaucoma. This may be an important consideration in patients with progressive glaucomatous optic neuropathy despite apparently controlled daytime IOP. Studies of the 24-hour IOP patterns in patients with glaucoma and in healthy subjects of comparable age are needed. Despite all the uncertainties raised, the present results suggest that nocturnal elevation of human IOP (at least the portion caused by the postural change) is a fundamental physiological fact. We should not ignore its significance, because approximately one third of our life is spent in the dark–sleep period.

The 24-hour IOP pattern has been extensively studied in laboratory rabbits. The nocturnal elevation of human IOP observed in the present study is somewhat different from the nocturnal IOP elevation seen in the laboratory rabbit. Under normal living conditions, the sharp elevation of human IOP in the early dark period is related to the postural change at bedtime. There seems to be no postural change in rabbits when awake and asleep, and generally, laboratory rabbits are more active in the dark period. The sharp elevation of rabbits’ IOP at the onset of dark is mainly caused by the activation of the ocular sympathetic nerves. In humans, there is no indication of a nocturnal increase in ocular sympathetic activity. As in humans, the physiological significance of nocturnal IOP elevation in rabbits is unclear.

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