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Association of 24-Hour Intraocular Pressure Fluctuation With Corneal Hysteresis and Axial Length in Untreated Chinese Primary Open-Angle Glaucoma Patients

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Purpose: The purpose of this study was to evaluate the association of 24-hour intraocular pressure (IOP) fluctuation with corneal biomechanics and ocular biometric parameters in Chinese patients with primary open angle glaucoma (POAG) before initial treatment.

Methods: Forty-nine Chinese patients with POAG (98 eyes) were recruited in this study before start of any POAG treatment. The 24-hour IOP was measured with a 2-hour interval by a noncontact tonometer. Corneal biomechanical properties and biometric parameters were measured once during 8 AM to 6 PM before 24-hour IOP measurement.

Results: The 24-hour IOP fluctuation was defined as the differences between the peak and trough IOP measurement and was significantly associated with axial length (AL) in the multivariate analysis. The POAG subjects with AL $\leq$ 26 mm had significantly larger 24-hour IOP fluctuation but lower corneal hysteresis, compared to those with AL $>$ 26 mm. In addition, subgroup analysis showed that high tension glaucoma subjects had larger 24-hour IOP fluctuation and higher corneal resistance factor than patients with normal tension glaucoma.

Conclusions: This study revealed the association of 24-hour IOP fluctuation with office hour corneal biomechanical properties and AL in patients with POAG. Their contributions to IOP fluctuation should be considered in the risk analysis of glaucoma development and progression.

Translational Relevance: Ocular biometric parameters are related with 24-hour IOP fluctuation in patients with POAG, which is potentially helpful in explaining different progression patterns in different types of patients.

Introduction

Glaucoma is a leading cause of irreversible blindness and visual impairment, affecting 80 million people worldwide.[1] Primary open angle glaucoma (POAG) is a major subtype of primary glaucoma with elevated intraocular pressure (IOP $>$ 21 mm Hg) as a treatable risk factor,[2] especially for the patients with high tension glaucoma (HTG). Yet, there is a substantial proportion of patients with POAG showing normal IOP levels ($\leq$ 21 mm Hg), who are regarded as normal

Table 1. Demographic Data, Corneal Biomechanical, and Ocular Biometric Parameters

Parameters	Mean ± SD	Range
Subjects (eyes)	49 (98)	/
OD: OS	49: 49	/
NTG: HTG subjects (eyes)	27 (54): 22 (44)	/
Sex (female : male)	20 (40): 29 (58)	/
Age	54.26 ± 14.54	26–82
Initial IOP, mm Hg	17.73 ± 2.97	13–26
IOP fluctuation, mm Hg	7.32 ± 2.64	2.1–14.4
Relative fluctuation %	44.54 ± 14.83	12.62–99.42
Mean circadian IOP, mm Hg	16.55 ± 3.31	10.87–24.13
IOPcc, mm Hg	18.42 ± 3.58	11.45–27.5
IOPg, mm Hg	18.01 ± 3.79	10.53–28
CH, mm Hg	10.14 ± 1.11	7.96–13.8
CRF, mm Hg	10.94 ± 1.41	8.23–14.51
CCT, µm	539.38 ± 34.25	476–616
Axial length, mm	25.61 ± 2.15	22.21–31.02
Mean Deviation, dB	8.07 ± 5.38	2.2–22.6
RNFL thickness, µm	81.42 ± 11.83	57.67–108.99

IOP, intraocular pressure; IOP fluctuation, Diurnal IOP maximum to IOP minimum; the relative fluctuation %, IOP fluctuation/mean IOP; IOPcc, corneal-compensated intraocular pressure; IOPg, Goldmann-correlated intraocular pressure; CH, corneal hysteresis; CRF, corneal resistance factor; CCT, central corneal thickness.

Data are shown as mean ± SD.

tension glaucoma (NTG). However, IOP is not static, but varies during the day.[3] Diurnal IOP fluctuations have been suggested to be associated with POAG, and large IOP fluctuation is a significant risk factor for glaucoma progression.[4] We previously also reported that the 24-hour IOP pattern in untreated patients with POAG were associated with different glaucoma severity stages.[3] Understanding the diurnal and nocturnal IOP fluctuations in patients with POAG could facilitate better interpretation of the progression of POAG and better treatment regimes.

IOP is associated with not only central corneal thickness (CCT) but also corneal biomechanics.[5,6] Corneal biomechanics reflects the viscoelasticity of the cornea, which contributes to the corneal shape and the stromal stiffness.[7] Corneal biomechanics can be changed with age,[8] smoking status,[9] refractive surgery,[10] and influenced by systematic and ocular diseases, such as diabetes mellitus,[11] keratoconus,[12] and Fuchs dystrophy.[13] Ex vivo experiments showed that an increase in corneoscleral stiffness can result in higher IOP spike magnitudes in porcine eyes at the same volumetric change.[14]

Although the 24-hour IOP pattern has been reported not to be associated with the changes in corneal biomechanical properties, including corneal hysteresis or corneal resistance factor, in healthy volunteers without ocular diseases,[15] the association of 24-hour IOP fluctuation with corneal biomechanics in patients with POAG remains unknown. Moreover, previous studies showed that the shorter axial length (AL) eyes had larger 24-hour IOP fluctuation than longer eyes in healthy young adults[16] and the nocturnal habitual IOP fluctuation was negatively correlated with AL in young patients with POAG.[17] Herein, in this study, we aimed to determine the 24-hour IOP pattern in Chinese patients with POAG before initial treatment, and to evaluate its association with corneal biomechanical properties and ocular biometric parameters.

Subjects and Methods

Study Subjects

Forty-nine newly diagnosed patients with POAG (98 eyes) were recruited at the Eye and Ear Nose Throat Hospital, Shanghai Medical College, Fudan University, Shanghai, China (Table 1). The inclusion criteria for the patients with POAG were as follows: (1) subjects with open angles on gonioscopy; (2) signs of glaucomatous damage defined as presence of at least

two of the following characteristics: cup/disc ratio $\geq$ 0.6, asymmetry of cup/disc $>$ 0.2 between eyes, diffuse or localized neuroretinal rim thinning, disc hemorrhage, and nerve fiber layer defects; (3) OCTOPUS 101 automated perimetry visual field abnormality defined as 1 spot depressed by 10 dB, or 2 contiguous spots depressed by 5 dB, or 3 contiguous spots depressed by 2 dB, presented reliable and reproducible visual field examinations (reliability factor $\leq$ 15%).[3] The exclusion criteria include: (1) previous or current treated with antiglaucoma medications, topical or systemic steroids; (2) histories of antiglaucoma surgery or laser treatment; (3) histories of refractive surgery or corneal abnormalities influencing reliable IOP measurement, and (4) presence of any other ocular diseases, which could result in optic nerve and visual field defects.

Comprehensive ophthalmic examinations, including best corrected visual acuity (BCVA; E-chart at a distance of 5 m), slit-lamp biomicroscopy (Type YZ5E, China), gonioscopy (Goldmann one-mirror lens, Switzerland), Goldmann applanation tonometry (GAT; Switzerland), funduscopy (Canon, Japan), and CCT and AL were measured with Lenstar (LS900). The ORA G3 (Reichert Ophthalmic Instruments, New York, NY) was used to measure the corneal biomechanical parameters and IOPs based on a dynamic bidirectional applanation process. RTVue-OCT (Optovue, Inc., Fremont, CA) was performed to measure the thickness of retinal nerve fiber layer (RNFL). Visual field was tested by OCTOPUS 101 automated perimetry. This study was approved by the medical ethics committee of the Eye and Ear Nose Throat Hospital, Fudan University, Shanghai, China and is in accordance with the tenets of the Declaration of Helsinki. Written informed consents were obtained from all study subjects after explanation of the nature and possible consequences of the study.

Twenty Four-Hour Intraocular Pressure Measurement

All patients with POAG were admitted to the hospital for 24-hour IOP measurement by a noncontact tonometer (NIDEK, Japan). All IOP measurements were taken by the same well-trained operator. The IOPs of both eyes were measured every 2 hours from 8:00 AM to 6:00 AM the next day, specifically at 8:00 AM, 10:00 AM, 12:00 PM, 2:00 PM, 4:00 PM, 6:00 PM, 8:00 PM, and 10:00 PM as the diurnal period, at 12:00 AM, 2:00 AM, 4:00 AM, and 6:00 AM as the nocturnal period. The subjects had normal indoor activities during the diurnal period and went to bed at 10:00 PM. They would be woken up every 2 hours and measured IOPs instantly in the sitting position during 12:00 AM to 6:00 AM. Each eye at each time point was measured three times. The average value was used for analysis without correction for CCT. A 24-hour IOP curve was generated from the average IOP values at each time point. The peak and trough IOPs were defined as the highest and lowest values among the 12 recorded IOPs measurements during 24 hours. The mean circadian IOP of the day was calculated from IOPs at all time points during 24 hours. IOP fluctuation was defined as the peak IOP subtracting the trough IOP.[3,18] The relative IOP fluctuation was calculated as the percentage of IOP fluctuation normalized to the mean IOP.

Measurement of Corneal Biomechanical Properties

The Ocular Response Analyzer (ORA G3; Reichert Ophthalmic Instruments, New York, NY) was used to measure the corneal biomechanical properties and IOPs based on a dynamic bidirectional applanation process.[19] The ORA measures the force-in applanation and the force-out applanation, and then the parameters of corneal biomechanics, including the corneal-compensated IOP (IOPcc), Goldmann-correlated IOP (IOPg), corneal hysteresis (CH), and corneal resistance factor (CRF). Both eyes of all study subjects were measured once at the office hour before 24-hour IOP measurement and any treatment was given by the same experienced physician according to regular clinical practice and the manufacturer's guidelines. Good quality was defined as the readings with a waveform of two distinct peaks, and the wave score was more than five. The mean value of four measurements recorded for each eye was used for analysis.

Statistical Analysis

Data of each parameter was presented as mean $\pm$ standard deviation (SD). Mixed effect linear models were used for repeated measurements of two-eye analyses to compare the means among different groups. The associations among the IOP fluctuation and AL, CCT, CH, CRF, and IOPg were analyzed by the generalized estimating equation (GEE) method for repeated measurements of the two eyes. Statistically significant level was defined as $P < 0.05$. All statistical analyses with adjustment for age and gender and were performed with SAS version 9.4.

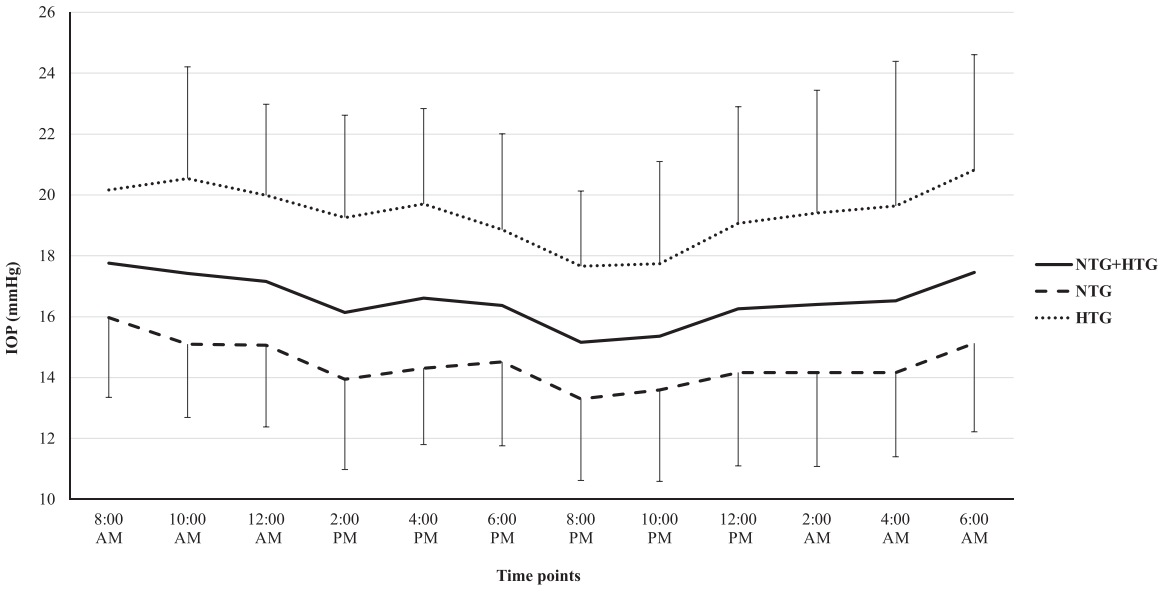

Figure. The 24-hour intraocular pressure patterns of the patients with POAG, HTG, and NTG before initial treatment. The 24-hour IOP was measured by a noncontact tonometer. The IOP of both eyes was measured every 2 hours from 8:00 AM to 6:00 AM the next day, specifically at 8:00 AM, 10:00 AM, 12:00 PM, 2:00 PM, 4:00 PM, 6:00 PM, 8:00 PM, and 10:00 PM (diurnal period IOP) and at 12:00 AM, 2:00 AM, 4:00 AM, and 6:00 AM (nocturnal period IOP). The IOP was highest at 6:00 to 8:00 AM, and gradually decreased along the diurnal period, then reached the lowest at 8:00 PM. The IOP progressively increased again along the nocturnal period. HTG, subjects with high tension glaucoma; NTG, subjects with normal tension glaucoma; NTG + HTG: subjects with normal tension glaucoma or high-tension glaucoma.

Results

In total, 49 newly diagnosed patients with POAG (98 eyes) were included in this study (Table 1). Twenty subjects (40.8%) were women and 29 (59.2%) were men. The mean age of patients with POAG was 54.26 ± 14.54 (approximately 26 to 82) years old. The initial IOP of patients with POAG was 17.73 ± 2.97 mm Hg (approximately 13 to 26 mm Hg). The highest IOP of patients with POAG (NTG + HTG) was at 8:00 AM (17.76 ± 3.55 mm Hg), and gradually decreased along the diurnal period, reaching the lowest at 8:00 PM (15.16 ± 3.37) mm Hg (Fig.). The IOP progressively increased again along the nocturnal period. The IOP fluctuation was 7.32 ± 2.64 mm Hg (approximately 2.1 to 14.4 mm Hg), and the relative fluctuation was 44.54 ± 14.83% (approximately 12.62 to 99.42%). The mean circadian IOP was 16.55 ± 3.31 mm Hg (approximately 10.87 to 24.13 mm Hg).

The corneal biomechanical properties were measured by the ORA (Table 1). The corneal-compensated IOP of the patients with POAG was 18.42 ± 3.58 mm Hg (approximately 11.45 to 27.50 mm Hg), and the IOPg was 18.01 ± 3.79 mm Hg (approximately 10.53 to 28.00 mm Hg). The CH of the patients with POAG was 10.14 ± 1.11 mm Hg (approximately 7.96 to 13.80 mm Hg), and the CRF was 10.94 ± 1.41 mm Hg (approximately 8.23 to 14.51 mm Hg). Moreover, the CCT of the patients with POAG subjects was 539.38 ± 34.25 μm (approximately 476 to 616 μm), and the AL was 25.61 ± 2.15 mm (approximately 22.21 to 31.02 mm). Both AL ($P = 0.001$) and the IOPg ($P = 0.017$) were significantly associated with IOP fluctuation in the multivariate analysis only, adjusting for age and gender (Table 4, Supplementary Figure S1). However, in the multivariate analysis adjusting for other ocular parameters, IOP fluctuation was only significantly associated with AL ($P = 0.011$; Table 4). Indicating that AL has strong impact on IOP fluctuation in patients with POAG.

In order to further delineate the association of the IOP fluctuation and corneal biomechanical properties, the patients with POAG were divided into two subgroups by AL > 26 mm and ≤ 26 mm. There were no statistically significant differences between the two groups of patients with POAG in age, gender, the relative IOP fluctuation, the mean circadian IOP, CRF, and CCT (Table 2). Instead, the patients with POAG with AL ≤ 26 mm had significantly higher initial IOP (18.44 ± 3.21 mm Hg, $P = 0.001$), IOP fluctuation (7.73 ± 2.51 mm Hg, $P = 0.017$), corneal-compensated IOP (19.32 ± 3.69 mm Hg, $P = 0.002$), and IOPg (18.82 ± 3.95 mm Hg, $P = 0.006$), but lower CH (9.96 ± 1.05 mm Hg, $P = 0.035$) than those with AL > 26 mm (initial IOP: 16.71 ± 2.33 mm Hg; IOP

Table 2. Comparison of the Intraocular Pressure and Ocular Structure Parameters Between the Shorter and Longer Axial Length Group

Parameters	Axial Length $<=$ 26 mm ($n = 56$) Mean $\pm$ SD (Range)	Axial Length $>$ 26 mm ($n = 42$) Mean $\pm$ SD (Range)	*P* Value
Initial IOP, mm Hg	18.44 $\pm$ 3.21 (13–26)	16.71 $\pm$ 2.33 (13–22)	**0.001**
IOP fluctuation, mm Hg	7.73 $\pm$ 2.51 (2.5–14.4)	6.56 $\pm$ 2.30 (2.1–14.8)	**0.017**
Relative fluctuation %	46.28 $\pm$ 14.21 (21.71–99.42)	42.19 $\pm$ 15.49 (12.62–77.12)	0.196
Mean circadian IOP, mm Hg	16.97 $\pm$ 3.45 (10.87–24.13)	15.99 $\pm$ 3.06 (11.73–23.05)	0.16
IOPcc, mm Hg	19.32 $\pm$ 3.69 (11.86–27.5)	17.04 $\pm$ 2.92 (11.45–25.48)	**0.002**
IOPg, mm Hg	18.82 $\pm$ 3.95 (11.5–28)	16.81 $\pm$ 3.28 (10.53–25.18)	**0.006**
CH, mm Hg	9.96 $\pm$ 1.05 (8.29–13.49)	10.46 $\pm$ 1.10 (8.59–13.8)	**0.035**
CRF, mm Hg	11.03 $\pm$ 1.41 (8.23–14)	10.86 $\pm$ 1.44 (8.91–14.51)	0.27
CCT, µm	533.68 $\pm$ 35.03 (482–614)	549.98 $\pm$ 28.88 (496–616)	0.054

IOP, intraocular pressure; IOP fluctuation, diurnal IOP maximum to IOP minimum; the relative fluctuation %, IOP fluctuation/mean IOP; CCT, central corneal thickness; IOPcc, corneal-compensated intraocular pressure; IOPg, Goldmann-correlated intraocular pressure; CH, corneal hysteresis; CRF, corneal resistance factor.

P values were adjusted for age and gender. Data are shown as mean $\pm$ SD. *P* values were in bold face if < 0.05.

Table 3. Comparison of the Intraocular Pressure and Ocular Structure Parameters Between Patients with NTG and HTG

Parameters	NTG ($n = 54$) Mean $\pm$ SD (Range)	HTG ($n = 44$) Mean $\pm$ SD (Range)	*P* Value
Initial IOP, mm Hg	16.39 $\pm$ 2.18 (13–21)	19.30 $\pm$ 3.02 (13–26)	**<0.0001**
IOP fluctuation, mm Hg	6.12 $\pm$ 2.35 (2.1–14.4)	8.93 $\pm$ 2.12 (5–14.8)	**<0.0001**
Relative fluctuation %	43.1 $\pm$ 16.73 (12.62–99.42)	46.49 $\pm$ 11.72 (26.2–77.12)	0.281
Mean circadian IOP, mm Hg	14.44 $\pm$ 2.14 (10.87–20.65)	19.41 $\pm$ 2.32 (14.93–24.13)	**<0.0001**
Axial length	26.01 $\pm$ 2.37 (22.69–31.02)	24.97 $\pm$ 1.72 (22.21–28.91)	**0.024**
IOPcc, mm Hg	16.78 $\pm$ 2.26 (11.45–20.44)	20.35 $\pm$ 3.89 (11.86–27.5)	**<0.0001**
IOPg, mm Hg	16.13 $\pm$ 2.33 (10.53–19.52)	20.21 $\pm$ 4 (11.66–28)	**<0.0001**
CH, mm Hg	10.17 $\pm$ 1.02 (8.59–13.8)	10.11 $\pm$ 1.23 (7.96–13.49)	0.819
CRF, mm Hg	10.40 $\pm$ 1.13 (8.23–14.51)	11.58 $\pm$ 1.45 (9.48–14.36)	**<0.0001**
CCT, µm	535.28 $\pm$ 33.34 (482–616)	544.20 $\pm$ 35.04 (476–614)	0.201

IOP, intraocular pressure; IOP fluctuation, diurnal IOP maximum to IOP minimum; the relative fluctuation %, IOP fluctuation/mean IOP; CCT, central corneal thickness; IOPcc, corneal-compensated intraocular pressure; IOPg, Goldmann-correlated intraocular pressure; CH, corneal hysteresis; CRF, corneal resistance factor; HTG, high tension glaucoma; NTG, normal tension glaucoma.

P values were adjusted for age and gender. Data are shown as mean $\pm$ SD. *P* values were bold face if < 0.05.

fluctuation: 6.56 $\pm$ 2.30 mm Hg; corneal-compensated IOP: 17.04 $\pm$ 2.92 mm Hg; IOPg: 16.81 $\pm$ 3.28 mm Hg; and CH: 10.46 $\pm$ 1.10 mm Hg; Table 2). Collectively, our findings indicated that the 24-hour IOP fluctuation was associated with AL.

Among the 98 studied eyes, 44 eyes were classified as HTG and 54 were classified as NTG according to the peak IOP recorded in the 24-hour IOP test (Table 3). The initial IOP of the patients with HTG was 19.30 $\pm$ 3.02 mm Hg (approximately 13 to 26 mm Hg), and that of the patients with NTG was 16.39 $\pm$ 2.18 mm Hg (approximately 13 to 21 mm Hg; $P <$ 0.0001). The mean highest IOP of the patients with HTG was at 6:00 AM (20.82 $\pm$ 3.79 mm Hg; Fig.), whereas that of the patients with NTG was at 8:00 AM (15.97 $\pm$ 2.62 mm Hg). The mean lowest IOPs of both patients with HTG (17.66 $\pm$ 2.47 mm Hg) and patients with NTG (13.30 $\pm$ 2.68 mm Hg) were at 8:00 PM. The 24-hour IOP fluctuation of the patients with HTG (8.93 $\pm$ 2.12 mm Hg; approximately 5.0 to 14.8 mm Hg) was significantly higher than that of the patients with NTG (6.12 $\pm$ 2.35 mm Hg; approximately 2.1 to 14.4 mm Hg; $P <$ 0.0001). Moreover, the mean circadian IOP of the patients with HTG (19.41 $\pm$ 2.32

mm Hg; approximately 14.93 to 24.13 mm Hg) was also significantly higher than that of the patients with NTG (14.44 ± 2.14 mm Hg; approximately 10.87 to 20.65 mm Hg; $P < 0.0001$). However, the relative fluctuation of the patients with HTG (46.49 ± 11.72%; approximately 26.20 to 77.12%) showed no significant difference from that of the patients with NTG (43.10 ± 16.73%; approximately 12.62 to 99.42%; $P = 0.281$).

Among biometric parameters, the AL of the patients with HTG (24.97 ± 1.72 mm; approximately 22.21 to 28.91 mm) was significantly shorter than that of the patients with NTG (26.01 ± 2.37 mm; approximately 22.69 to 31.02 mm; $P = 0.024$; Table 3). Yet, the CCT showed no significant difference between the patients with HTG (544.20 ± 35.04 µm; approximately 476 to 614 µm) and patients with NTG (535.28 ± 33.34 µm; approximately 482 to 616 µm; $P = 0.201$). With respect of corneal biomechanical properties, the CRF of the patients with HTG was significantly higher 11.58 ± 1.45 mm Hg (approximately 9.48 to 14.36 mm Hg) than that of the patients with NTG (10.40 ± 1.13 mm Hg; approximately 8.23 to 14.51 mm Hg; $P < 0.0001$). However, there were no significant differences in CH between the patients with HTG (10.11 ± 1.23 mm Hg; approximately 7.96 to 13.49 mm Hg) and patients with NTG (10.17 ± 1.02 mm Hg; approximately 8.59 to 13.80 mm Hg; $P = 0.819$).

Discussion

In this study, we demonstrated in patients with POAG before initial treatment, that (1) the 24-hour IOP fluctuation is associated with AL and office hour IOP; (2) patients with POAG with AL ≤ 26 mm have higher 24-hour IOP fluctuation but lower CH than those with AL > 26 mm; (3) the patients with HTG have higher 24-hour IOP fluctuation and CRF than the patients with NTG.

IOP varies every minute in the daily activities. Single IOP measurement may not reflect the true average IOP level of an individual even though IOP measured at office hour has been shown to be a significant risk factor for the development and progression of POAG.[20,21] Instead, the 24-hour IOP measurement has better understanding of the IOP pattern within a day. Our previous study reported the 24-hour IOP pattern in untreated patients with POAG with different glaucoma severity stages,[3] and found that IOP decreased along the diurnal period and increased progressively during the nocturnal period, with the peak IOP at from 2:00 AM to 10:00 AM. Consistently, in this study, we showed that the IOP was highest at 8:00 AM (17.76 ± 3.55 mm Hg), and decreased along the diurnal period (Fig.). The lowest IOP was found at 8:00 PM (15.16 ± 3.37 mm Hg), and the IOP progressively increased again along the nocturnal period.

Considering the influence of CCT and corneal biomechanical properties on the IOP measurement and the risk of glaucoma,[5,6] the association of CCT and corneal biomechanical properties with the 24-hour IOP pattern needs in-depth evaluation. CCT is a well-known influencing factor for IOP measurement by applanation tonometry.[22] A previous study on Caucasian patients with glaucoma showed that IOP fluctuation is not significantly correlated with office hour CCT.[23] Another study on patients with cataract without glaucoma in Korea also indicated no relationship between CCT and diurnal IOP fluctuation, although CCT is positively correlated with the mean IOP.[24] Similarly, in this study, we did not find an association between IOP fluctuation and office hour CCT in patients with POAG before initial treatment (Table 4), suggesting that 24-hour IOP fluctuation is possibly independent of CCT. Besides CCT, corneal biomechanical properties can also influence the IOP measurement in applanation tonometry.[25] CH reflects the viscous, whereas CRF reflects the elastic properties of the cornea.[26] Lower level of CH is associated with higher level of IOP,[27] and low CH has been shown to be correlated with visual field progression[28,29] and IOP-induced optic nerve head surface deformation.[30] In this study, there was no association between IOP fluctuation and CH in the multivariate analysis (Table 4). However, when the patients with POAG were subgrouped based on the AL, the patients with POAG with AL ≤ 26 mm had significantly lower CH and higher 24-hour IOP fluctuation than those with AL > 26 mm (Table 2).

In the multivariate analysis, 24-hour IOP fluctuation was shown to be statistically significantly associated with AL in patients with POAG before treatment (Table 4). Similar results with statistical significance association were obtained when the IOP fluctuation was defined as the standard deviation of 12 recorded IOPs during 24 hours (Supplementary Table S1). Our results are consistent with a previous study on healthy young adults with diverse ethnicities that the 24-hour habitual IOP fluctuation is larger in hyperopic eyes than in emmetropic or myopic eyes.[31] Moreover, AL is also suggested to contribute to the asymmetrical diurnal IOP fluctuation between the left and right eye in nonglaucomatous subjects.[32] In the subgroup analysis, we observed that the patients with POAG with AL ≤ 26 mm had significantly higher IOP fluctuation, corneal-compensated IOP, and IOPg, but lower CH than those with AL > 26 mm (Table 2), supporting that

Table 4. Risk Factors Associated With Intraocular Pressure Fluctuation in Multivariable Analysis

	Model 1		Model 2	
Parameters	β Coefficient (SE)	*P* Value	β Coefficient (SE)	*P* Value
Axial length (AL)	−0.454 (0.138)	**0.001**	−0.401 (0.157)	**0.011**
Central corneal thickness (CCT, μm)	−0.003 (0.010)	0.784	0.009 (0.014)	0.524
Corneal hysteresis (CH, mm Hg)	−0.298 (0.252)	0.238	−0.180 (0.305)	0.554
Corneal resistance factor (CRF, mm Hg)	0.191 (0.236)	0.417	−0.022 (0.384)	0.953
Goldmann-correlated IOP (IOPg, mm Hg)	0.160 (0.067)	**0.017**	0.186 (0.118)	0.116

the AL is an important factor contributing to 24-hour IOP fluctuation in patients with POAG. The underling mechanisms might include the following reasons. First, axial myopia was characterized by reduction of sclera collagen fiber bundles. It results in low scleral rigidity leading to less epi-scleral venous pressure with increased aqueous outflow, and provides the ability to absorb and dump IOP spikes.[33,34] The longer the AL, the better the compliance of the eyeball, therefore, the smaller IOP fluctuation. Second, myopic eyes associated with choroidal thinning may have less choroidal vascular volume change during the posture change and lower the IOP elevation.[17] Third, wide anterior chambers in myopia eyes facilitate aqueous outflow and result in lower IOP fluctuation.

Our previous study demonstrated that the mean IOP, peak IOP, trough IOP, and IOP fluctuation are significantly higher in the patients with HTG than the patients with NTG, and the increase in IOP is more predominant in the patients with HTG during the nocturnal period.[3] A similar trend of IOP changes has also been reported in other studies.[35,36] In this study, we observed that the patients with HTG have larger 24-hour IOP fluctuation than the patients with NTG, whereas the patients with NTG have lower CRF than the patients with HTG (Table 3). Similar findings of lower CRF in patients with NTG have also been reported.[37] Our results suggested the difference of IOP fluctuation between patients with HTG and patients with NTG might be the result of the difference of ocular wall compliance, which is reflected by the corneal biomechanical parameters.

There were a few limitations of this study. First, only single measurement for CCT and corneal biomechanical properties was performed during the office hours. That is because a previous study reported that CCT and IOP fluctuate along the 24-hour period, but CH remains relatively constant throughout the 24-hour period.[38] Moreover, the 24-hour IOP pattern in healthy volunteers without ocular diseases has suggested not to be associated with the changes in CCT.[17] Similarly, we demonstrated that CCT was not associated with 24-hour IOP fluctuation (Table 4, Supplementary Table S1). Therefore, office hour CCT and CH measurement should not influence our association analysis and the results' interpretation. Second, although we measured the nocturnal IOP immediately after patients were awaken, the physiological condition of the sitting position is different from while asleep. A continuous IOP measurement, such as a contact lens-based sensor would be better. Finally, the data were subgrouped based on the AL (> 26 mm and ≤ 26 mm) to elaborate the association of AL and IOP fluctuation. Stratification by the refractive error to further interpret the impact of AL on IOP fluctuation is probably needed in the future.

In summary, this study revealed the association of a 24-hour IOP fluctuation with AL and office hour corneal biomechanical properties in patients with POAG. Longer eyes have smaller higher 24-hour IOP fluctuation than shorter eyes. The patients with HTG have higher 24-hour IOP fluctuation and CRF than the patients with NTG. Further investigations are expected for the association of the IOP fluctuation and ocular biometric parameters with the severity and progression of visual function impairment.

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