Intraocular Pressure Change Over a Habitual 24-Hour Period After Changing Posture or Drinking Water and Related Factors in Normal Tension Glaucoma

Rei Sakata,1,2 Makoto Aihara,1 Hiroshi Murata,1 Hitomi Saito,3 Aiko Iwase,4 Noriko Yasuda,5 and Makoto Araie3

1Department of Ophthalmology, University of Tokyo, Graduate School of Medicine, Tokyo, Japan
2Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan
3Kanto Central Hospital, Tokyo, Japan
4Tajimi Iwase Eye Clinic, Gifu, Japan
5Tokyo Metropolitan Police Hospital, Tokyo, Japan

Correspondence: Rei Sakata, Department of Ophthalmology, Tokyo Metropolitan Geriatric Hospital, 35-2 Sakaecho Iabashi, Tokyo, 173-0015, Japan; reisakata-tky@umin.ac.jp.
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Purpose. We investigated the correlation between 24-hour IOP in the habitual (sitting during day and supine during night) position (H24h-IOP) and IOP after a postural-change test (PCT-IOP) and a water-drinking test (WDT-IOP). We also investigated ocular and systemic factors related with them in patients with normal tension glaucoma (NTG).

Methods. Japanese NTG patients underwent H24h-IOP, PCT-IOP, and WDT-IOP measurements during a 24-hour period. Correlations among H24h-IOP, PCT-IOP, and WDT-IOP, and contributing ocular/systemic factors were investigated using regression analysis.

Results. There were 35 patients included. Peak H24h-IOP correlated positively with peak PCT-IOP and peak WDT-IOP (estimate = 0.422 and 0.419, P < 0.010), and peak PCT-IOP with WDT-IOP (0.44, P = 0.002). Peak H24h-IOP correlated with refraction (0.36, P = 0.048) and negatively with the mean deviation (MD, −0.066, P = 0.031). MD and baseline IOP (the mean of H24h-IOP) correlated negatively with the H24h-IOP fluctuation (−0.058 and −0.58, P ≤ 0.050). Refraction, baseline IOP, mean blood pressure (mBP), and body mass index (BMI) correlated with peak PCT-IOP (0.23, 0.52, 0.097, and 0.32, respectively, P ≤ 0.038). PCT-IOP difference correlated with refraction and mBP (0.31 and 0.093, P ≤ 0.016) and negatively with age (−0.069, P = 0.003). Central corneal thickness, baseline IOP, age, and BMI correlated with peak WDT-IOP (0.030, 0.40, 0.088, and 0.26, P ≤ 0.050). Age and BMI correlated with WDT-IOP difference (0.086 and 0.20, P < 0.032).

Conclusions. Positive correlation was found among the peaks of H24h-, PCT-, and WDT-IOP. A worse visual field was associated with higher peak and greater fluctuation of H24h-IOP in NTG. Several ocular/systemic factors were important in interpreting H24h-, PCT-, and WDT-IOP.

Keywords: habitual 24h-IOP, postural changing, water drinking, normal tension glaucoma, generalized estimating equation

Previous randomized clinical trials have established the efficacy of reducing IOP in glaucoma,1–5 confirming that the management of IOP has a central role in preventing further progression of glaucomatous optic neuropathy.6–8 even in glaucoma cases with statistically normal pressure.9,10

IOP does not remain constant, but varies during the day,11,12 with nocturnal IOP in the supine position consistently being higher than diurnal IOP in the sitting position.13–17 Thus, a single IOP recording during office hours is insufficient to determine IOP variations in glaucoma patients.18–21 It has also been suggested that a wider variation of IOP over a diurnal period in the sitting position is a significant risk factor for glaucoma progression.22–25 It would be ideal to measure 24-hour IOP in all patients with glaucoma. A contact lens censor for continuous 24-hour monitoring of IOP had shown fair to good reproducibility without severe side effects.24,25 However, this instrument is not always available commercially and does not provide absolute IOP value.

The postural-change test (PCT) and the water-drinking test (WDT) are two classic provocative tests used to change IOP.26–30 IOP increases by several millimeters of mercury after a postural change from a sitting to a supine position.28,30 Several investigators have reported that the IOP response to the PCT in patients with open angle glaucoma may be correlated with pre-PCT-IOP31,32 existing glaucomatous damage,33–35 or its rate of progression.36 Similarly, the IOP response to the WDT has been reported to correlate with the peak for 24-hour IOP measured in the sitting position (S24h-IOP),37–39 existing glaucomatous damage, or its rate of progression.40,41 Although the reproducibility of the WDT is unsatisfactory,42,43 it still is considered a useful clinical test because of its simplicity.44,45 Measurement of 24-hour IOP in the habitual body position (sitting during the day and spine during the night, H24h-IOP)
would be more useful in estimating the IOP variation during daily life of each patient. Despite the well-documented importance of 24-hour IOP measurements, and the clinical potential of the PCT and WDT, information is scarce regarding the relationship between H24h-IOP and the results of the PCT (PCT-IOP) and WDT (WDT-IOP) in the same patient, as well as the ocular and systemic factors that affect these parameters.

In our study, the correlations of the H24h-IOP with the PCT-IOP and WDT-IOP were determined in untreated normal tension glaucoma (NTG) patients, and the effects of ocular and systemic factors on the H24h-IOP, PCT-IOP, and WDT-IOP were analyzed.

**Methods**

**Patients**

Our study was performed prospectively as part of a hospital-based examination on 24-hour IOP variations in untreated NTG patients at clinics of the Department of Ophthalmology, University of Tokyo Graduate School of Medicine (Tokyo, Japan), Tajimi Municipal Hospital (Gifu, Japan), and Tokyo Metropolitan Police Hospital (Tokyo, Japan) in consecutive untreated NTG patients who agreed to participate in the study from January 2008 to December 2009. Current diagnosis of NTG was based on the following criteria according to many previous studies,9,10,34,36: glaucomatous optic nerve head or retinal nerve fiber layer defects with corresponding reproducible visual field damage, unoccludable normal open angle, IOP recordings of ≤21 mm Hg during follow-up, no other ocular abnormalities or history of other ocular diseases, no history of massive bleeding or hemodynamic crisis, and no rhinologic or neurosurgical disorders. Visual field was assessed using a Humphrey Field Analyzer with the central 24-2 program Swedish interactive threshold algorithm standard (HFA 24-2; Zeiss-Humphrey, San Leandro, CA), and reliable test results (<30% fixation loss, false-negative, and <15% false-positive rate) were adopted. The visual field was judged according to the Anderson-Patella criterion; that is, the visual field was judged to be abnormal when the pattern deviation probability plot showed a cluster of three or more contiguous points having sensitivity with a probability of less than 5%, with one of these with a probability of less than 1% in the upper or lower hemifield.46 Central corneal thickness (CCT) was measured optically with a specular microscope (SP-2000; Topcon, Tokyo, Japan), and refraction was measured with an autorefract-keratometer (ARK-900; Nidek, Tokyo, Japan) without using cycloplegics.

The exclusion criteria were eyes treated with any topical or systemic antiglaucoma drugs, eyes with excessive myopia (spherical equivalent less than −10 diopters), history of intraocular surgery including laser treatment, and other ocular diseases that may affect IOP. Patients with cardiovascular or renal diseases also were excluded. A full explanation of the study was given to eligible patients, and written informed consent was obtained. All protocols and methods adhered to the tenets of the Declaration of Helsinki and were approved by the institutional review board of each institution.

**Ocular and Systemic Measurements**

Systolic/diastolic blood pressure and pulse rate were recorded with an electronic manometer (H55 Terumo electronic sphygmomanometer; Terumo, Tokyo, Japan), and the patient’s height and weight were checked at 11 AM during hospitalization.

**Variation of H24h-IOP.** IOP was recorded every 3 hours (9 AM; 12; 3, 6, and 9 PM; and 12, 3, and 6 AM). IOP in the sitting position was measured using a calibrated Goldmann applanation tonometer (GAT; Haag Streit, Koeniz, Switzerland) from 9 AM to 9 PM, and IOP in the supine position was measured using a calibrated pneumatonometer (PTG; Reichert Model 50 Classic; Reichert Technologies, Depew, NY) from 12 to 6 AM, while patients were lying in bed.

IOP was measured at 5-minute intervals with both instruments at 9 AM and 3 PM with subjects in the sitting position. Patients were asked to get into bed at 10 PM and to get out of bed after measuring IOP at 6 AM. Patients were asked to sit on a chair calmly for 3 minutes before the IOP was measured in the sitting position. One drop of topical anesthesia (0.4% oxybuprocaine hydrochloride) was applied before each measurement. After measuring IOP by PTG, the record was inspected, and the measurement was accepted when the tonograph pattern was normal and the standard deviation for a 5-second recording was <1 mm Hg. The IOP measurement was repeated when these conditions were not met. The IOP peak (peak_H24h-IOP) was defined as the highest measured IOP in the sitting or supine position, and the IOP fluctuation (fluc_H24h-IOP) was the difference between the highest and lowest measured IOP values.

**Postural Change Test.** The PCT was performed between 3 and 3:30 PM during the H24h-IOP measurements. After the patient sat on a chair calmly for 3 minutes, IOP was measured by GAT in the sitting position and by PTG 5 minutes later. The subjects were asked to lie in the supine position for 30 minutes, and IOP was measured again by PTG.51 The peak_PCT-IOP was the IOP measured at 30 minutes in the supine position, and the diff_PCT-IOP was defined as the difference between the IOP measured in the sitting position before PCT (pre–PCT-IOP) using PTG and the peak_PCT-IOP. Systolic/diastolic blood pressure and pulse rate were recorded before the GAT measurement at 3 PM in the sitting position, as described above.

**Water Drinking Test.** WDT also was done during the H24h-IOP measurements. The patients were asked to get out of bed after measuring IOP in the supine position at 6 AM. After confirming fasting for at least 4 hours, IOP was measured with the GAT at 7 AM in the sitting position. The subjects were asked to drink bottled water at 14 mL/kg body weight within 5 minutes,59 and then the IOP was taken every 15 minutes for 1 hour using the GAT in the sitting position. The peak_WDT-IOP was the highest IOP during the test, and the diff_WDT-IOP was the difference between peak_WDT-IOP and pre_WDT-IOP was taken at 7 AM before drinking water. Systolic/diastolic blood pressure and pulse rate were recorded before starting the WDT.

**Analytical Method**

The correlations between peak_H24h-IOP or fluc_H24h-IOP and peak_WDT-IOP or diff_WDT-IOP, diff_PCT-IOP, and diff_PCT-IOP, and that of peak_WDT-IOP or diff_WDT-IOP to peak_PCT-IOP and diff_PCT-IOP were assessed. Next, peak_H24h-IOP, fluc_H24h-IOP, peak_WDT-IOP, diff_WDT-IOP, diff_PCT-IOP, and diff_PCT-IOP were correlated with systemic and ocular factors. The systemic factors considered were the mean of mean blood pressures (mBPs), where mBP = diastolic blood pressure + (systolic blood pressure − diastolic blood pressure)/3, measured at 11 AM, 3 PM, and 7 AM in the sitting position during hospitalization; age; and body mass index (BMI). Ocular factors were refraction, CCT, mean deviation (MD) of the HFA 24-2 values, and the mean of the H24h-IOP measurement results (defined as baseline IOP).
Ocular data obtained at the outpatient clinic within 3 months of hospitalization were used.

Data obtained from both eyes were analyzed using the generalized estimating equation (GEE) model and univariate and multivariate regression models from the GEE model were used. Intercorrelation among the explanatory variables was assessed using the variance inflation factor.

All data analyses were performed with a personal computer using the R2.13.2 statistical software package (R Foundation for Statistical Computing, Vienna, Austria) with GEE solver version 4.13-17. Two-sided P values < 0.05 were considered to indicate significance.

**RESULTS**

We included 66 eyes of 33 patients with NTG. The patients' characteristics are shown in Table 1. All patients underwent the scheduled examinations, and none had other health problems.

### H24h-IOP Analysis

The mean H24h-IOP was 15.6 ± 2.6 mm Hg, peak_H24h-IOP was 19.6 ± 4.3 mm Hg, and fluc_H24h-IOP was 6.8 ± 3.9 mm Hg (see Fig.). The time distributions of the peak_H24h-IOP in both eyes were 6/33 patients at 6 AM, 5/33 at 3 AM, 5/33 at 12 AM, 1/33 at 6 PM, 1/33 at 12 PM, and 3/33 at 9 AM. Bilateral differences in the time of peak_H24h-IOP occurred in 10 cases (20 eyes), with a 3-hour difference (12 AM or later in all cases) in 5/33 patients, a 6-hour difference (12 and 6 AM) in 4/33, and a 12-hour difference (left eye at 6 PM, right eye at 6 AM) in 1/33. The comparison between these 10 cases and the other 23 cases revealed that there was no intergroup difference in BMI, mBP, MD of the worse eye, and mean refraction of both eyes. Association was higher and the ratio of male was higher in the former than the latter (56.1 ± 9.5 and 47.8 ± 11.2, respectively, P = 0.005, Fisher's exact test). Regarding intereye difference, refraction, CCT, MD, or baseline IOP showed no significant difference in these 10 cases (P = 0.12, 0.25, 0.59, and 0.26, respectively, paired t-test between the two groups). Peak_H24h-IOP was measured in the supine position in 55 of 66 eyes. There were 13 patients (21 eyes) who showed IOPs > 21 mm Hg during H24h.

The average GaT and PtG values for a total of 132 measurements (at 9 AM and 3 PM) were 14.5 ± 2.6 and 14.7 ± 2.6 mm Hg, respectively (P = 0.53, paired t-test), with a Pearson’s correlation coefficient of 0.95.

Peak_H24h-IOP was correlated positively with peak_WDT-IOP and peak_PCT-IOP in the univariate analysis (estimate = 0.422, P = 0.007 and estimate = 0.419, P = 0.010, respectively). Peak_PCT-IOP was correlated positively with peak_WDT-IOP (estimate = 0.44, P = 0.002). PCT-IOP or WDT-IOP showed no correlation with fluc_H24h-IOP. Peak_H24h-IOP was correlated positively with peak_WDT-IOP (estimate = 0.48, P = 0.004) and tended to be correlated positively with peak_PCT-IOP (estimate = 0.42, P = 0.062) in the multivariate analysis (Table 2).

Peak_H24h-IOP was correlated positively with refraction (P = 0.048) and negatively with MD (P = 0.031). MD and baseline IOP were correlated negatively with fluc_H24h-IOP (P = 0.050 and 0.008, Table 3).

### PCT-IOP Assessment

The mean IOP before and 30 minutes after the PCT was 14.1 ± 2.4 mm Hg and 18.7 ± 3.4 mm Hg (peak_PCT-IOP, respectively, and diff_PCT-IOP was 4.6 ± 2.6 mm Hg. Refraction, mBP, BMI, and baseline IOP were correlated positively with peak_PCT-IOP (P = 0.034, 0.038, 0.026, 0.007, respectively). Refraction and the mean of mBP were correlated positively with diff_PCT-IOP (P = 0.002, 0.016), whereas age was correlated negatively (P = 0.005).

### WDT-IOP Assessment

The mean IOP before the WDT was 14.1 ± 2.6 mm Hg, peak_WDT-IOP was 18.8 ± 3.5 mm Hg, and diff_WDT-IOP was 5.0 ± 2.1 mm Hg. IOP peaked at 15 minutes in 23 cases (70%) and at 30 minutes in five cases (15%). Bilateral differences (15 minutes) in the time of peak_WDT-IOP occurred in 5 cases, with peak values at 15 and 30 minutes, respectively, in 4/33 cases and at 30 and 45 minutes, respectively, in 1/33 cases. IOP decreased gradually with time, but remained higher than pre-WDT-IOP (starting point) at 60 minutes (15.2 ± 2.9 mm Hg; P < 0.001). Age, CCT, BMI, and baseline IOP were correlated positively with peak_WDT-IOP (P = 0.015, 0.005, 0.050, 0.005, respectively). Age and BMI were correlated positively with diff_WDT-IOP (P < 0.001 and P = 0.032, respectively).

### DISCUSSION

In previous reports, IOP was lower during the nocturnal period than during the diurnal period of 24-hour IOP cycles in patients with glaucoma when all IOP measurements were performed in the sitting31-35 or supine position.54 However, habitual IOP measurements would be more useful in estimating IOP variations during the daily life of each patient. In the habitual body position, nocturnal IOP was higher than diurnal IOP13-17,55,56 and the IOP variation (i.e., the difference between the diurnal and nocturnal IOPs) was less in eyes with glaucoma and those with greater axial length.15,16 Furthermore, IOP rhythms are reported to be influenced by age; peak_H24h-IOP tends to be delayed toward daylight in older subjects compared to younger subjects.15

The 24-hour IOP variations are thought to be influenced not only by circadian cycles, but also by other systemic or ocular factors. The change in IOP upon changing body position or drinking water also may provide information regarding the way in which IOP fluctuations. The correlation between 24-hour IOP and WDT-IOP in the sitting position, or PCT-IOP in the sitting and spine positions has been analyzed previously.37-39 Particularly, Fogagnolo et al. emphasized the importance of sitting and spine office-hour IOP measurements in estimating H24h-IOP characteristics (peak, mean, and fluctuation).37 To our knowledge, our study is the first to report the relationship between 24-hour IOP in the habitual position (H24h-IOP), and
Although the mean age of the patients shows IOP. Data are value).

This suggests Liu et al. measured H24h-IOP in young recent studies showed a correlation factors were reported to be correlated with IOP in population-based studies in Japan.

We also examined the ocular and systemic factors correlated with H24h-IOP, PCT-IOP, and WDT-IOP. The explanatory ocular factors were refraction, CCT, MD, and baseline IOP, and the systemic factors were mBP, age, and BMI. These factors were reported to be correlated with IOP in population-based studies in Japan.

Table 2. Multivariate GEE Analysis of Factors Associated With peak_H24h-IOP and fluc_H24h-IOP

<table>
<thead>
<tr>
<th></th>
<th>Peak_H24h-IOP</th>
<th>Fluc_H24h-IOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak_PCT-IOP*</td>
<td>0.42 (0.062)</td>
<td>0.025 (0.93)</td>
</tr>
<tr>
<td>Diff_PCT-IOP†</td>
<td>−0.15 (0.54)</td>
<td>0.18 (0.55)</td>
</tr>
<tr>
<td>Peak_WDT-IOP‡</td>
<td>0.48 (0.040)</td>
<td>0.0046 (0.99)</td>
</tr>
<tr>
<td>Diff_WDT-IOP§</td>
<td>−0.34 (0.14)</td>
<td>0.085 (0.73)</td>
</tr>
</tbody>
</table>

Data are presented as estimate (P value).

Notably, in our study, a worse MD was associated significantly with higher peak_H24h-IOP and fluctuation_H24h-IOP, although another recent study showed no relationship between MD and peak_H24h-IOP or fluc_H24h-IOP. Our results, showing a significant and stronger correlation of the visual field status with H24h-IOP than with PCT-IOP or WDT-IOP in NTG eyes, may emphasize the clinical importance and usefulness of H24h-IOP measurements, especially measurements taken during the night in the supine position, as most of the peak_H24h-IOP values occurred between 12 and 6 AM in the supine position.

In previous studies, the visual field damage or progression of visual field were correlated with the peak or fluctuation of IOP measured during the day in the sitting position in primary open angle glaucoma (POAG) patients or NTG patients, including those who were treated medically. This suggests the importance of IOP during the diurnal period. Higher IOP in the habitual supine position during the night results in lower ocular perfusion pressure because blood pressure generally is low during the night. Recent studies showed a correlation between the fluctuation of ocular perfusion pressure and the progression of NTG with medical treatment. The current finding, a significant correlation between peak_H24h-IOP, which was observed mostly in the supine position during the night, and the overall extent of visual field damage, would suggest the importance of IOP control during the night for managing NTG.

The correlation between the refractive error and IOP is well known. Liu et al. measured H24h-IOP in young subjects and showed that subjects with high myopia demonstrated smaller night-time IOP fluctuations in the supine position, compared to subjects with low myopia. They also reported that shorter axial length was related to a larger IOP fluctuation. This relationship may be explained by a difference in ocular volume as a smaller ocular volume may be influenced more easily by choroidal congestion after postural change. Although the mean age of the patients in our study was higher than that in previous reports, the positive correlation between refractive power and peak_H24h-IOP is in agreement with previous results, and the positive correlation between refractive power and peak_PCT-IOP in our study may be explained by the same mechanism.

CCT influences IOP measurements on contact applanation tonometry. GAT and PTG overestimate IOP in eyes with a thicker cornea and vice versa. Thus, the IOP change could be somewhat overestimated in eyes with a thicker cornea. The positive correlation of CCT with peak_WDT-IOP, and the
positive, but insignificant, correlation with peak_H24h-IOP and peak_PCT-IOP may be explained at least in part by this mechanism.

Baseline IOP was correlated negatively with fluc_H24h-IOP. Most of the current subjects’ eyes (55/66) showed peak IOP at night (12 AM or later) in the supine position. The magnitude of the difference in IOP between the diurnal (sitting position) and nocturnal (supine position) periods is smaller in glaucoma eyes than in normal eyes, which may at least partly explain the current findings. The fluctuation and average IOP were correlated positively (r = 0.61, p = 0.026) when only IOPs measured in the sitting position between 9 AM and 9 PM were considered. This result agrees with previous reports showing that higher baseline IOP was associated with greater 24-hour IOP fluctuation measured in the sitting position.

The mBP in our study was correlated positively with peak_PCT-IOP and diff_PCT-IOP, which is compatible with the findings of Williams et al., who demonstrated that patients with systemic vascular diseases, such as hypertension or diabetes, show greater IOP changes compared to normal subjects after changing body position. Age was correlated positively with peak_WDT-IOP and diff_WDT-IOP but correlated negatively with diff_PCT-IOP. Older subjects tended to have lower outflow capability, resulting in higher IOP after the WDT. Additionally, the WDT results might have been affected by the systemic capacity to stabilize water-loading. The IOP increase after the WDT has been attributed to changes in blood osmolarity and alterations in episcleral venous pressure (EVP), whereas the IOP increase after the PCT is due to an elevation in EVP and choroidal vascular congestion with the change in blood pressure caused by circulatory or neural system responses to a change from a sitting to a supine position. Although both provocative tests invoke a rise in IOP, the main mechanism of IOP elevation is thought to be different. The transient decrease in blood osmolarity in the WDT would cause fluid to shift from the systemic circulation to the extracellular space, after which EVP would increase. In contrast, EVP is thought to increase rapidly after changing from the sitting to the supine position, followed by choroidal congestion. Although the exact mechanisms of IOP elevation in both tests have not been elucidated completely, the difference in the age effect on PCT-IOP and WDT-IOP may be related to a difference between the underlying mechanisms described above.

BMI is correlated positively with IOP. Our result that peak_PCT-IOP, peak_WDT-IOP, and diff_WDT-IOP were correlated positively with BMI does not conflict with the finding that higher BMI was associated with elevated EVP which is a common contributing factor to an elevation of IOP on the PCT and WDT. However, Lima et al. investigated patients with POAG under treatment and reported the association of a higher BMI, and a lower IOP peak and difference after the WDT. Nevertheless, the effects of glaucoma medications would be difficult to exclude in their study.

The current study had several limitations. First, the relatively small sample size might have limited the sensitivity in identifying significant correlations between variables, particularly the correlation between MD (overall visual field damage), and PCT-IOP and WDT-IOP. Second, our results may not be applicable to patients with open-angle glaucoma (OAG) with elevated IOP (HTG) because we limited our study to patients with normal IOP (<21 mm Hg), because of difficulty in recruiting typical HTG patients for clinical studies where a provocative test to increase the IOP further is included. Since clinical applicability of H24h-, PCT-, and WDT-IOP measurement results excluding HTG patients is limited, additional studies were needed to determine whether these results can be reproduced in patients with HTG. Comparison of the results between NTG and HTG patients should yield useful and clinically significant information on the IOP variation as one of the causative factors of glaucoma. Third, the H24h-IOP measurements were thought to be affected by many factors, such as hospitalization and disturbed sleep during IOP measurement. These factors might have confounded our attempt to reproduce the physiologic IOP fluctuation by measuring the IOP during the night in the supine position. Finally, almost one-third of the subjects showed peak_H24h-IOP higher than 21 mm Hg. This may contradict the current diagnosis of NTG for these subjects. In the current study, NTG and POAG were diagnosed based on the highest IOP of 21 mm Hg recorded during the follow-up. Since NTG and POAG are now considered to be subtypes of the same disease entity, we think it is not necessary to exclude these patients as POAG from NTG.

In conclusion, we measured H24h-IOP, PCT- and WDT-induced IOP changes in Japanese patients with NTG. The peak_H24h-IOP was significantly and positively correlated with peak_WDT-IOP and peak_PCT-IOP, and a worse visual field was associated significantly with a higher peak_H24h-IOP and a greater fluc_H24h-IOP. These results may emphasize the clinical importance and usefulness of measuring 24-hour IOP in the habitual position in patients with NTG. Additionally, several ocular/systemic factors, including refraction, CCT, baseline IOP, mBP, age, and BMI, were positively or negatively associated with H24h-IOP, PCT-IOP, and WDT-IOP. These ocular/systemic factors are thought to be important when interpreting the results of H24h-IOP, PCT-IOP, and WDT-IOP measurements in future studies.

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