

Twenty-four–Hour Intraocular Pressure Pattern Associated with Early Glaucomatous Changes

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PURPOSE. To characterize the 24-hour pattern of intraocular pressure (IOP) in untreated patients with newly diagnosed early glaucomatous changes.

METHODS. Measurements of IOP, blood pressure, and heart rate were taken every 2 hours during a 24-hour period from a group of 24 untreated patients (ages 40–78 years) with newly diagnosed abnormal optic discs and/or abnormal visual fields. In the 16-hour diurnal awake period, IOP was measured sitting and supine, and blood pressure and heart rate were measured supine. In the 8-hour nocturnal sleep period, all measurements were taken in the supine position. Mean diurnal and nocturnal IOP, blood pressure, and heart rate in the glaucoma group were compared with data obtained from an age-matched control group of 24 individuals with healthy eyes.

RESULTS. Mean diurnal IOP, either sitting or supine, was significantly higher in the glaucoma group than in the control group. For both subject groups, nocturnal supine IOP was higher than diurnal sitting IOP. However, this diurnal-to-nocturnal increase in IOP was significantly smaller in the glaucoma group. When compared with the diurnal supine IOP, the nocturnal supine IOP was lower in the glaucoma group but higher in the control group. Around normal awakening time, the supine IOP increased in the glaucoma group and did not change in the control group. There was a diurnal-to-nocturnal decrease in mean blood pressure only in the glaucoma group.

CONCLUSIONS. Compared with healthy eyes, the diurnal IOP is higher, the diurnal-to-nocturnal change of habitual IOP is less, and the posture-independent IOP pattern around normal awakening time is different in eyes with early glaucomatous changes. (*Invest Ophthalmol Vis Sci.* 2003;44:1586–1590) DOI:10.1167/iovs.02-0666

Intraocular pressure (IOP) is a major risk factor for the development of glaucoma. A single IOP measurement in the clinician's office is probably not adequate for the optimal management of glaucoma. Although the diurnal IOP curve provides a better estimate of an individual's IOP variation than a single office reading,¹ measurements of IOP for the diurnal IOP curve usually do not cover the nocturnal sleep period. Because of the inconvenience of measuring IOP at night, there is limited available information about the association of 24-hour variation in IOP and the development of glaucoma.

In the present study, we collected 24-hour data on IOP, blood pressure, and heart rate in a group of untreated patients with newly diagnosed early glaucomatous changes in their eyes. Diurnal, nocturnal, and 24-hour patterns of IOP and cardiovascular parameters in these patients (glaucoma group) were compared with data obtained in an age-matched control group of individuals with healthy eyes. The goal was to search and characterize alterations in the 24-hour IOP profile associated with early stages of glaucoma.

METHODS

The study adhered to the tenets of the Declaration of Helsinki and was approved by our Institutional Review Board. Experimental subjects were recruited consecutively from patients referred to the Hamilton Glaucoma Center of the University of California, San Diego. Reasons for the referrals might include high IOP, family history of glaucoma, and suspected change of optic disc or visual field. Each patient underwent a complete ophthalmic examination in the Glaucoma Center that included a review of relevant medical history, best corrected visual acuity, slit lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, dilated funduscopy, and visual field test. Patients with early glaucomatous changes in at least one eye were considered for inclusion in the study.

Glaucomatous changes included abnormal optic discs and repeatable abnormal visual fields. Abnormal discs might include excavation, rim defect, hemorrhage, notching, nerve fiber layer defect, or cup-to-disc asymmetry between the eyes of 0.2 or more. An abnormal visual field was determined by clinical review and by the manufacturer's criteria for abnormality (Statpac II; full-threshold 24-2 examination, Humphrey Field Analyzer; Zeiss-Humphrey, Dublin, CA). The corrected pattern standard deviation was outside 95% or glaucoma hemifield test outside 99% of the age-specific norms. The office IOP reading was not used as an inclusion or exclusion criterion for two reasons. First, there was no long-term follow-up of IOP in these patients. Second, we have observed in previous studies^{2–4} that one or a few office IOP readings do not correlate well with the 24-hour IOP profile.

Individuals who had any use of glaucoma medication or systemic β -adrenergic blocking agents, a history of eye surgery, ocular inflammation or trauma, a narrow iridocorneal angle, or advanced glaucomatous changes that needed immediate treatment were excluded. Individuals who smoked or had an irregular daily sleep schedule were also excluded. Informed consent was obtained after explanation of the nature and possible consequences of the study. Fourteen patients with abnormal optic discs and abnormal visual fields, eight patients with abnormal optic discs only, and two patients with abnormal visual fields only were recruited as the glaucoma group. The group included 11 men and 13 women who were 40 to 78 years old (59 ± 12 years, mean \pm SD). There were 17 whites, 4 African Americans, and 3 Asians. Their sitting IOP levels were in the range of 12 to 34 mm Hg (21.6 ± 6.0 mm Hg; mean \pm SD) during office evaluations.

Experiments in the sleep laboratory took place within a few weeks after recruitment. Subjects were instructed to maintain a daily 8-hour sleep period for 7 days before the experiment. Daily wake-sleep schedules were verified using a wrist monitor for light exposure and physical activity (Actiwatch; Mini Mitter, Sunriver, OR) and by the wake-sleep log. Subjects were asked to abstain from alcohol and caffeine for 3 days and to arrive at the laboratory at approximately 2 PM on the study day.

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They stayed indoors for the next 24 hours. Light intensity in the laboratory was kept at 500 to 1000 lux at eye level. The 8-hour period of darkness in the subject's room was adjusted to correspond to each individual's sleep time. Times for measurements were also individualized to coordinate with the sleep period. Although sleep and the measurement schedules were individualized, corresponding clock times were normalized for data presentation as if each subject had a sleep period from 11 PM to 7 AM.

Over 24 hours, IOP, blood pressure, and heart rate were measured by experienced personnel every 2 hours. IOP was measured in both eyes with a pneumatonometer (model 30 classic, Mentor O&O, Norwell, MA). Topical 0.5% proparacaine was applied as the local anesthetic. The pneumatonometer was calibrated against the manufacturer's verifier, and it was confirmed that different measurement angles produced the same IOP reading. A printout of every IOP measurement was obtained and evaluated according to generally accepted standards.² Blood pressure and heart rate were measured using an automated wrist blood pressure monitor (model HEM-608; Omron, Vernon Hills, IL).⁵ The automated device was used to minimize the variability between researchers. A wrist model was chosen for convenience of use at night.

Before the sleep period, measurements were taken at 3:30, 5:30, 7:30, and 9:30 PM. Subjects were instructed to lie in bed for 5 minutes before the measurements of blood pressure, heart rate, and IOP. They then sat for 5 minutes before the sitting IOP measurements. Subjects were encouraged to continue normal indoor activities. Food and water were available, and meal times were not regulated. Lights in individual sleep rooms were turned off at 11 PM. Measurements of blood pressure, heart rate, and IOP were taken in supine subjects at 11:30 PM and 1:30, 3:30, and 5:30 AM. Subjects were awakened, if necessary, and the measurements were completed in a few minutes. A dim room light (<10 lux) was used to assist the nocturnal measurements. Nocturnal IOP in the sitting position was not measured because of the concern that activation of the sympathetic nervous system while changing body position to sitting (baroreflex) at night could be substantially nonphysiological. Room activities were continuously videotaped with infrared recording systems. Daytime room lighting was restored at 7 AM, and subjects were awakened, if necessary. Measurements were taken again at 7:30, 9:30, and 11:30 AM and at 1:30 PM, as previously described.

Data of IOP from the glaucomatous eyes were used for analyses. In the 22 patients in whom both eyes had glaucomatous changes (either optic disc or visual field, or both), IOPs of both eyes were averaged. Mean blood pressure was calculated as the diastolic blood pressure plus one third of the difference between the systolic and the diastolic blood pressures. Means of IOP, blood pressure, and heart rate in all subjects were calculated for each clock time point, the diurnal period, and the nocturnal period. Statistical comparisons of the means between two time points (e.g., 5:30 and 7:30 AM) and between the diurnal and the nocturnal periods were made with the paired *t*-test. Correlation analyses were performed to explore the association between the diurnal or nocturnal IOP and the diurnal-to-nocturnal change in IOP, blood pressure, or heart rate. The criterion for statistical significance was $P < 0.05$.

Estimation of the 24-hour IOP rhythm was performed for habitual body positions (sitting during the day and supine at night) and for the supine position throughout.⁴ The best-fitting cosine curve was determined for each experimental subject by using IOP data obtained from the 12 time points.⁶ The peak of the fitted curve (acrophase) represented the phase timing. The null hypothesis of a random distribution of acrophases around the 24 hours was evaluated statistically by the Rayleigh test.⁷ Lack of significance indicated no 24-hour IOP rhythm in the group, whereas the alternative conclusion indicated a synchronized 24-hour rhythm timing. The amplitude (height of the fitted curve) estimated the magnitude of the 24-hour IOP variation.

Under similar experimental conditions, data on sitting and supine IOP, blood pressure, and heart rate were obtained from an age-matched control group of 10 men and 14 women. We assumed that potential modifications of IOP and cardiovascular parameters due to

the experimental procedures, such as awakening the experimental subject during the nocturnal period, would be similar in the control and the glaucoma groups. Nonsmoking volunteers with healthy eyes were recruited from university employees and local residents for the control group. They underwent a complete ophthalmic examination, demonstrating absence of any eye disease. Normal visual fields were confirmed with a full-threshold examination (24-2 program; Zeiss-Humphrey). Other excluding criteria were similar to those used for the glaucoma group. The control subjects were 40 to 74 years of age (mean, 56 ± 9) and included 18 whites, 3 African Americans, and 3 Asians. Office IOP readings were in the range of 12 to 21 mm Hg (mean, 16.0 ± 2.4). Experimental data were analyzed as described previously. Statistical comparisons between the glaucoma group and the control group were performed using Student's *t*-test, except that acrophases and amplitudes were compared using the Mann-Whitney rank-sum test, if 24-hour IOP rhythms were detected.

RESULTS

Data are presented as the mean \pm SEM unless otherwise indicated. Figure 1 presents the 24-hour IOP profiles for the two subject groups. Sitting or supine IOP was higher in the glaucoma group than in the control group, except in the late nocturnal sleep period. During the diurnal wake period, sitting and supine IOP decreased progressively. In contrast, supine IOP progressively increased during the nocturnal period. At 5:30 AM, the mean supine IOP levels in the two groups were very close. Considering the habitual body positions, IOP peaked at 5:30 AM and the trough occurred at 9:30 PM in both groups. Considering only the supine IOP, the peak occurred at 7:30 AM in the glaucoma group and at 5:30 AM in the control group. In both groups, the trough of the supine IOP occurred at 9:30 PM.

A difference in the change of supine IOP between 5:30 and 7:30 AM was observed. The supine IOP increased from 22.7 ± 0.6 to 24.4 ± 0.7 mm Hg in the glaucoma group ($P < 0.05$). Individually, there were 16 increases, 7 decreases, and 1 no change. In the control group, the supine IOP levels were 22.4 ± 0.5 and 21.4 ± 0.5 mm Hg at the two time points, respectively ($P > 0.05$). Individually, there were 15 decreases and 9 increases. Between the two subject groups, IOP changes observed during this 2-hour period were significantly different ($P < 0.01$). No significant change in mean blood pressure was found during the same period for both subject groups.

Mean diurnal and nocturnal IOP, blood pressure, and heart rate in the two groups are summarized in Table 1. Diurnal IOP, either sitting or supine, was significantly higher in the glaucoma group than in the control group ($P < 0.01$). In both groups, the nocturnal supine IOP was higher than the diurnal sitting IOP. However, this diurnal-to-nocturnal elevation of IOP was significantly less ($P < 0.01$) in the glaucoma group than in the control group. When diurnal and nocturnal IOPs in the supine position were compared, a decrease occurred in the glaucoma group and an increase in the control group. These changes in IOP in the two groups were significantly different ($P < 0.01$). Among the 24 subjects in the glaucoma group, the magnitude of the diurnal-to-nocturnal change in IOP (either habitual or supine) did not correlate with the average diurnal sitting or supine IOP, according to linear regression.

The diurnal variation of sitting IOP (the difference between maximum and minimum) was 5.9 ± 0.4 mm Hg in the glaucoma group, which was significantly larger than the variation in the control group (4.0 ± 0.3 mm Hg; $P < 0.01$). The variation in diurnal supine IOP was also larger in the glaucoma group (5.3 ± 0.4 vs. 4.1 ± 0.3 mm Hg; $P < 0.05$). In the nocturnal period, however, the variations of supine IOP in the two groups were not different (both 2.9 ± 0.3 mm Hg).

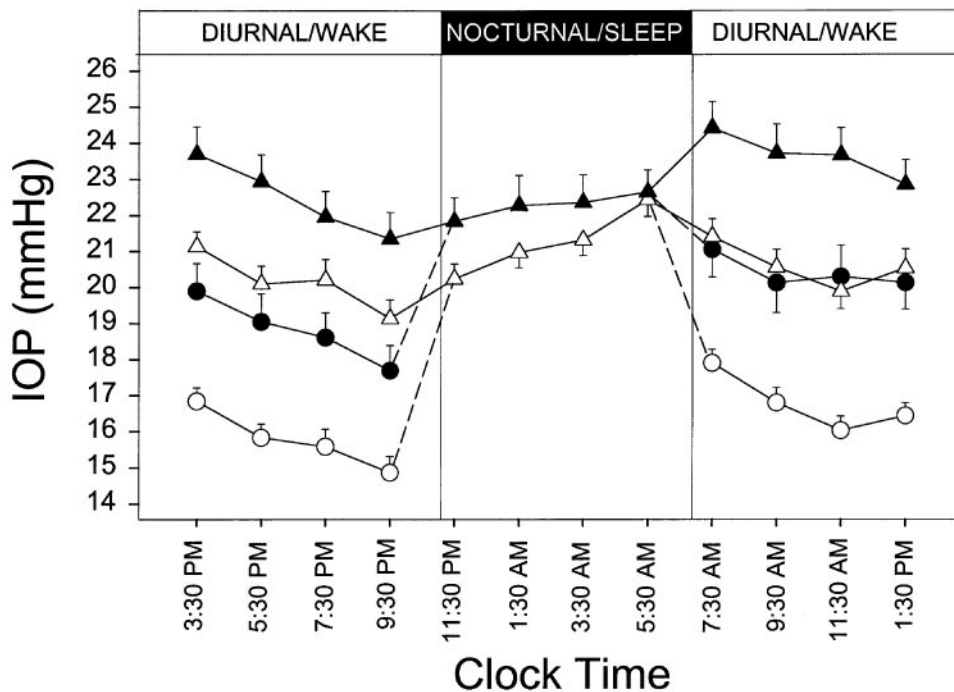


FIGURE 1. A comparison of 24-hour IOP patterns. *Filled symbols:* a group of 40- to 78-year-old untreated patients with newly diagnosed early glaucomatous changes ($n = 24$). *Open symbols:* age-matched control group of 24 individuals with healthy eyes. Measurements were taken in the sitting (*circles*) and supine (*triangles*) positions. Error bars, SEM.

There was a significant decrease in mean blood pressure between the diurnal and nocturnal periods in the glaucoma group only (Table 1). Although the average reduction in mean blood pressure was only 3 mm Hg, there was a significant trend for a larger reduction when the nocturnal IOP was low. The mean nocturnal supine IOPs in the glaucoma group were in the range of 17 to 33 mm Hg. Linear regression showed a positive correlation between the nocturnal IOP and the diurnal-to-nocturnal change in mean blood pressure (Fig. 2). No correlation was found between the nocturnal IOP and the diurnal-to-nocturnal change of supine IOP or heart rate. In the control group, there was no correlation between the nocturnal IOP and the diurnal-to-nocturnal change of mean blood pressure, supine IOP, or heart rate using the similar analyses of linear regression.

The Rayleigh test detected 24-hour rhythms of habitual IOP for both subject groups ($P < 0.01$; Fig. 3A). The acrophase of 5:26 AM \pm 0.7 hour in the glaucoma group was significantly different from the acrophase of 3:49 AM \pm 0.2 hour in the

control group ($P < 0.05$). The amplitude of 2.3 ± 0.3 mm Hg (a mathematical estimation of the 24-hour IOP variation; half of the cosine-fit maximum minus the minimum) in the glaucoma group was significantly less than the amplitude of 3.0 ± 0.2 mm Hg in the control group ($P < 0.05$). There were also 24-hour rhythms in the supine IOP ($P < 0.01$; Fig. 3B). The acrophase in the glaucoma group, 10:46 AM \pm 0.8 hour, was significantly different from the acrophase in the control group, 6:38 AM \pm 1.3 hour ($P < 0.01$). The amplitude in the glaucoma group, 1.8 ± 0.2 mm Hg, was significantly larger than that in the control group, 1.3 ± 0.1 mm Hg ($P < 0.05$).

DISCUSSION

Considering 24-hour IOP patterns with the same body position, our results showing the 24-hour supine IOP profile in the glaucoma group are compatible with those in previous reports of the 24-hour IOP pattern associated with glaucoma.⁸⁻¹⁵ Noc-

TABLE 1. Diurnal and Nocturnal IOP, Blood Pressure, and Heart Rate

	Diurnal Period (7 AM-11 PM)	Nocturnal Period (11 PM-7 AM)	Difference
Habitual IOP (mm Hg)			
Glaucoma group	19.6 \pm 0.7	22.3 \pm 0.7	2.7 \pm 0.6*
Control group	16.3 \pm 0.4	21.2 \pm 0.4	5.0 \pm 0.3*
Supine IOP (mm Hg)			
Glaucoma group	23.1 \pm 0.7	22.3 \pm 0.7	-0.8 \pm 0.4
Control group	20.4 \pm 0.4	21.2 \pm 0.4	0.9 \pm 0.4†
Mean blood pressure (mm Hg; supine rest)			
Glaucoma group	99 \pm 2	95 \pm 3	-3 \pm 1†
Control group	100 \pm 2	99 \pm 2	-1 \pm 1
Heart rate (beats/min; supine rest)			
Glaucoma group	67 \pm 2	65 \pm 2	-2 \pm 1
Control group	69 \pm 2	67 \pm 2	-2 \pm 1

Data are expressed as the mean \pm SEM; $N = 24$.

† $P < 0.05$.

* $P < 0.01$; paired t -test between the diurnal and nocturnal periods.

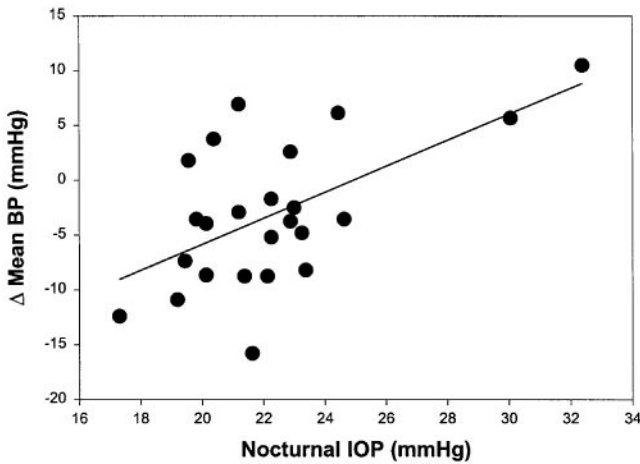


FIGURE 2. Linear regression showing a correlation ($P < 0.01$, $r = 0.59$) between the nocturnal IOP and the diurnal-to-nocturnal change of mean blood pressure in the glaucoma group ($n = 24$).

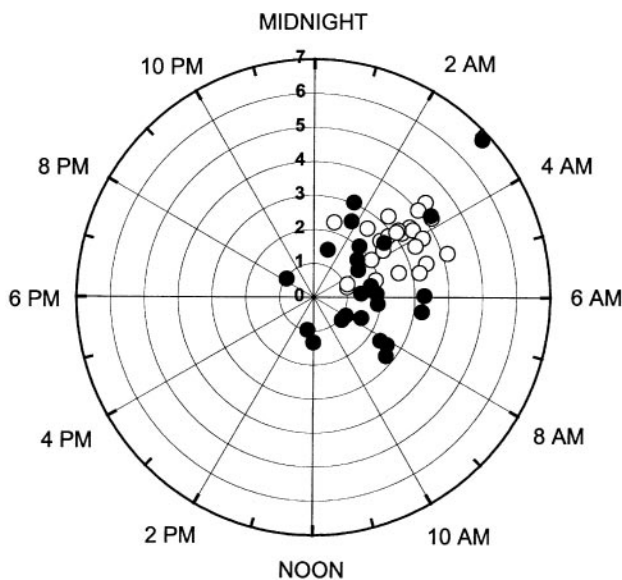
turnal IOP in untreated patients with glaucoma was reported to be lower than IOP in the diurnal period, based on measurements in one body position, either sitting^{8,11-14} or supine.^{9,10,14,15} A few additional studies involving treated patients with glaucoma^{16,17} have shown a nocturnal increase in supine IOP from the level obtained just before sleep, as observed in the present study. However, the 24-hour IOP pattern in ordinary life situations would be different because of habitual body positions: vertical during the day and recumbent at night. Confirmed in the present study, the nocturnal supine IOP was higher than the diurnal sitting IOP in individuals with healthy eyes.^{4,15} In untreated patients with newly diagnosed early glaucomatous changes, the nocturnal supine IOP was also higher than the diurnal sitting IOP. However, the magnitude of this diurnal-to-nocturnal IOP elevation was significantly smaller than that observed in the healthy eyes. Therefore, the differ-

ence in IOP between the two subject groups was less at night, compared with the intergroup difference in sitting IOP during daytime. These observations are preliminary and should be validated in a large number of experimental subjects. In addition, whether a similar 24-hour IOP pattern appears in untreated patients with more advanced glaucoma remains to be determined.

There was an alteration in the IOP pattern in the glaucoma group between the period from 5:30 to 7:30 AM. In the two groups, the posture-independent IOP level changed in opposite directions: an increase in the glaucoma group and a decrease in the control group. This suggests that regulation of IOP in the glaucoma group was different from the control group during this period, which may be relevant to the early pathogenesis of glaucoma. If certain endogenous mechanisms, yet to be identified, are responsible for the patterns of supine IOP observed in both subject groups, estimations of the 24-hour IOP rhythm show a 4-hour phase delay of these endogenous mechanisms in the glaucoma group. This phase delay also shifted the 24-hour rhythm of habitual IOP by 1.5 hours in the glaucoma group. These changes in IOP phase contributed to the apparent diurnal-to-nocturnal IOP differences between the two groups (Table 1).

Our data show that the variation in diurnal IOP (also termed the diurnal IOP fluctuation¹⁸), either sitting or supine, was larger in the glaucoma group than in the control group. A larger variation in sitting IOP in patients with glaucoma is well known during the diurnal awake period.^{1,18} However, the variations of supine IOP at night in the present study were not found to be different between the two subject groups. When considering the 24-hour variation in IOP in habitual body positions, the magnitude of the variation (by judging the amplitude of the 24-hour IOP rhythm) in the glaucoma group was actually less than that in the control group (Fig. 3A). This observation failed to support the notion that a large 24-hour variation in IOP in ordinary life situations is associated with early glaucomatous changes.

A. HABITUAL BODY POSITIONS



B. SUPINE BODY POSITION

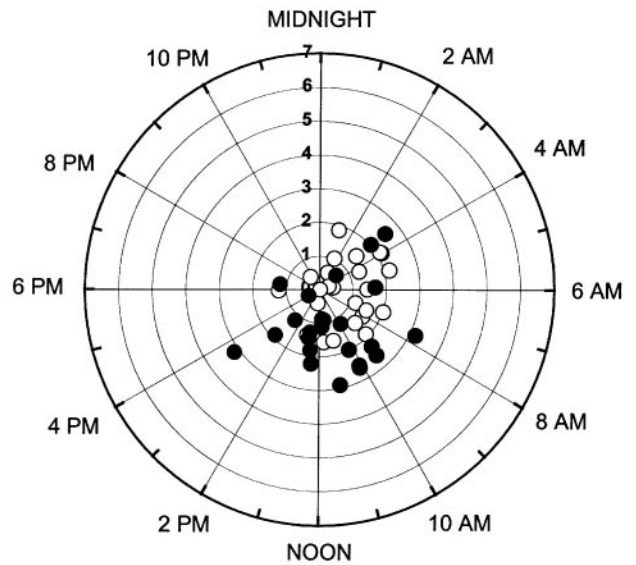


FIGURE 3. Estimated 24-hour rhythm of IOP in (A) habitual body positions and (B) the supine position. The clock time of the acrophase is shown with the amplitude in the radial scale (mm Hg). (●) Glaucoma group ($n = 24$); (○) control group ($n = 24$). Measurements in (A) are based on diurnal sitting IOP and nocturnal supine IOP.

When measured at supine rest, there was no change in blood pressure between the diurnal and nocturnal periods in the control group. Because the measurements during the diurnal period were taken after a 5-minute bed rest, influences of physical activities and upright posture on the blood pressure were minimized.¹⁹ However, a moderate diurnal-to-nocturnal decrease in blood pressure was observed in the glaucoma group. This change in blood pressure may be related to systemic medications taken by the subjects. Medical records showed that 16 subjects in the glaucoma group and 16 subjects in the control group used at least one systemic medicine. Notably, seven subjects in the glaucoma groups and nine subjects in the control group used some systemic antihypertensive drugs (other than β -blockers), which may influence the nocturnal pattern of blood pressure.²⁰ However, excluding these subjects from the data analyses did not change the nocturnal patterns of blood pressure in either group. Other significant medications used by the experimental subjects included anti-inflammatory, antilipemic, antidepressant, and estrogen replacement agents. Their combined effects on nocturnal blood pressure are unknown.

If the overall use of systemic medications had little effect on nocturnal blood pressure, the diurnal-to-nocturnal decrease in blood pressure in the glaucoma group may be meaningful. There have been indications that nocturnal arterial hypotension may be a risk factor for glaucoma in some individuals.²¹⁻²⁴ Ocular perfusion pressure (mean blood pressure in the ophthalmic artery minus IOP) can be compromised at night by systemic hypotension, even in patients with normal IOP. In the present study, it was of interest that the diurnal-to-nocturnal change in mean blood pressure correlated positively with the nocturnal IOP in the glaucoma group. Subjects with glaucoma with a lower nocturnal IOP seemed to have a larger reduction in blood pressure. In these patients, a significant reduction in nocturnal blood pressure alone may adversely affect ocular perfusion pressure at night. It suggests that glaucoma pathogenesis can happen in patients in whom ocular perfusion pressure is normal during daytime. The nocturnal hemodynamics associated with development of early glaucoma, as well as the mechanisms causing the postural-independent elevation in IOP at normal awakening time warrant further investigation.

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