Circadian (24-hour) Pattern of Intraocular Pressure and Visual Field Damage in Eyes with Normal-Tension Glaucoma

Young Rok Lee,[1] *Michael S. Kook,*[1] *Soo Geun Joe,*[1] *Jung Hwa Na,*[1] *Seungbong Han,*[2] *Seonok Kim,*[2] *and Cheol Jin Shin*[1]

Purpose. To characterize the circadian (24-hour) pattern of habitual-position intraocular pressure (IOP) and its association with visual field (VF) damage in eyes with normal-tension glaucoma (NTG).

Methods. A total of 177 eyes with NTG were examined over a 3-year period. IOP was recorded at 8 AM, 10 AM, 12 PM, 2 PM, 4 PM, 6 PM, 8 PM, 10 PM, 12 AM, 3 AM, and 6 AM by a single, well-trained ophthalmology resident using a hand-held tonometer. The circadian pattern and peak hours of habitual-position IOP and seated IOP were analyzed in all patients. Subgroup analysis was also performed, with groups defined by the time of maximum habitual-position IOP. The relationship between 24-hour habitual-position IOP parameters and VF indices was evaluated.

Results. There were 72 men and 105 women, all of whom were Koreans. Analysis of the entire population indicated a nocturnal peak (acrophase) for habitual-position IOP. Subgroup analysis indicated that 28 (15.8%) patients had diurnal acrophase, 91 (51.4%) patients had nocturnal acrophase, and 58 (32.8%) patients had no evident acrophase. There were no correlations between various 24-hour habitual-position IOP parameters and VF indices.

Conclusions. In the 177 NTG patients, there was a significant nighttime elevation of habitual-position IOP, and nocturnal seated IOP was significantly less than nocturnal habitual-position IOP. Subgroup analysis indicated three distinct daily patterns of peak IOP in the patients. There was no relationship between nocturnal elevation of habitual IOP and the magnitude of VF damage. (*Invest Ophthalmol Vis Sci.* 2012;53: 881–887) DOI:10.1167/iovs.11-7846

Elevated intraocular pressure (IOP) is the primary risk factor for the onset and progression of glaucoma, and lowering of IOP is the only method that slows the progression of the disease. Similar to other biological parameters, IOP varies over the course of a day. Previous studies have reported that the diurnal variation in IOP is larger in glaucomatous subjects and that a larger diurnal variation is an independent risk factor for progression of glaucoma.[1,2]

Currently, there is no agreement on the time of day when the maximum IOP occurs, particularly in patients with glaucoma. In a 1975 study of normotensive and hypertensive subjects, Kitazawa and Horie[3] analyzed IOP (measured with a Goldmann applanation tonometer [GAT]) every hour for 24 hours and reported that IOP was typically highest during the day and lowest early in the morning in both groups of patients.[3] Subsequently, Ido et al.[4] reported no particular pattern in the IOP of patients with normal-tension glaucoma (NTG), when IOP was measured while subjects were seated (seated IOP). However, Sacca et al.[5] reported that IOP was highest in the morning in subjects with primary open-angle glaucoma (POAG), normal-tension glaucoma (NTG), and healthy controls. The reasons for these conflicting results may be differences in measurement techniques, in study populations, or in body positions during IOP measurements.

More recently, Hara and Tsuru[6] used a noncontact tonometer to measure IOP over 24 hours with patients seated when they were awake and supine when they were asleep ("reproduced" IOP). They reported that the diurnal (seated) IOP was significantly lower than the nocturnal (supine) IOP. Similarly, based on pneumotonometry, Liu et al.[7] reported that 24 patients with untreated open-angle glaucoma (OAG) had nocturnal (supine) IOP that was significantly higher than diurnal (seated) IOP. Subsequently, it has been suggested that nocturnal IOP elevation occurring in the supine position may play an important role in damaging the optic nerve and visual field (VF) in OAG patients.

With this notion in mind, we measured the time course of IOP changes in a large group of subjects who were newly diagnosed with NTG. Our purposes of the present study were to (1) characterize the daily IOP pattern of NTG subjects in their habitual position (habitual-position IOP; i.e., seated during the day and supine at night) and seated position (seated IOP); (2) analyze the association of the 24-hour IOP parameters (including magnitude of IOP fluctuation) with glaucoma status, as measured according to retinal perimeter indices (Humphrey field analyzer [HFA]; Carl Zeiss Meditec, Dublin, CA); and (3) predict circadian peak IOP from daytime IOP parameters.

Patients and Methods

Subjects

We performed a prospective recruitment of NTG patients examined by a single glaucoma specialist (MSK) consecutively from February 2007 through January 2010 in the glaucoma clinic of the Asan Medical Center (Seoul, Korea).

All patients had been newly diagnosed with NTG on the basis of clinical evaluations and VF examinations at our glaucoma clinic and

From the [1]Department of Ophthalmology, Asan Medical Center and the [2]Division of Biostatistics, Center for Medical Research and Information, University of Ulsan, College of Medicine, Seoul, Korea.

Presented at the American Academy of Ophthalmology Annual Meeting, Chicago, Illinois, October 2010.

Submitted for publication May 9, 2011; revised August 28 and November 16, 2011; accepted January 3, 2012.

Disclosure: **Y.R. Lee**, None; **M.S. Kook**, None; **S.G. Joe**; None; **J.H. Na**, None; **S. Han**; None; **S. Kim**, None; **C.J. Shin**, None

Corresponding author: Michael S. Kook, Department of Ophthalmology, Asan Medical Center, University of Ulsan College of Medicine, Pungnap-dong, Songpa-gu, Seoul, Korea; mskook@amc.seoul.kr.

underwent in-hospital 24-hour monitoring of IOP when eligible for the study. All eligible NTG patients had optic nerves that appeared to be glaucomatous based on diffuse or focal neural rim thinning, disc hemorrhage, enlarged vertical cupping greater than 0.7, vertical cupping asymmetry greater than 0.2, or nerve fiber layer defects indicative of glaucoma, in addition to corresponding loss of VF on repeated examination; best corrected visual acuity greater than 20/40; maximum untreated IOP less than 22 mm Hg in both eyes at 8 AM, 12 PM, and 4 PM in the same day based on GAT; normal anterior chamber and open-angle based on slit-lamp and gonioscopic examination; and glaucomatous VF damage.

Patients were excluded if one or more of the following were present: untreated IOPs (recorded during normal clinic hours at 8 AM, 12 PM, and 4 PM during the same day) greater than 21 mm Hg in at least one eye based on GAT; evidence of intracranial or otolaryngological lesion; history of massive hemorrhage or hemodynamic crisis; previous or current use of antiglaucoma medications or systemic or topical steroids; presence of any other ophthalmic disease that could result in optic nerve and VF defects; or a history of diabetes mellitus. Individuals who smoked or had an irregular daily sleep schedule were excluded. Finally, patients who had undergone ocular surgery or had corneal abnormalities that prevented reliable IOP measurement (including refractive surgery) were also excluded.

The central corneal thickness (CCT) was measured three times by ultrasonic pachymetry (DGH-550; DGH Technology Inc., Exton, PA) at the initial visit, and the average was calculated. All procedures conformed to the Declaration of Helsinki, and the study was approved by the Institutional Review Board of the Asan Medical Center at the University of Ulsan (Seoul, Korea). All patients provided informed consent.

VF Examination

This examination was performed with the 24-2 Swedish Interactive Thresholding Algorithm (SITA) standard program on the retinal perimeter. Eyes with glaucomatous VF defects had at least two of the following characteristics in the second VF examination for minimizing learning effect: (1) a cluster of three points with a probability less than l% on a pattern deviation map in at least one hemifield, including at least one point with a probability less than 1%; or a cluster of two points with a probability less than 1%; (2) glaucoma hemifield test (GHT) results outside 99% of the age-specific normal limits; and (3) pattern standard deviation (PSD) outside 95% of normal limits. We included only patients who had reliable VF measurements within 1 month of the initial evaluation, defined as a false-positive error less than 15%, false-negative error less than 15%, and a fixation loss less than 20%. VF data were analyzed for determination of mean deviation (MD) and PSD from the second VF examination.

Measurement of In-hospital, 24-Hour IOP

All IOP measurements were performed by a single well-trained ophthalmology resident (CJS). First, in a separate pilot study to test the accuracy of the tonometer (TonoPen XL; Mentor Ophthalmics, Santa Barbara, CA) against GAT, we compared the handheld tonometer and GAT readings by performing a cross-sectional study of 50 consecutive patients (100 eyes) with NTG or suspected NTG. The results indicated an excellent correlation between IOP readings obtained by the tonometer and GAT ($r = 0.91$; $P < 0.001$). The difference between the GAT and the tonometer was less than 2 mm Hg in 93% of the measurements.

All eligible patients in our main study were instructed to abstain from alcohol and caffeine for 3 days before hospital admission. The diurnal and nocturnal periods may have differed among enrolled patients at home. All measurements of IOP were obtained with the handheld tonometer at 8 AM, 10 AM, 12 PM, 2 PM, 4 PM, 6 PM, 8 PM, and 10 PM (diurnal IOP) and at 12 AM, 3 AM, and 6 AM (nocturnal IOP) in both eyes of each patient. Three measurements were taken for each eye, and the average value was used for analysis without correction for CCT in both the sitting and supine positions.

The subjects were instructed to continue normal indoor activities during the diurnal period, and diurnal IOP was measured when the patients were seated. During the nocturnal period, lights in individual rooms were turned off by the nurse, and the patients were instructed to sleep with the position of the head on same level as body. They were awakened (if necessary), and the IOP measurements were performed with the tonometer under dim light, with patients supine (because activation of the sympathetic nervous system while changing body position at night could be nonphysiological). After the subjects had a 10-minute rest period in the upright position, the nocturnal IOP was measured while they were seated. Blood pressure and heart rate were measured simultaneously with the 24-hour IOP measurements with an automated ambulatory blood pressure (BP) monitor device (Space Laboratories Medical Inc., Redmond, WA).

Statistical Analysis

We measured the IOPs of both eyes in all enrolled NTG patients. If both eyes were affected, the left eye was selected for analysis. The 24-hour pattern and peak hours of habitual-position IOP were analyzed for the entire group. Subgroup analysis was also performed on the basis of the timing of peak habitual-position IOP.

A cosinor model was used to describe the pattern of the 24 hours (nychthemeral) IOP; this model has been shown to be useful for fitting symmetric and stationary rhythmic patterns.[8] The cosinor model uses sine and cosine terms to describe a diurnal variation and is expressed as:

$$y(t) = b_0 + b_1 \times \cos[(2\pi/24) \times t] + b_2 \times \sin[(2\pi/24) \times t] \quad (1)$$

where y is the observed IOP at time t after the IOP measurement is initiated, and b_0, b_1, and b_2 are regression coefficients. The constant $(2\pi/24)$ and the coefficient b_0 represent the 24-hour periodicity of IOP and the 24-hour rhythm-adjusted mean IOP, respectively. Thus, the amplitude (A) that represents half of the extent of rhythmic change in a cycle can be given as:

$$A = \sqrt{b_1^2 + b_2^2} \quad (2)$$

Various IOP parameters, separated by different periods (diurnal, nocturnal, and circadian), were compared for measurements performed with patients in different body postures (seated versus habitual). Differences in IOP obtained at different times of day and different body postures were compared by paired t-tests. A difference was considered significant at $P < 0.003$ since $P < 0.05$/the number of the comparisons ($n = 15$) was considered statistically significant with consideration for the multiple comparisons according to the Bonferroni correction method. We also determined the time and frequency at which the peak IOP was recorded for seated and habitual-position IOP measurements. The percentages of eyes with IOPs of 22 mm Hg or greater and 24 mm Hg or greater were recorded for habitual-position and seated IOP.

The correlation between various habitual-position IOP parameters at different times of day (office hour, diurnal, nocturnal, and circadian) and VF indices (MD and PSD) were analyzed by Pearson's correlation coefficient. In addition, the effect of these parameters on VF indices were adjusted for age, CCT, and refractive error based on spherical equivalent (SE) data using multivariate linear regression. As the increase in cerebrospinal fluid (CSF) pressure may be related to the glaucomatous damage due to hydrostatic change with different body height and position, body height was also correlated with VF indices.

A statistical analysis along with sample size calculation was performed to acquire 80% power to detect correlations $\geq \pm 0.20$, while controlling the probability of a type I error at 0.05 in a two-tailed test. A sample size of at least 170 subjects or greater was needed to meet these conditions.

Multiple linear regression analysis was used to determine associations between various diurnal IOP parameters (office and in-hospital), peak 24-hour habitual-position IOP, and the peak nocturnal IOP. The

TABLE 1. Demographic and Ophthalmic Characteristics of Patients with NTG

Demographics	Values
Age, y	
Mean ± SD	57.20 ± 12.23
Range	35~87
Sex, M/F	72/105
Pachymetry, μm	
Mean ± SD	530.14 ± 52.5
Range	401~661
Visual field MD	
Mean ± SD	−4.69 ± 2.20
Range	−25.51~−2.99
Visual field PSD	
Mean ± SD	5.03 ± 3.87
Range	0.97~16.17
Mean clinic IOP, GAT	
Mean ± SD	14.6 ± 2.55
Range	8~20
Mean 24-hour IOP ± SD, entire group	
Sitting position	16.1 (9–22.9)
Habitual position	16.6 (9.2–22.4)
SD, sitting position	2.12
SD, habitual position	2.11
Fluctuation, sitting position	6.33 ± 1.86
Fluctuation, habitual position	6.95 ± 2.32
Peak, sitting position	19.41 ± 2.45
Peak, habitual position	20.28 ± 2.83
Mean 24-hour IOP ± SD, diurnal peak group	
Sitting position	17.05 (13.4–22.9)
Habitual position	17.4 (14–22.5)
SD, sitting position	2.2
SD, habitual position	2.1
Fluctuation, sitting position	6.8 ± 1.6
Fluctuation, habitual position	6.7 ± 1.5
peak, sitting position	20.7 ± 2.6
peak, habitual position	20.9 ± 2.6
Mean 24-hour IOP ± SD, no pattern group	
Sitting position	15.56 (9–20.6)
Habitual position	15.88 (9.4–21)
SD, sitting position	2.35
SD, habitual position	2.31
Fluctuation, sitting position	6.5 ± 1.5
Fluctuation, habitual position	5.7 ± 1.5
Peak, sitting position	18.9 ± 2.5
Peak, habitual position	18.6 ± 2.4
Mean 24-hour IOP ± SD, nocturnal peak group	
Sitting position	16.2 (10.5–20.5)
Habitual position	16.8 (11.9–21.4)
SD, sitting position	1.83
SD, habitual position	1.85
Fluctuation, sitting position	6.1 ± 2.1
Fluctuation, habitual position	7.7 ± 2.6
Peak, sitting position	19.3 ± 2.2
Peak, habitual position	21.1 ± 2.7

$n = 177$.

magnitude of the peak 24-hour habitual-position IOP and the peak nocturnal IOP were estimated based on the significant diurnal IOP parameters (SPSS 15.0 for Windows; SPSS Inc., Chicago, IL).

RESULTS

One hundred seventy-seven patients were enrolled in this prospective study. Among the 177 NTG subjects, 72 were men, 105 were women, and all were native Koreans. Table 1 summarizes the additional demographic and clinical characteristics of our study group.

Analysis of the entire population indicated a nocturnal peak (acrophase) of habitual-position IOP, with a peak at approximately 6 AM (Fig. 1A). Further analysis of individual patients indicated that 28 (15.8%) patients had a diurnal acrophase, 91 (51.4%) patients had a nocturnal acrophase, and 58 (32.8%) patients had no evident acrophase (Fig 1B). The distribution of age, sex, and VF indices was not significantly different among the three groups. However, eyes with a diurnal acrophase showed higher mean 24-hour IOP in both sitting and habitual positions, whereas those with a nocturnal acrophase showed higher habitual-position IOP fluctuation and peak IOP during 24-hour monitoring than did eyes with no evident acrophase (Table 1).

Figure 2 shows the average 24-hour seated IOP pattern of all 177 patients. Analysis of the entire group indicated a diurnal acrophase, with peak seated IOP in the morning (8–10 AM). The resulting cosinor regression models for each of the 24-hour curves in Figures 1 and 2 are given in the figure legends. Our cosinor model fitted values followed the observed average value for rhythms of habitual-position IOP and seated IOP, respectively. Based on the standard residuals (SRs) plot, each of five predicted cosinor model IOP curves (Figs. 1, 2) showed an excellent fit with the observed data. More than 95% of the SRs (observed value-predicted value/SD) were in the range be-

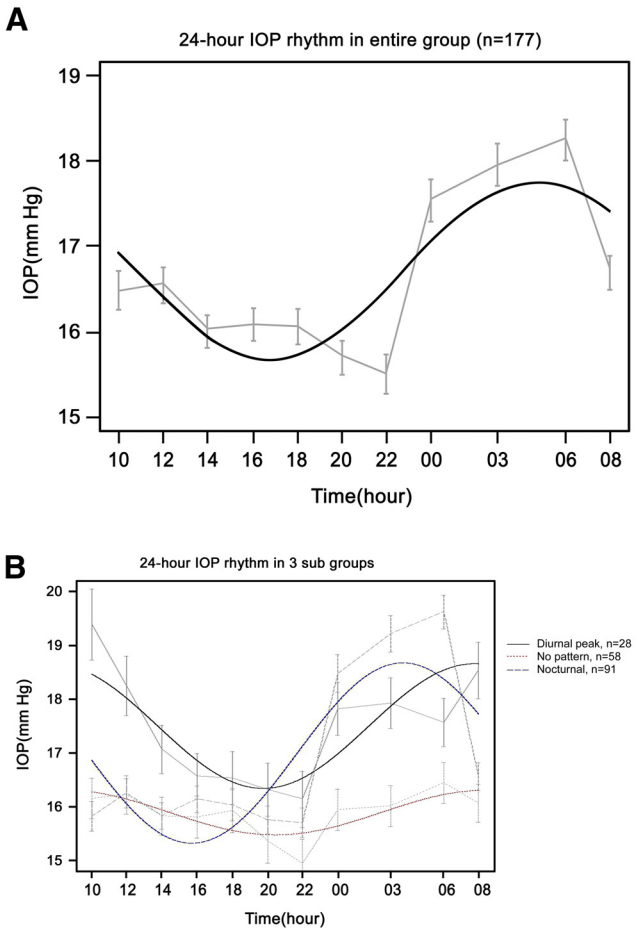

FIGURE 1. Average 24-hour (nychthemeral) rhythms of habitual-position IOP of all patients (**A**) and for three subgroups of patients (**B**), based on the cosinor model (mean ± SE). (**A**) The 24-hour IOP rhythm in the entire group ($n = 177$): $y(t) = 16.714 + 0.208 \times \cos[(2\pi/24) \times t] - 1.014 \times \sin[(2\pi/24) \times t]$. (**B**) The 24-hour IOP rhythm in the three subgroups: diurnal peak group: $y(t) = 17.498 + 0.965 \times \cos[(2\pi/24) \times t] - 0.642 \times \sin[(2\pi/24) \times t]$; no pattern group: $y(t) = 15.891 + 0.382 \times \cos[(2\pi/24) \times t] - 0.164 \times \sin[(2\pi/24) \times t]$; nocturnal peak group: $y(t) = 16.998 - 0.134 \times \cos[(2\pi/24) \times t] - 1.671 \times \sin[(2\pi/24) \times t]$.

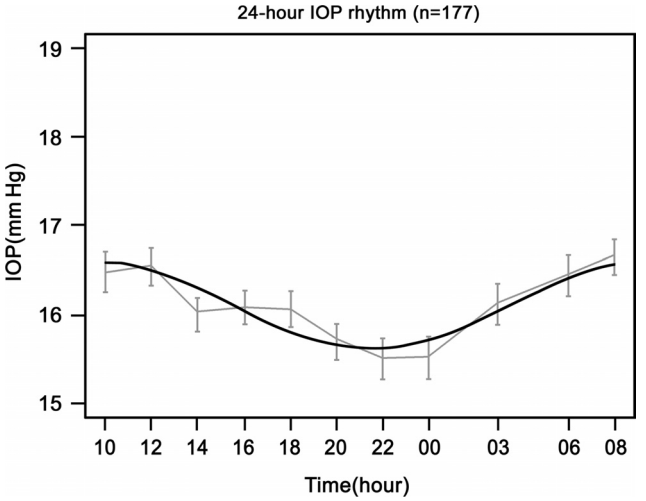

FIGURE 2. Average 24-hour (nychthemeral) rhythm of seated IOP for all patients (mean ± SE; $n = 177$). Entire group: $y(t) = 16.115 + 0.483 \times \cos[(2\pi/24) \times t] - 0.063 \times \sin[(2\pi/24) \times t]$.

tween −2 and +2. No values suspicious of being outliers or influential points were detected.

Mean habitual-position IOP during waking hours was significantly different from mean habitual-position IOP during sleeping hours ($P < 0.001$; Table 2). However, mean seated IOPs during waking and sleeping hours were not significantly different ($P = 0.47$; Table 2).

Mean habitual-position IOP and seated IOP during the sleeping hours also differed significantly. In particular, the maximum and minimum IOP during the nocturnal period were significantly different for seated and supine measurements ($P < 0.001$; Table 3, Fig. 3). There were similar differences between these two groups in the 24-hour peak, trough, fluctuation, and standard deviation IOP parameters, but not in the average 24-hour IOP (Table 3). The mean nocturnal peak IOP value was close to the mean peak 24-hour IOP in our NTG eyes.

We also analyzed the maxima of seated IOP and habitual-position IOP for individual patients (Fig. 4). Most patients had maximum habitual-position IOPs during the nocturnal hours (3–6 AM) and maximum seated IOP during the morning (8–10 AM). None of the study subjects had IOPs over 21 mm Hg at the outpatient clinic in at least three visits on the same day (8 AM, 12 PM, and 4 PM). However, 22.6% of the subjects had habitual-position IOPs over 21 mm Hg, and 9.6% of subjects had habitual-position IOPs over 23 mm Hg during the 24-hour measurement period. In contrast, 15.0% of the subjects had seated IOP over 21 mm Hg and 5.6% had seated IOP over 23 mm Hg during the 24-hour measurement period.

Table 4 illustrates the relationships between various parameters and VF MD and PSD. There were no evident associations between body height and 24-hour IOP parameters, including the magnitude of nocturnal IOP elevation in the habitual position and HFA indices, according to Pearson's correlation analysis. Estimate of the type II error was between 0.597 and 0.950 for the MD and 0.622 and 0.949 for the PSD, based on the current data. After adjustment for possible confounders for glaucoma (age, CCT, and refractive error), no parameter was significantly associated with the VF indices.

Finally, peak 24-hour habitual-position IOP and peak nocturnal IOP could be estimated from the diurnal measurement of IOP with the following regression equations based on our multiple linear regression analysis:

$$\text{Peak 24-hour habitual-position IOP} = 3.455 + 0.887 \times \text{diurnal peak IOP}$$

$$\text{Peak nocturnal habitual-position IOP} = 5.352 + 0.749 \times \text{diurnal peak IOP}$$

The coefficient of determination R^2 provides a measure of how well future outcomes are likely to be predicted by the model. R^2 of peak 24-hour habitual-position and peak nocturnal habitual-position with the simple linear regression equations were 0.71 (correlation coefficient $r = 0.841$) and 0.43 (correlation coefficient $r = 0.66$), respectively.

TABLE 2. Comparison of Mean IOP at Different Times and Positions

	Daytime		Nighttime		
	Mean	SD	Mean	SD	*P**
Habitual position	16.14	1.88	17.92	1.76	<0.001
Sitting position	16.14	1.88	16.04	1.68	0.47

Difference between daytime mean and nighttime mean.

TABLE 3. Comparison of Various IOP Parameters Different Times and Patient Positions

	Sitting Position	Habitual Position	*P*
24-Hour average	16.12 ± 2.12	16.15 ± 2.12	0.402
24-Hour peak	19.41 ± 2.44	20.28 ± 2.82	<0.001*
24-Hour trough	13.07 ± 2.30	13.32 ± 2.29	<0.001*
24-Hour fluctuation	6.33 ± 1.86	6.95 ± 2.32	<0.001*
24-Hour SD	2.12	2.12	<0.001*
Diurnal average	16.15 ± 2.12	16.15 ± 2.12	N/A
Diurnal peak	18.95 ± 2.40	18.95 ± 2.40	N/A
Diurnal trough	13.49 ± 2.28	13.49 ± 2.28	N/A
Diurnal fluctuation	5.46 ± 1.75	5.46 ± 1.75	N/A
Diurnal SD	2.12	2.12	N/A
Nocturnal average	16.05 ± 2.64	17.92 ± 2.80	<0.001*
Nocturnal peak	17.63 ± 3.00	19.55 ± 3.08	<0.001*
Nocturnal trough	14.46 ± 2.74	16.23 ± 2.93	<0.001*
Nocturnal fluctuation	3.18 ± 2.11	3.32 ± 2.20	0.420
Nocturnal SD	2.64	2.80	0.384

Data are expressed as the mean ± SD.

* Statistically significant with consideration for the multiple comparisons ($P < 0.003$).

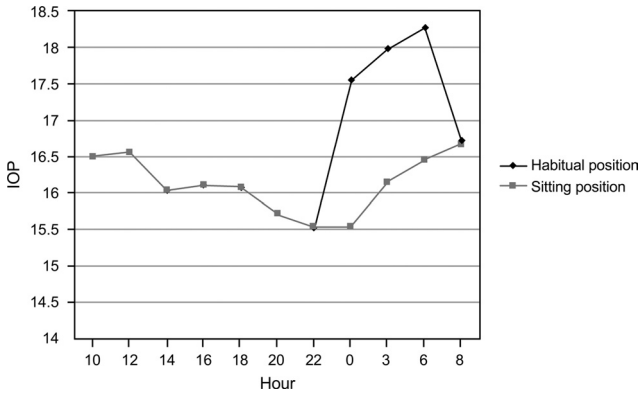

FIGURE 3. Average 24-hour habitual-position and seated IOPs of patients with normal-tension glaucoma ($n = 177$; mean ± SE).

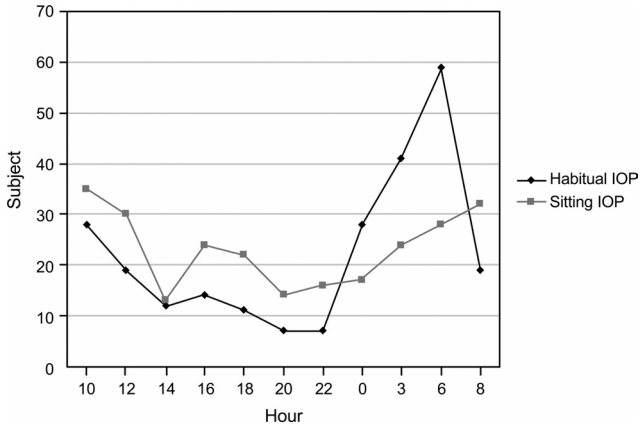

FIGURE 4. Frequency distribution showing the time of maximum habitual-position and seated IOPs for each patient (n = 177).

DISCUSSION

This study is unique in that our study population consisted of a relatively large number of Asians (Koreans) with NTG who underwent 24-hour IOP measurement. For all NTG eyes considered together, there was a nocturnal elevation of habitual-position IOP, but nighttime had no significant effect on the seated IOP. This finding suggests that nocturnal elevation of IOP is primarily due to postural changes, in agreement with the results of Hara and Tsuru,[6] who measured seated and supine IOP by noncontact tonometry over 24 hours. Other researchers have also speculated that nocturnal IOP elevation is due to changes of body posture that lead to increased episcleral venous pressure.[9–11] Our observation that the highest IOP values occurred in the morning in NTG eyes with patients seated is consistent with the observations of Sacca et al.[5]

Although the analysis of our entire population indicated that mean IOP was highest at night when the patients were supine, we also identified three major IOP rhythms among our 177 patients: diurnal acrophase (15.8%), nocturnal acrophase (51.4%), and no acrophase (32.8%). Mosaed et al.[12] analyzed 24-hour data of IOP in 33 young healthy subjects, 35 elderly healthy subjects, and 35 untreated long-term glaucoma patients housed in a sleep laboratory. In the glaucoma group, 33% of patients had maximum habitual-position IOP in the diurnal period, and 67% had maximum habitual-position IOP during the nocturnal period. Although the exact physiologic mecha-

TABLE 4. Correlation between IOP and Body Height Parameters and MD and PSD in Patients with NTG

	Univariate Analysis		Multivariate Analysis*		
Parameters	**Pearson's Correlation (R)**	**P**	**Estimated Coefficient**	**95% CI**	**P**
Parameters versus MD					
Average, 24 h	0.053	0.485	−0.0682	−0.4887 to 0.3522	0.7509
SD	0.048	0.528	0.6402	−0.7043 to 1.9847	0.3522
Peak	0.060	0.428	−0.0007	−0.3304 to 0.3290	0.9966
Trough	−0.006	0.935	−0.1372	−0.5226 to 0.2482	0.4864
Fluctuation	0.058	0.449	0.1577	−0.2569 to 0.5723	0.4571
Day average	0.065	0.395	−0.0765	−0.5018 to 0.3489	0.7251
Day SD	0.078	0.305	0.6402	−0.7043 to 1.9847	0.3522
Day peak	0.050	0.513	−0.0007	−0.3304 to 0.3290	0.9966
Day trough	0.000	0.996	−0.1843	−0.5709 to 0.2024	0.3517
Day fluctuation	0.073	0.336	0.2118	−0.2037 to 0.6272	0.3193
Night Average	0.026	0.737	−0.0220	−0.3411 to 0.2971	0.8926
Night SD	0.088	0.247	0.5790	−0.1916 to 1.3496	0.1429
Night peak	0.062	0.413	0.0536	−0.2564 to 0.3635	0.7353
Night trough	−0.012	0.875	−0.1043	−0.4021 to 0.1935	0.4935
Night fluctuation	0.077	0.313	0.2881	−0.1175 to 0.6936	0.1659
Night peak to day average	−0.016	0.836	0.2492	−0.2537 to 0.7520	0.3329
Office IOP	0.129	0.089	0.1903	−0.1408 to 0.5215	0.2618
Body height	0.021	0.798	−0.0300	−0.1371 to 0.0771	0.5833
Parameters versus PSD					
Average, 24 h	0.004	0.963	0.0191	−0.0407 to 0.0790	0.5322
SD	−0.014	0.858	−0.0146	−0.2067 to 0.1775	0.8820
Peak	−0.001	0.984	0.0204	−0.0265 to 0.0672	0.3956
Trough	0.062	0.414	0.0236	−0.0312 to 0.0785	0.3997
Fluctuation	−0.034	0.654	0.0050	−0.0542 to 0.0641	0.8700
Day average	−0.009	0.901	0.0225	−0.0381 to 0.0830	0.4684
Day SD	−0.108	0.154	−0.0146	−0.2067 to 0.1775	0.8820
Day peak	0.003	0.964	0.0204	−0.0265 to 0.0672	0.3956
Day trough	0.062	0.416	0.0316	−0.0235 to 0.0866	0.2628
Day fluctuation	−0.095	0.210	−0.0039	−0.0633 to 0.0555	0.8976
Night Average	0.017	0.818	0.0213	−0.0241 to 0.0666	0.3591
Night SD	−0.056	0.459	−0.0421	−0.1525 to 0.0683	0.4561
Night peak	0.001	0.991	0.0185	−0.0256 to 0.0626	0.4113
Night trough	0.050	0.511	0.0244	−0.0718 to 0.0668	0.2593
Night fluctuation	−0.051	0.504	−0.0137	−0.0718 to 0.0444	0.6453
Night peak to day average	0.046	0.548	0.0175	−0.0543 to 0.0893	0.6339
Office IOP	−0.124	0.102	−0.0227	−0.0716 to 0.0261	0.3629
Body height	−0.010	0.900	0.0028	−0.0126 to 0.0182	0.7272

n = 177.

* Each parameter effect was adjusted for age, CCT, and refractive error.

nisms underlying nocturnal IOP change are unknown, our study and the study of Mosaed et al. indicate that more than 50% of glaucomatous subjects have nocturnal elevation of habitual-position IOP. Interestingly, a significant portion of our NTG eyes (32.8%) had no clearly identifiable acrophase for habitual-position IOP.

Renard et al.,[13] using an electronic tonometer, identified two major IOP rhythms in 22 NTG subjects—diurnal acrophase (54.5%) and nocturnal acrophase (36.4%)—when IOP was measured every hour, with patients in a physiological posture. In contrast to our present findings and those of Mosaed et al.,[12] this study demonstrated a significantly greater proportion of eyes with diurnal acrophase (n = 12, 54.5%) than with nocturnal acrophase (n = 8, 36.4%). However, direct comparison of different studies may be problematic because of the differences in study populations, number of enrolled subjects, study designs, and definition of NTG.

Another crucial finding of our study was that 9.6% of eyes that never had IOP elevation over 21 mm Hg during outpatient clinic hours had habitual-position IOP more than 23 mm Hg during the study period. This percentage is similar to that reported by Hara and Tsuru.[6] Our findings suggest that a certain percentage of NTG patients experience IOP elevation outside office hours, particularly during the nocturnal period when patients are supine. Barkana et al.[14] performed 24-hour monitoring of habitual-position IOP in glaucoma patients with advanced disease and reported higher maxima and more significant fluctuations of nocturnal IOP than during typical office hours.

Kiuch et al.[15,16] reported that more advanced VF damage and progression of VF damage in NTG were associated with a greater IOP elevation due to postural changes. However, in our large series of Asian (Korean) NTG subjects, despite the overall nocturnal elevation of habitual-position IOP, no IOP parameters including posture-related IOPs (24-hour IOP fluctuation, 24-hour IOP SD, nighttime average IOP, nighttime peak IOP, nighttime trough IOP, and nighttime peak–day average IOP) were associated with the extent of initial VF damage at presentation after adjustment for possible confounders that may be associated with glaucoma in a multivariate analysis. This result may indicate that IOP changes after postural changes at night do not occur in every NTG subject and may not play a critical role in every NTG progression. Similar to our study, the Low-Pressure Glaucoma Treatment Study did not demonstrate a relationship between any 24-hour IOP parameter measured in the sitting posture and VF MD or CPSD at baseline in the eyes with NTG.[17]

In our recent studies of NTG,[18,19] we found that 24-hour ocular perfusion pressure (OPP) fluctuation, due to the significant blood pressure (BP) dip at night, was the most consistent risk factor for both severity and progression of glaucoma. We suggest that a future longitudinal study should investigate the influence of various 24-hour IOP parameters in conjunction with OPP, including those that accompany posture changes, on glaucoma progression. Although we did not directly measure OPP in this study, 24-hour habitual-position IOP data provide a more accurate assessment of IOP and OPP status of glaucoma patients, if needed, than does seated IOP data acquired during office hours.

A study by Magnaes[20] showed that the intracranial CSF pressure at eye level falls by an average of 14 mm Hg as a subject changes position from the left lateral decubitus posture to the sitting or standing posture. Although the change in CSF pressure may be related to glaucomatous damage of hydrostatic causes with different body height, body height was found not to be associated with VF indices. In fact, CSF pressure increases more or less parallel to the IOP in supine position. Thus, this increase in CSF pressure at night may act as a stable support of the lamina cribrosa against the nocturnal rise in IOP. This may also explain our finding that IOP changes after postural changes at night did not show a significant association with glaucomatous damage.

Estimation of the 24-hour maximum IOP in untreated glaucoma patients is clinically relevant. Previous studies have indicated the inadequacy of office-hour seated IOP and have shown that IOP maxima occur outside of office hours in 52% to 66% of patients.[21–23] Mosaed et al.[12] studied a group of untreated patients with glaucoma and suggested that IOP assessment could be improved by using a formula to predict the peak IOP based on office-hour readings. They found that the average values of supine IOP during office hours had the strongest correlation with maximum nocturnal IOP in elderly glaucoma subjects (r = 0.713; $P < 0.001$), and that the correlation between average seated IOP during office hours and maximum nocturnal IOP was also strong (r = 0.60; $P < 0.001$). Of interest, we found that maximum diurnal seated IOP had the strongest correlations with maximum 24-hour IOP (r = 0.78; $P < 0.001$) and nocturnal IOP (r = 0.61; $P < 0.001$). Again, differences in the study designs, sample sizes, and study population may explain these discrepancies.

Although a clinician can estimate or extrapolate the peak 24-hour habitual-position IOP in untreated NTG patients by measuring the highest daytime IOP, the absolute magnitudes of the difference between the highest daytime IOP and the peak 24-hour habitual and nocturnal IOP were relatively small (nearly 3 and 4 mm Hg IOP, respectively). Enrollment of NTG subjects according to our study design may have contributed to a relatively small range of IOP change over 24 hours. A limitation of using our estimation formula is its main applicability to subjects who show a nocturnal acrophase pattern, whereas clinicians often do not know the pattern of IOP elevation in each patient. Further studies are needed to assess the utility of various proposed models for estimation of 24-hour maximum and nocturnal IOP in NTG subjects.

Our study has a few limitations. Calculation of habitual-position IOP using a handheld tonometer (TonoPen XL; Mentor Ophthalmics) may be subject to different accuracy and variability, although the tonometer has shown good agreement with the GAT in eyes with normal corneas in previous studies.[24–27] However, this is a minor limitation in the present study, as it may have affected the absolute values of IOP, not the rhythm of 24-hour IOP in each individual. Moreover, we tested the agreement of the measurement with that of the GAT with NTG patients or suspects and the agreement was excellent. A second limitation is the inability to generalize our findings to other POAG and NTG subjects with different definitions or race, such as those studies referenced, since 2-hour monitoring of habitual-position IOP was performed in Korean patients with maximum multiple untreated IOPs less than 22 mm Hg during office hours using the GAT in our study. Because of the complexity of hourly measurements of IOP, we measured the IOP every 2 hours over 24 hours. Hourly measurements may have made the modeling of IOP rhythms and prediction of the peak 24-hour habitual position and nocturnal IOP more precise and physiological. However, waking patients up every hour at night for IOP measurement could lead to nonphysiological acquisition of IOP. Another limitation is that no control group was included in the present study. As an increase in IOP during nocturnal period in supine position may be a physiological phenomenon, it remains unclear whether the NTG patients with nocturnal acrophase have a pathologic or physiological IOP curve. Finally, measurement of habitual-position IOP using the tonometer may not provide the best physiological 24-hour ocular tension data in our NTG subjects, as our IOP measurement was based on the theoretical assumption (sitting during the day and supine at night).

In conclusion, we found that nocturnal elevation of IOP occurs in a large proportion of NTG patients when IOP is measured with patients in their habitual positions. Analysis of IOP patterns in individual patients indicated three distinct IOP patterns among our NTG subjects. VF indices were not correlated with nocturnal IOP elevation in the habitual position. Our study suggests that clinicians should consider the daytime peak IOP to estimate the 24-hour or the nighttime maximum habitual-position IOP.

References

1. Asrani S, Zeimer R, Wilensky J, Gieser D, Vitale S, Lindenmuth K. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. *J Glaucoma.* 2000;9:134–142.
2. David R, Zangwill L, Briscoe D, Dagan M, Yagev R, Yassur Y. Diurnal intraocular pressure variations: an analysis of 690 diurnal curves. *Br J Ophthalmol.* 1992;76:280–283.
3. Kitazawa Y, Horie T. Diurnal variation of intraocular pressure in primary open-angle glaucoma. *Am J Ophthalmol.* 1975;79:557–566.
4. Ido T, Tomita G, Kitazawa Y. Diurnal variation of intraocular pressure of normal-tension glaucoma: influence of sleep and arousal. *Ophthalmology.* 1991;98:296–300.
5. Sacca SC, Rolando M, Marletta A, Macri A, Cerqueti P, Ciurlo G. Fluctuations of intraocular pressure during the day in open-angle glaucoma, normal-tension glaucoma and normal subjects. *Ophthalmologica.* 1998;212:115–119.
6. Hara T, Tsuru T. Increase of peak intraocular pressure during sleep in reproduced diurnal changes by posture. *Arch Ophthalmol.* 2006;124:165–168.
7. Liu JH, Zhang X, Kripke DF, Weinreb RN. Twenty-four-hour intraocular pressure pattern associated with early glaucomatous changes. *Invest Ophthalmol Vis Sci.* 2003;44:1586–1590.
8. Yamagami J, Araie M, Aihara M, Yamamoto S. Diurnal variation in intraocular pressure of normal-tension glaucoma eyes. *Ophthalmology.* 1993;100:643–650.
9. Liu JH. Diurnal measurement of intraocular pressure. *J Glaucoma.* 2001;10:S39–S41.
10. Liu JH, Kripke DF, Hoffman RE, et al. Nocturnal elevation of intraocular pressure in young adults. *Invest Ophthalmol Vis Sci.* 1998;39:2707–2712.
11. Liu JH, 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.
12. Mosaed S, Liu JH, Weinreb RN. Correlation between office and peak nocturnal intraocular pressures in healthy subjects and glaucoma patients. *Am J Ophthalmol.* 2005;139:320–324.
13. Renard E, Palombi K, Gronfier C, et al. Twenty-four hour (nycthemeral) rhythm of intraocular pressure and ocular perfusion pressure in normal-tension glaucoma. *Invest Ophthalmol Vis Sci.* 2010;51:882–889.
14. Barkana Y, Anis S, Liebmann J, Tello C, Ritch R. Clinical utility of intraocular pressure monitoring outside of normal office hours in patients with glaucoma. *Arch Ophthalmol.* 2006;124:793–797.
15. Kiuchi T, Motoyama Y, Oshika T. Relationship of progression of visual field damage to postural changes in intraocular pressure in patients with normal-tension glaucoma. *Ophthalmology.* 2006;113:2150–2155.
16. Kiuchi T, Motoyama Y, Oshika T. Postural response of intraocular pressure and visual field damage in patients with untreated normal-tension glaucoma. *J Glaucoma.* 2010;19:191–193.
17. Greenfield DS, Liebmann JM, Ritch R, Krupin T. Visual field and intraocular pressure asymmetry in the low-pressure glaucoma treatment study. *Ophthalmology.* 2007;114:460–465.
18. Choi J, Kim KH, Jeong J, Cho HS, Lee CH, Kook MS. Circadian fluctuation of mean ocular perfusion pressure is a consistent risk factor for normal-tension glaucoma. *Invest Ophthalmol Vis Sci.* 2007;48:104–111.
19. Sung KR, Lee S, Park SB, et al. Twenty-four hour ocular perfusion pressure fluctuation and risk of normal-tension glaucoma progression. *Invest Ophthalmol Vis Sci.* 2009;50:5266–5274.
20. Magnaes B. Body position and cerebrospinal fluid pressure. Part 2: clinical studies on orthostatic pressure and the hydrostatic indifferent point. *J Neurosurg.* 1976;44:698–705.
21. Hughes E, Spry P, Diamond J. 24-hour monitoring of intraocular pressure in glaucoma management: a retrospective review. *J Glaucoma.* 2003;12:232–236.
22. Nakakura S, Nomura Y, Ataka S, Shiraki K. Relation between office intraocular pressure and 24-hour intraocular pressure in patients with primary open-angle glaucoma treated with a combination of topical antiglaucoma eye drops. *J Glaucoma.* 2007;16:201–204.
23. Tajunisah I, Reddy SC, Fathilah J. Diurnal variation of intraocular pressure in suspected glaucoma patients and their outcome. *Graefes Arch Clin Exp Ophthalmol.* 2007;245:1851–1857.
24. Abrams LS, Vitale S, Jampel HD. Comparison of three tonometers for measuring intraocular pressure in rabbits. *Invest Ophthalmol Vis Sci.* 1996;37:940–944.
25. Horowitz GS, Byles J, Lee J, D'Este C. Comparison of the Tono-Pen and Goldmann tonometer for measuring intraocular pressure in patients with glaucoma. *Clin Exp Ophthalmol.* 2004;32:584–589.
26. Lim KS, Wickremasinghe SS, Cordeiro MF, Bunce C, Khaw PT. Accuracy of intraocular pressure measurements in New Zealand White rabbits. *Invest Ophthalmol Vis Sci.* 2005;46:2419–2423.
27. Sudesh S, Moseley MJ, Thompson JR. Accuracy of Goldmann tonometry in clinical practice. *Acta Ophthalmol* (*Copenh*). 1993;71:185–188.