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Glaucoma

Association of Ambulatory Blood Pressure and Other Factors With Intraocular Pressure–Related 24-Hour Contact Lens Sensor Profile in Untreated Glaucoma

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Purpose: To investigate the association of diurnal blood pressure (BP) and other factors with the intraocular pressure (IOP)–related 24-hour contact lens sensor (CLS) profile of patients with untreated glaucoma.

Methods: The prospective study included 82 patients with untreated normal-tension glaucoma. CLS measurements and ambulatory BP monitoring were performed simultaneously for 24 hours. The association between the mean arterial pressure (MAP) and CLS profile was examined for the daytime and nocturnal periods using linear regression analysis. The associations between other factors and the CLS profile were also examined.

Results: Multivariate analysis of data from 63 eligible patients showed that higher average MAPs were significantly associated with larger average nocturnal CLS values (β coefficient = 0.273; $P = 0.023$); a larger increase in the last CLS value (β coefficient = 0.366; $P = 0.003$); larger standard deviations (SDs) of CLS values for the daytime, nocturnal, and 24-hour periods (β coefficient = 0.407, 0.293, and 0.375; $P < 0.001$, $P = 0.032$ and 0.002, respectively); and higher average ocular pulse frequencies for the daytime, nocturnal, and 24-hour periods (β coefficient = 0.268, 0.380, and 0.403; $P = 0.029$, 0.002, and 0.001, respectively). Thicker subfoveal choroids and shorter axial length were significantly associated with larger SDs and larger average CLS values, respectively. Smaller anterior chamber volume and lower corneal hysteresis were associated with larger SDs or larger average ocular pulse amplitude.

Conclusions: Ambulatory BP and several ocular parameters were significantly associated with various parameters of the 24-hour CLS profile.

Translational Relevance: Ambulatory BP and ocular parameters may be modifiers of the 24-hour IOP-related profile of CLS.

Introduction

Various devices are clinically available for measuring intraocular pressure (IOP); however, noninvasive monitoring of ambulatory IOP remains an unmet need. Therefore a contact lens sensor (CLS; SENSIMED Triggerfish; Sensimed AG, Lausanne, Switzerland) has been developed. It captures the changes in curvature near the corneoscleral junction through embedded strain gauges. The CLS is used to assess 24-hour profiles of IOP-related ocular volumetric changes rather than the IOP itself.[1] Furthermore, high-frequency sampling at 10 Hz for 30 seconds every five minutes enables the CLS to capture changes caused by transient IOP fluctuation by blinking, saccade, or

ocular pulse amplitude (OPA).[2,3] Several studies have shown that the CLS profile is associated with IOP changes.[4–8] The simulated peak timing for the 24-hour CLS profile was similar to that for the 24-hour IOP peak timing obtained using a pneumatonometer.[4] Furthermore IOP reductions by medical, laser, or surgical treatments were successfully detected based on changes in the CLS profile.[5–8] Moreover, recent studies have revealed the potential usefulness of the CLS in glaucoma management. CLS information in conjunction with a single tonometric reading was useful for identifying patients with IOP exceeding the diagnostic threshold within 24 hours.[9] The CLS profile of patients with untreated normal-tension glaucoma (NTG) was different from that of normal participants.[10] The fluctuation of the CLS profile was greater for eyes with medically treated glaucoma than that for eyes with surgically treated glaucoma.[11] Furthermore, some CLS parameters were significantly associated with more rapid deterioration of the visual field (VF) in patients with treated glaucoma.[3,12,13] The 24-hour CLS profile had a stronger association with prior rates of VF progression of glaucoma than IOP values measured using Goldmann applanation tonometry.[3] Therefore CLS may provide additional useful information relative to IOP alone for glaucoma management. However, factors affecting the CLS profile, other than IOP or glaucoma status, are unknown.

The effect of blood pressure (BP) on glaucomatous optic neuropathy (GON) has received attention as several meta-analyses have shown a positive association between systemic hypertension and prevalence of primary open-angle glaucoma.[14–17] The pathogenesis of GON induced by systemic hypertension may partly be explained by a small increase in IOP along with an increase in BP (Δ0.27 mm Hg of IOP/Δ10 mm Hg of BP) possibly because of the sympathetic tone, aqueous overproduction, or elevated episcleral venous pressure.[18] However, diastolic hypotension was associated with the prevalence and progression of GON, suggesting the involvement of low ocular perfusion at the optic nerve head in the pathology of GON.[16,19] According to a meta-analysis, a decrease in nocturnal BP, as assessed by ambulatory blood pressure monitoring (ABPM), currently considered the best out-of-office BP measurement method,[20] was a risk factor for progressive VF loss in primary open-angle glaucoma or NTG.[21] Moreover, several studies have shown that increased fluctuation in ocular perfusion pressure, defined as two thirds of mean arterial pressure (MAP) minus IOP, was associated with the development and progression of glaucoma[22] These findings indicate that vascular dysregulation and subsequent chronic ischemia are important IOP-independent causes of GON. Collectively, BP measurements, especially ABPM, may provide insights into the association of BP with IOP and GON in patients with glaucoma. However, to our knowledge, the association between BP and 24-hour IOP variation has not been reported.

This study investigated the association of 24-hour BP, assessed by ABPM, with the IOP-related CLS profile for untreated NTG. We also attempted to determine other factors associated with the CLS profile.

Methods

This single-center prospective study was conducted at the Department of Ophthalmology, Kanazawa University Hospital. The study protocol was approved by the institutional review board of Kanazawa University Hospital, and written informed consent was obtained from all patients. We recruited patients referred to our department for further examination or treatment of glaucoma from September 2016 to October 2020.

The eligibility criteria were as follows: age between 20 and 69 years, NTG without anti-glaucoma medication for four weeks or more, VF mean deviation (MD) ≥ -15 dB by standard automated perimetry (Humphrey Visual Field Analyzer II, 24–2 Swedish interactive threshold algorithm; Carl Zeiss Meditec, Inc, Dublin, CA, USA), and best-corrected visual acuity of $\geq$0.8. If both eyes were eligible, CLS measurements were conducted for the eye with worse VF. NTG was diagnosed based on the presence of glaucomatous optic disc abnormalities corresponding to VF defects judged using the Anderson-Patella criteria,[23] a normal open angle, and untreated IOP $\leq$ 20 mm Hg, verified by diurnal IOP measurements every three hours from 9:00 to 24:00. The exclusion criteria included a history of intraocular surgeries, ocular or systemic diseases other than glaucoma that could cause VF defects or affect VF test results, ocular trauma or inflammation, systemic hypertension, sleep disorder, mental illness, and shift work.

All enrolled participants underwent complete ophthalmic examinations, including central corneal thickness (CCT) and anterior chamber volume (ACV) measurements (Pentacam 70700; Oculus, Wetzlar, Germany), refractive power and corneal radius measurements (ark-530a; Nidek, Inc., San Jose, CA, USA), axial length measurement (OA-2000; Tomey Corporation, Nayoga, Japan), VF tests

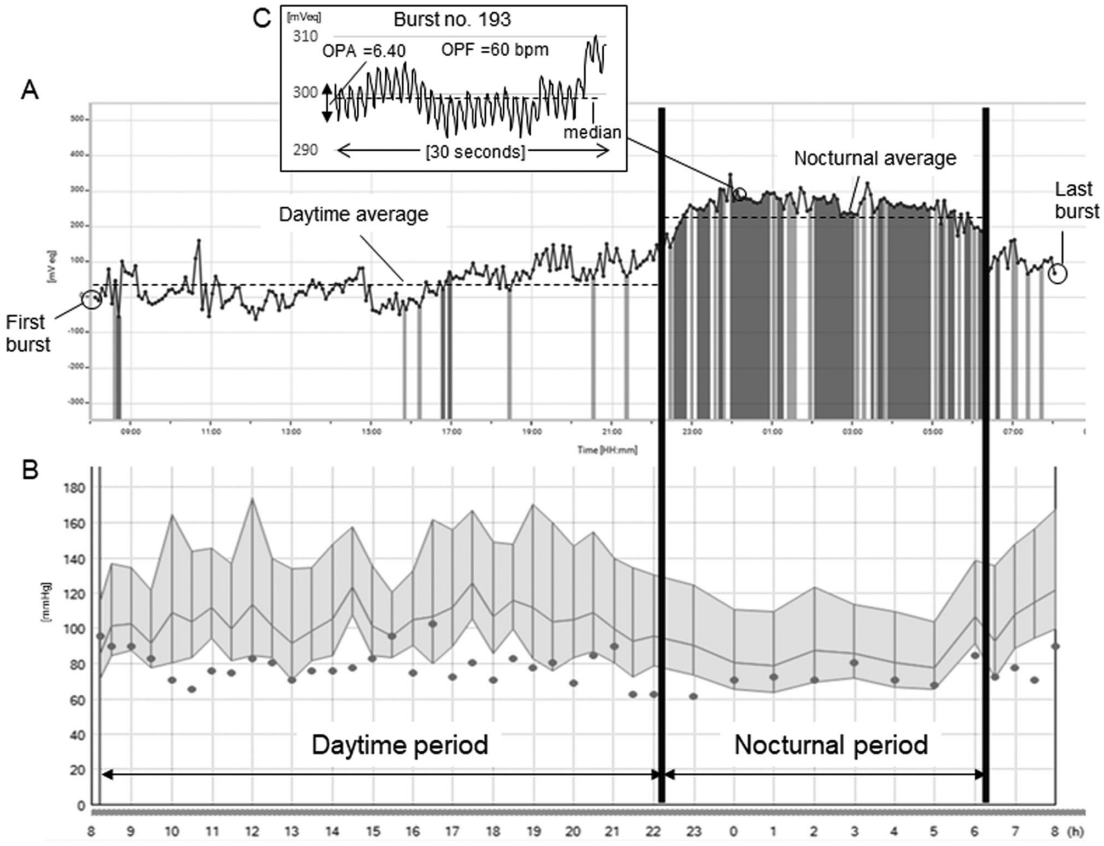

Figure 1. Simultaneous CLS and ABPM measurements. Examples of the 24-hour CLS (A) and ABPM (B) profiles. The *dark columns* under the CLS plot indicate the sleeping periods judged by the CLS software based on the blinking frequency. (A) Positions of the first and the last bursts are marked with *open circles*. *Dashed lines* indicate the daytime and nocturnal average CLS values. (C) Raw data of Burst no. 193 are shown. OPA is 6.40 mVeq and OPF is 60 beats per minute. The *dashed line* indicates the median value.

(Humphrey Field Analyzer II, 24-2 program; Carl Zeiss Meditec, Dublin, CA, USA), corneal hysteresis (CH) measurement (ORA; Reichert Ophthalmic Instruments, Depew, NY, USA), and OCT (RS 3000 Advance Retina Scan; Nidek). The subfoveal choroidal thickness (SFCT) was measured in the horizontal and vertical B scan images centered on the fovea using built-in OCT software. The average value of horizontal and vertical scans was used for the analysis.

ABPM and CLS measurements were performed during hospitalization from 8:30 for 24 hours (Fig. 1). IOP was measured using a Goldmann applanation tonometer before and after CLS measurements. CLS measurements were performed for a period of 30 seconds every five minutes (referred to as "burst") for 24 hours. BP was measured every 30 minutes from 6:00 to 22:00 and every hour from 22:00 to 6:00 using an ABPM device (TM-2433; A & D Medical, Tokyo, Japan). Heart rate was also recorded simultaneously. The daytime (i.e., waking until bedtime) and nocturnal (i.e., sleeping) periods were determined using built-in CLS software based on blinking detection and behavior records. Patients who complained about sleep disturbance (i.e., difficulty getting to sleep, arousal during sleep, interruption of measurements, or short sleep duration of three hours or more due to CLS or ABPM measurements) were excluded. MAP was defined as diastolic BP plus the difference between systolic and diastolic BP divided by 3. MAP dipper was defined as a decrease of $\geq$10% in the average MAP for the nocturnal period relative to that for the daytime period.[24] The median CLS values of all bursts were collected for the daytime, nocturnal and 24-hour periods (Fig. 1C).[10] The median CLS value of the first burst is set as 0 mVeq; the unit of mVeq in CLS measurements is not compatible with mm Hg. The average and standard deviations (SDs) of median CLS values in the bursts (average and SDs of CLS values) and MAP for the daytime and nocturnal periods were evaluated. An increase in the nocturnal average CLS values relative to the daytime average and an increase in CLS values in the last burst relative to the first burst (namely, the median CLS value in the last burst) were also used as CLS parameters. The

high-frequency parameters of CLS, OPA (mean amplitude of the ocular pulse), and ocular pulse frequency (OPF, number of ocular pulses per minute) were extracted for each burst from raw CLS data measured at 10 Hz (Fig. 1C).[3] The average and SD of OPA and OPF were also calculated.

The Kolmogorov–Smirnov test was used to evaluate normality of CLS and MAP data. The paired *t*-test or Wilcoxon signed-rank test was used to compare the normally or non-normally distributed data, respectively, for the daytime and nocturnal periods. Pearson's correlation (*r*) or Spearman's rank correlation coefficients (rs) were used to assess the relationship between the normally or non-normally distributed CLS and MAP data, respectively. Linear regression analysis was used to examine the effects of various factors on CLS parameters. Multivariate linear regression analysis was performed with independent variables with *P* values < 0.2 in univariate analysis. MAP-related variables were also entered in multivariate analysis regardless of their *P* values in univariate analysis. A final multivariate model was created by backward elimination until only variables with *P* values < 0.05 remained. For the relationship between ABPM (i.e., MAP and heart rate) and high-frequency CLS parameters measured simultaneously, ABPM parameters were compared with OPA and OPF measured at the nearest time point of ABPM by using the mixed-effects models accounting for the repeated paired measurements of ABPM and CLS in the same eye. Regarding the relationship between OPF and heat rate, the accuracy of OPF was defined as the proportion of OPF within ±15% of the heart rate measured at the nearest time points.[25] Statistical analysis was performed using SPSS software (IBM SPSS Statistics 20, IBM Corp., Armonk, NY, USA).

Results

Study Participants

CLS and ABPM parameters of 82 patients were measured. Seven patients were excluded due to technical problems related to CLS measurements: two patients had poor CLS recording, and five patients had artifacts caused by eyeglasses or a radio receiving set. Moreover, there were technical problems associated with ABPM recording in nine patients, and four patients experienced sleep disturbance during ABPM recording. Accordingly, the data of the remaining 63 patients were analyzed. Their demographics are shown in Table 1. The mean patient age was 48.0 ± 11.2 years. MD of VF was −6.0 ± 3.5 dB, and IOP before CLS recording was 13.7 ± 2.8 mm Hg.

Table 1. Demographics of Study Participants

Age (y)	48.0 ± 11.2
Gender	
Male	23
Female	40
Eye	
Right	32
Left	31
MD (dB)	−6.0 ± 3.5
PSD (dB)	7.6 ± 3.8
cpRNFLT (µm)	71.2 ± 13.1
Anterior chamber volume (mm^3)	175.0 ± 45.5
Axial length (mm)	26.1 ± 1.8
CCT (mm)	542 ± 29
Spherical equivalent (diopter)	−5.8 ± 3.2
Corneal curvature (mm)	7.8 ± 0.3
SFCT (µm)	211.5 ± 74.6
Bedtime (hh:mm)	22:24 ± 0:55
Wake-up time (hh:mm)	5:58 ± 0:45
Total sleep time (hh:mm)	7:33 ± 1:04
IOP before CLS (mm Hg)	13.7 ± 2.8
IOP after CLS (mm Hg)	13.5 ± 2.3
CH (mm Hg)	10.5 ± 1.1

MD, mean deviation; PSD, pattern standard deviation; cpRNFLT, circumpapillary retinal nerve fiber layer thickness.
The mean ± standard deviation for numerical variables.

Comparison of CLS and MAP Parameters for the Daytime and Nocturnal Periods

The average CLS values for the daytime, nocturnal, 24-hour periods were 49.7 ± 76.4, 229.6 ± 96.2, and 117.4 ± 74.2 mVeq, respectively. The average was significantly higher for the nocturnal period than for the daytime period ($P < 0.001$, Fig. 2A). The SDs of CLS values for the daytime, nocturnal, and 24-hour periods were 69.5 ± 27.9, 37.9 ± 11.8, and 107.7 ± 31.6 mVeq, respectively. The SD was significantly lower for the nocturnal period than for the daytime period ($P < 0.001$, Fig. 2B). The average MAP values for the daytime, nocturnal, and 24-hour periods were 99.1 ± 13.0, 89.2 ± 15.6, and 94.6 ± 13.2 mm Hg, respectively. The average was significantly higher for the daytime period than the nocturnal period ($P < 0.001$, Fig. 2C). The SDs of MAP for the daytime, nocturnal, and 24-hour periods were 10.5 ± 2.7, 9.3 ± 3.0, and 11.3 ± 2.6 mm Hg, respectively. The SD was significantly higher for the daytime period than the nocturnal period ($P = 0.012$, Fig. 2D).

In addition, the average and SD of high-frequency CLS parameters (OPA and OPF) were compared between the daytime and nocturnal periods (Supple-

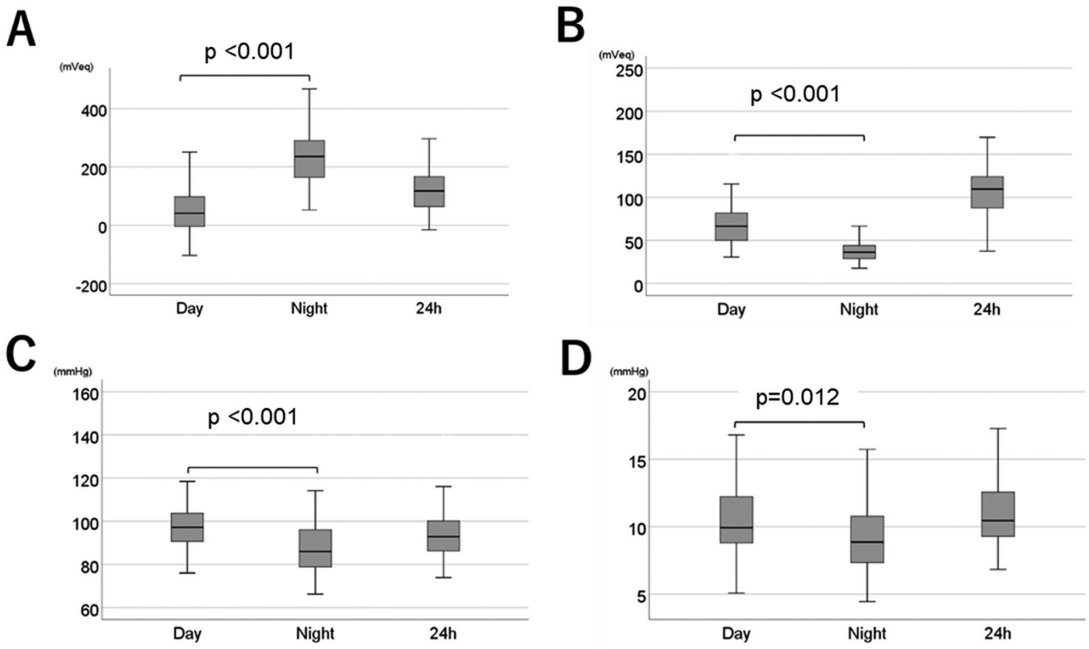

Figure 2. Comparison of daytime and nocturnal CLS and MAP parameters. (A) CLS average. (B) CLS SD. (C) MAP average. (D) MAP SD. Values by Wilcoxon signed-rank test.

mentary Fig. S4). Although the average OPA was not significantly different between the daytime and nocturnal periods ($P = 0.07$), the average OPF and SD of both OPA and OPF were significantly higher for the daytime period than for the nocturnal period (all $P < 0.001$).

Correlation Between CLS and MAP Parameters in the Daytime, Nocturnal and 24-hour Periods

The average MAP was significantly and positively correlated with the SD of CLS values for the daytime and 24-hour periods (rs = 0.266 and 0.381; $P = 0.035$ and 0.002, respectively) and increase in the nocturnal average CLS values relative to the daytime average (rs = 0.266, $P = 0.035$). The SDs of the MAP had no significant correlation with any non-high-frequency CLS parameters for any period (Supplementary Figs. S1–S3).

Relationship Between ABPM and High-Frequency CLS Parameters Measured Simultaneously

Increased MAP was significantly associated with increased OPF for the daytime and 24-hour periods (coefficient = 0.094 and 0.073, $P < 0.001$ and < 0.001, respectively), but not with OPA for any period (Supplementary Fig. S5). Regarding the relationship between OPF and heart rate, 82.0% of OPF data was considered accurate.

Factors Associated With Non-High-Frequency CLS Parameters for Daytime, Nocturnal and 24-Hour Periods

The factors associated with the non-high-frequency CLS parameters for the daytime, nocturnal, and 24-hour periods are shown in Tables 2 to 5. The following factors were significantly associated with CLS parameters in more than one multiple regression analysis: higher average MAPs were significantly associated with higher average CLS values for the nocturnal periods (β coefficient = 0.273, $P = 0.023$), a larger increase in CLS values in the last burst relative to the first burst (β coefficient = 0.366, $P = 0.003$) and increased SDs of CLS values for the daytime, nocturnal, and 24-hour periods (β coefficient = 0.407, 0.293, and 0.375; $P < 0.001$, $P = 0.032$ and 0.002, respectively). Increased SFCT was significantly associated with larger SD of CLS values for the daytime and nocturnal periods (β coefficient = 0.214 and 0.323; $P = 0.039$ and 0.008, respectively). A shorter axial length was significantly associated with a larger nocturnal average CLS value and increase in the nocturnal average CLS values relative to the daytime average (β coefficient = −0.331 and −0.298; $P = 0.013$ and 0.016, respectively). A larger SD of OPA was significantly associated with larger SD

Table 2. Factors Associated With the Average and SD of CLS Values During the Daytime Period

	Average (mVeq)				SD (mVeq)			
	Univariate		Multivariate		Univariate		Multivariate	
Factors	β	*P* Value	β	*P* Value	β	*P* Value	β	*P* Value
Age (y)	−0.14	0.274			0.201	0.114		
Sex (male)	0.004	0.973			0.03	0.816		
MD (dB)	−0.101	0.432			−0.092	0.475		
PSD (dB)	−0.012	0.928			0.096	0.454		
cpRNFLT (μm)	−0.177	0.166			0.052	0.684		
Anterior chamber volume (mm^3)	−0.065	0.611			−0.05	0.696		
CCT (mm)	−0.017	0.896			−0.242	0.056		
Axial length (mm)	0.045	0.726			−0.13	0.308		
Spherical equivalent (diopter)	−0.069	0.593			0.215	0.09		
Corneal curvature (mm)	0.03	0.816			−0.217	0.087		
SFCT (μm)	0.034	0.793			0.226	0.074	0.214	0.039
Bedtime (time)	0.186	0.145			0.394	0.001	0.251	0.027
Wake-up time (time)	0.048	0.709			0.047	0.713		
Total sleep time (h)	−0.128	0.318			−0.309	0.014		
IOP before CLS (mm Hg)	0.038	0.765			−0.015	0.905		
IOP after CLS (mm Hg)	0.114	0.372			−0.077	0.546		
Daytime average MAP (mm Hg)	0.131	0.305			0.281	0.026	0.407	<0.001
Daytime SD of MAP (mm Hg)	−0.134	0.294			−0.162	0.203	−0.253	0.019
MAP dipper (yes)	−0.074	0.563			−0.217	0.088		
CH (mm Hg)	−0.135	0.47			−0.061	0.746		
Daytime average OPA (mVeq)	0.183	0.152			0.281	0.026		
Daytime SD of OPA (mVeq)	0.149	0.243			0.344	0.006	0.358	0.003
Daytime average OPF (bpm)	−0.128	0.316			−0.05	0.699		
Daytime SD of OPF (bpm)	−0.034	0.792			−0.097	0.449		

MD, mean deviation; PSD, pattern standard deviation; cpRNFLT, circumpapillary retinal nerve fiber layer thickness; bpm, beats per minute.

Multivariate linear regression analysis was performed with independent variables with *P* values <0.2 in univariate linear regression analysis. MAP-related variables were also entered in multivariate analysis regardless of *P* values in univariate analysis. The final multivariate model was created by backward elimination. Standardized β coefficients and *P* values are shown.

of CLS values for the daytime and 24-hour periods (β coefficient = 0.358 and 0.308; $P = 0.003$ and 0.01, respectively).

Factors Associated With High-Frequency CLS Parameters for the Daytime, Nocturnal, and 24-Hour Periods

The factors associated with OPA and OPF parameters for each period are shown in Supplementary Tables S1 to S3 and S4 to S6, respectively. The following factors were significantly associated with multiple parameters in the multiple regression analysis: a smaller ACV was significantly associated with a larger SD of OPA for the daytime and 24-hour periods (β coefficient = −0.239 and −0.286; $P = 0.044$ and 0.015, respectively) and a larger average OPA for the nocturnal period (β coefficient = −0.365; $P = 0.002$). A lower CH was significantly associated with a larger SD of OPA for the nocturnal period and a larger average OPA for the 24-hour period (β coefficient = −0.369 and −0.365; $P = 0.041$ and 0.021, respectively). A higher average MAP was consistently associated with a higher average OPF for the daytime, nocturnal and 24-hour periods (β coefficient = 0.268, 0.380, and 0.403; $P = 0.029$, 0.002, and 0.001, respectively). Male sex was significantly associated with a lower average OPF for the nocturnal and 24-hour periods (β coefficient = −0.349 and −0.331; $P = 0.004$ and 0.006, respectively). A later bedtime was significantly associated with a larger average OPA for all periods and a larger SD of OPA for the daytime and 24-hour periods; however, it was significantly associated with a smaller average OPF for all measurement periods.

Table 3. Factors Associated With the Average and SD of CLS Values During the Nocturnal Period

	Average (mVeq)				SD (mVeq)			
	Univariate		Multivariate		Univariate		Multivariate	
Factors	β	*P* Value	β	*P* Value	β	*P* Value	β	*P* Value
Age (yrs)	−0.203	0.111	−0.339	0.011	0.045	0.725		
Sex (male)	0.213	0.094			0.139	0.279		
MD (dB)	−0.201	0.115			−0.03	0.815		
PSD (dB)	0.042	0.746			0.097	0.45		
cpRNFLT (µm)	0.043	0.736			−0.032	0.801		
Anterior chamber volume (mm^3)	−0.1	0.437			−0.082	0.524		
CCT (mm)	−0.042	0.745			−0.107	0.405		
Axial length (mm)	−0.169	0.186	−0.331	0.013	−0.127	0.322		
Spherical equivalent (diopter)	0.149	0.242			0.03	0.817		
Corneal curvature (mm)	−0.059	0.645			−0.176	0.168		
SFCT (µm)	0.231	0.068			0.311	0.013	0.323	0.008
Bedtime (time)	0.136	0.286			−0.133	0.297		
Wake-up time (time)	0.005	0.971			−0.105	0.413		
Total sleep time (h)	−0.115	0.368			0.042	0.741		
IOP before CLS (mm Hg)	0.044	0.735			0.175	0.171		
IOP after CLS (mm Hg)	0.009	0.945			0.147	0.249		
Nocturnal average MAP (mm Hg)	0.251	0.047	0.273	0.023	0.158	0.217	0.293	0.032
Nocturnal SD of MAP (mm Hg)	−0.005	0.967			−0.05	0.698		
MAP dipper (yes)	−0.183	0.152			0.16	0.209	0.337	0.014
CH (mm Hg)	−0.154	0.408			0.005	0.977		
Nocturnal average OPA (mVeq)	0.135	0.292			−0.07	0.585		
Nocturnal SD of OPA (mVeq)	0.161	0.208			0.128	0.319		
Nocturnal average OPF (bpm)	−0.122	0.339			0.107	0.403		
Nocturnal SD of OPF (bpm)	0.099	0.44			0.143	0.264		

MD, mean deviation; PSD, pattern standard deviation; cpRNFLT, circumpapillary retinal nerve fiber layer thickness; bpm, beats per minute.

Multivariate linear regression analysis was performed with independent variables with *P* values <0.2 in univariate linear regression analysis. MAP-related variables were also entered in multivariate analysis regardless of *P* values in univariate analysis. The final multivariate model was created by backward elimination. Standardized β coefficients and *P* values are shown.

Discussion

We simultaneously measured CLS and ABPM for 24 hours in untreated NTG patients to investigate the possible association between BP and the IOP-related CLS profile. To our knowledge, no study has shown the association of BP with IOP based on simultaneous ambulatory 24-hour measurements of BP and IOP. We found several significant associations between MAP and CLS parameters in multivariate analysis. Higher average MAPs were significantly associated with larger average nocturnal CLS values, larger increases in CLS values in the last burst, larger SDs of CLS values, and a higher average OPF for all periods. The other significant associations with CLS parameters were as follows: a larger SFCT was associated with larger SDs of the daytime and nocturnal CLS values and shorter axial lengths were associated with larger average nocturnal CLS values and larger increases in nocturnal average CLS values relative to the daytime average. A smaller ACV and lower CH were associated with a larger SD and average OPA, while male sex was associated with a lower average OPF. Thus, BP and several ocular parameters were identified as possible modifiers of the 24-hour IOP-related CLS profile.

We employed two common statistics (i.e., average and SD) to represent the CLS and ABPM profiles for each period. Notably, a higher average MAP for the 24-hour period was significantly associated with increased CLS values in the last burst. The upward trend of CLS values over time, referred to as "upward drift,"[26] has been commonly observed in many CLS studies.[26–29] The cause of the upward drift is largely

Table 4. Factors Associated With the Average and SD of CLS Values During the 24-Hour Period

	Average (mVeq)				SD (mVeq)			
	Univariate		Multivariate		Univariate		Multivariate	
Factors	β	*P* Value	β	*P* Value	β	*P* Value	β	*P* Value
Age (yrs)	−0.183	0.151			0.008	0.948		
Sex (male)	0.113	0.376			0.22	0.083		
MD (dB)	−0.151	0.236			−0.146	0.254		
PSD (dB)	0.009	0.942			0.084	0.513		
cpRNFLT (µm)	−0.109	0.396			0.173	0.174	0.266	0.026
Anterior chamber volume (mm^3)	−0.083	0.515			−0.058	0.653		
CCT (mm)	−0.027	0.835			−0.149	0.243		
Axial length (mm)	−0.04	0.756			−0.217	0.088		
Spherical equivalent (diopter)	0.018	0.886			0.213	0.094		
Corneal curvature (mm)	0.024	0.853			−0.193	0.13		
SFCT (µm)	0.107	0.405			0.262	0.038		
Bedtime (time)	0.11	0.391			0.155	0.225		
Wake-up time (time)	0.028	0.829			−0.032	0.803		
Total sleep time (hour)	−0.076	0.553			−0.157	0.218		
IOP before CLS (mm Hg)	0.028	0.83			0.02	0.878		
IOP after CLS (mm Hg)	0.086	0.501			−0.083	0.517		
24h average MAP (mm Hg)	0.217	0.088			0.3	0.017	0.375	0.002
24h SD of MAP (mm Hg)	−0.075	0.56			−0.003	0.98		
MAP dipper (yes)	−0.139	0.277			−0.178	0.162		
CH (mm Hg)	−0.171	0.358			−0.101	0.59		
24h average OPA (mVeq)	0.179	0.159			0.053	0.678		
24h SD of OPA (mVeq)	0.133	0.299			0.235	0.064	0.308	0.010
24h average OPF (bpm)	−0.108	0.4			0.075	0.557		
24h SD of OPF (bpm)	0.306	0.015	0.306	0.015	0.058	0.649		

MD, mean deviation; PSD, pattern standard deviation; cpRNFLT, circumpapillary retinal nerve fiber layer thickness; bpm, beats per minute.

Multivariate linear regression analysis was performed with independent variables with *P* values <0.2 in univariate linear regression analysis. MAP-related variables were also entered in multivariate analysis regardless of *P* values in univariate analysis. The final multivariate model was created by backward elimination. Standardized β coefficients and *P* values are shown.

unknown. Beltran-Agulló et al.[26] showed similar upward trends of IOP and CLS values in patients with OAG, but both did not correlate with each other. Tojo et al.[29] reported that the last values of CLS in eyes with glaucoma were significantly correlated with the IOP measured just after removal of CLS and with changes in corneal curvature after CLS measurements. In the present study, the last values of CLS were not significantly correlated with IOP immediately after CLS measurements (rs = 0.12, $P = 0.18$). Corneal thickness changes by CLS may be related to the upward drift. CCT increased by 1%–4% on average in three studies,[27,29,30] but decreased by 2% in another study.[25] Furthermore, CCT changes did not correlate with CLS changes.[27,29] The increase in IOP by transition to supine position in the nocturnal period may be relevant to the upward drift. Kim et al. reported that the percentage of time spent in the decubitus posture during sleep had a weakly positive correlation with mean CLS values during sleep.[10] However, a randomized cross-over trial showed that mean CLS values did not differ between sleeping with and without 30° head elevation.[26] According to our data, the average MAP for the 24-hour period had a squared semi-partial correlation of 13.4% for the total variance of the increase in last CLS values. Therefore the average MAP level may be a factor responsible for the upward drift.

As indicators for variability or fluctuation of the CLS values, the range (maximum minus minimum CLS values),[7,13] amplitude (half the distance between the cosine-fit maximum and minimum),[4,6,31] and SD[10,13]

Table 5. Factors Associated With Other CLS Parameters During the 24-Hour Period

	Increase in Nocturnal Average CLS Values Relative to the Daytime Average (mVeq)				Increase in CLS Values in the Last Burst Relative to the First Burst (mVeq)			
	Univariate		Multivariate		Univariate		Multivariate	
Factors	β	*P* Value	β	*P* Value	β	*P* Value	β	*P* Value
Age (yrs)	−0.126	0.326			−0.116	.365		
Sex (male)	0.275	0.029	0.325	0.009	0.209	0.099		
MD (dB)	−0.144	0.259			−0.274	0.03		
PSD (dB)	0.053	0.681			0.176	0.168		
cpRNFLT (μm)	0.229	0.072			−0.151	0.237		
Anterior chamber volume (mm^3)	−0.053	0.679			0.027	0.835		
CCT (mm)	−0.047	0.713			−0.058	0.649		
Axial length (mm)	−0.244	0.054	−0.298	0.016	0.019	0.883		
Spherical equivalent (diopter)	0.249	0.049			0.042	0.744		
Corneal curvature (mm)	−0.091	0.478			0.131	0.304		
SFCT (μm)	0.243	0.055			−0.041	0.75		
Bedtime (time)	0.002	0.985			0.121	0.345		
Wake-up time (time)	−0.033	0.798			−0.034	0.789		
Total sleep time (h)	−0.025	0.845			−0.129	0.312		
IOP before CLS (mm Hg)	0.012	0.923			0.071	0.578		
IOP after CLS (mm Hg)	−0.107	0.405			0.143	0.264		
24h average MAP (mm Hg)	0.189	0.137			0.366	0.003	0.366	0.003
24h SD of MAP (mm Hg)	0.012	0.927			−0.114	0.375		
MAP dipper (yes)	−0.15	0.239			−0.246	0.052		
CH (mm Hg)	−0.067	0.722			−0.303	0.097		
24h average OPA (mVeq)	−0.012	0.923			0.19	0.136		
24h SD of OPA (mVeq)	0.132	0.304			0.143	0.265		
24h average OPF (bpm)	0.076	0.554			−0.14	0.273		
24h SD of OPF (bpm)	0.113	0.378			−0.033	0.796		

MD, mean deviation; PSD, pattern standard deviation; cpRNFLT, circumpapillary retinal nerve fiber layer thickness; bpm, beats per minute.

Multivariate linear regression analysis was performed with independent variables with *P* values <0.2 in univariate linear regression analysis. MAP-related variables were also entered in multivariate analysis regardless of *P* values in univariate analysis. The final multivariate model was created by backward elimination. Standardized β coefficients and *P* values are shown.

were used in previous studies. Kim et al.[10] reported that the SD of CLS values for 24 hours was significantly greater for patients with untreated glaucoma (112.5 ± 26.9 mVeq) than for healthy controls (85.2 ± 29.6 mVeq) although peri-CLS IOP was not different for the groups. The SD of CLS values for untreated NTG patients in their study was comparable to that reported in our study. In their study, the control group had more participants with systemic hypertension than the glaucoma group, although the average BP determined using ABPM was not significantly different between the groups. Therefore the greater SD of CLS values for the untreated NTG patients than for the healthy controls was irrelevant to BP. However, the possible effects of antihypertensive medication could not be ruled out.

Our study consistently observed a positive association between the SD of CLS values and average MAP values for the diurnal, nocturnal, and 24-hour periods. Tojo et al.[13] reported that larger SDs of CLS values during all three periods were significantly correlated with rapid VF progression. Thus. the association between the SD of CLS values and VF progression may be mediated not only by IOP but also by MAP.

Given that CLS is designed to measure 24-hour profiles of the IOP-related ocular volumetric changes, factors that can affect ocular volumetric changes may also be associated with CLS parameters. In our study,

greater SFCT was significantly associated with greater SDs of CLS values for the daytime and nocturnal periods independent of MAP. The choroid accounts for approximately 90% of ocular blood flow as demonstrated by the microsphere method applied to cynomolgus monkeys.[32] Therefore, choroidal thickness changes should represent ocular volumetric changes. Recently, Sayah et al.[33] developed a technique for measuring ocular rigidity involving the use of high-speed OCT imaging to measure the pulsatile choroidal volume changes and their extrapolation to determine pulsatile ocular volume changes. The amplitude of diurnal variation of choroidal thickness in normal participants was reported to be significantly greater for eyes with thick choroids than those with thin choroids.[34] Collectively, participants with greater SFCT may show larger fluctuations of ocular volume resulting in larger SDs of CLS values.

Axial length may also affect the CLS profile. Longer axial lengths were associated with lower pulsatile ocular blood flow (POBF) in the sitting position in healthy participants, independent of age, IOP, or BP.[35] In our study, multivariate analysis showed that axial length was negatively associated with the average CLS value for the nocturnal period, which is more relevant to the supine POBF than to upright POBF. In this regard, a study involving anisometropic healthy participants showed that supine POBF was significantly lower in eyes with greater axial lengths than in fellow eyes.[36] The same authors examined the effect of age on supine POBF and found a significant decrease in POBF with age.[37] We showed that older age was associated with a lower nocturnal average CLS value in multivariate analysis. Although axial length and age were not significant in univariate analysis, they became significant in multivariate analysis when both factors were included as independent variables. Because axial length had a significant negative correlation with age ($r = -0.42$, $P = 0.0006$), multivariate regression after controlling for age was more appropriate for evaluating the effect of axial length on average CLS values. Therefore supine POBF in the previous studies and the average nocturnal CLS in the current study have the same characteristics, and their decrease were associated with greater axial lengths and older age, which may indicate the status of choroidal blood flow as a determinant of the average nocturnal CLS value.

The high-frequency CLS parameters have received attention as SDs of nocturnal OPA and OPF have been reported to be associated with rapid VF progression.[3] In our study, a lower CH, which indicates less resilient cornea, was associated with a higher SD of nocturnal OPA. Of note, a lower CH was also associated with faster VF progression.[38] Therefore the association between SD of nocturnal OPA and glaucoma progression might be confounded by CH. OPA measured by tonometry reflects transient IOP changes due to fluctuation of ocular blood volume during the cardiac cycle. OPA recorded by dynamic contour tonometry was lower in eyes with lower IOP, longer axial length or thinner SFCT, but not correlated with CCT, corneal curvature or anterior chamber depth in healthy participants.[39,40] In contrast, we found that ACV, but not axial length or SFCT, was associated with several OPA parameters of CLS. The discrepancy may stem from the differences in characteristics of the study participants and the position and mechanism for detecting ocular pulse between dynamic contour tonometry and CLS. Regarding OPF, MAP was positively associated with OPF measured simultaneously, and a higher average MAP was consistently associated with a higher average OPF. Given that most OPF data accurately represented the heat rate measured by ABPM, the significant association between MAP and OPF can be explained by the close relationship between MAP and heart rate.

The strength of the current study is the exclusion of patients using IOP-lowering medication, those with systemic hypertension, and those using antihypertensive drugs that may affect the diurnal profile of IOP and BP. However, our study has several limitations. The study participants were relatively young and myopic and may not represent older or emmetropic NTG patients. CLS and ABPM allow us to obtain ambulatory data; however, the devices may interfere with some aspects of daily activities or ordinary sleep. The data of four patients were excluded from analysis due to sleep disturbance by ABPM measurements. The lack of control group is another limitation of this study. Kim et al.[10] reported that the SD of 24-hour CLS values was significantly greater in patients with untreated glaucoma than in healthy controls. Therefore the association between BP and CLS parameters may be different or less prominent in healthy controls than in patients with glaucoma. Since we performed many statistical tests (20 multiple linear regressions for various CLS parameters) for a relatively small sample size, we focused the discussion on factors with P values < 0.05 in more than one multiple linear regression analysis. The final multivariate models were created by backward elimination and contained one to five independent variables with P values < 0.05. When the Benjamini-Hochberg method was used to control the false discovery rate (FDR), almost all coefficients for independent variables remained significant at an FDR of 0.05, and none were rejected at an FDR of 0.1, indicating that family-wise error rates were controlled.[3] Finally, as CLS measures IOP-related ocular volume

changes, the effects of ambulatory BP on IOP remain to be elucidated.

In conclusion, we investigated the association of 24-hour ambulatory BP with the IOP-related CLS profile of untreated NTG patients. MAP and several ocular parameters were significantly associated with various CLS parameters. These new findings should provide valuable information that improves our understanding of the diurnal profile of IOP-related ocular volumetric changes, which is relevant to glaucoma and its progression.

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References

1. Leonardi M, Leuenberger P, Bertrand D, Bertsch A, Renaud P. First steps toward noninvasive intraocular pressure monitoring with a sensing contact lens. *Invest Ophthalmol Vis Sci.* 2004;45:3113–3117.
2. Gisler C, Ridi A, Hennebert J, Weinreb RN, Mansouri K. Automated detection and quantification of circadian eye blinks using a contact lens sensor. *Transl Vis Sci Technol.* 2015;4:4.
3. De Moraes CG, Mansouri K, Liebmann JM, RRTConsortium. Association between 24-hour intraocular pressure monitored with contact lens sensor and visual field progression in older adults with glaucoma. *JAMA Ophthalmol.* 2018;136:779–785.
4. Liu JH, Mansouri K, Weinreb RN. Estimation of 24-hour intraocular pressure peak timing and variation using a contact lens sensor. *PLoS One*. 2015;10(6):e0129529.
5. Mansouri K, Medeiros F, Weinreb R. Effect of glaucoma medications on 24-hour intraocular pressure-related patterns using a contact lens sensor. *Clin Exp Ophthalmol* 2015;43:787–795.
6. Lee JWY, Fu L, Chan JCH, Lai JSM. Twenty-four-hour intraocular pressure related changes following adjuvant selective laser trabeculoplasty for normal tension glaucoma. *Medicine (Baltimore)*. 2014;93(27):e238.
7. Tojo N, Oka M, Miyakoshi A, Ozaki H, Hayashi A. Comparison of fluctuations of intraocular pressure before and after selective laser trabeculoplasty in normal- tension glaucoma patients. *J Glaucoma.* 2014;23(8):e138–e143.
8. Rekas M, Danielewska ME, Byszewska A, et al. Assessing efficacy of canaloplasty using continuous 24-hour monitoring of ocular dimensional changes. *Invest Ophthalmol Vis Sci*. 2016;57:2533–2542.
9. Shioya S, Higashide T, Tsuchiya S, et al. Using 24-hr ocular dimensional profile recorded with a sensing contact lens to identify primary open-angle glaucoma patients with intraocular pressure constantly below the diagnostic threshold. *Acta Ophthalmol.* 2020;98(8):e1017–e1023.
10. Kim YW, Kim JS, Lee SY, et al. Twenty-four–hour intraocular pressure–related patterns from contact lens sensors in normal-tension glaucoma and healthy eyes: the Exploring Nyctohemeral Intraocular pressure related pattern for Glaucoma Management (ENIGMA) Study. *Ophthalmology.* 2020;127(11):1487–1497.
11. Muniesa MJ, Ezpeleta J, Benítez I. Fluctuations of the intraocular pressure in medically versus surgically treated glaucoma patients by a contact lens sensor. *Am J Ophthalmol.* 2019;203:1–11.
12. De Moraes CG, Jasien J V, Simon-Zoula S, Liebmann JM, Ritch R. Visual field change and 24-hour IOP-related profile with a contact lens sensor in treated glaucoma patients. *Ophthalmology*. 2016;123:744–753.
13. Tojo N, Hayashi A, Otsuka M. Correlation between 24-h continuous intraocular pressure measurement with a contact lens sensor and visual field progression. *Graefes Arch Clin Exp Ophthalmol.* 2020;258:175–182.
14. Zhao D, Cho J, Kim MH, Guallar E. The association of blood pressure and primary open-angle glaucoma: a meta-analysis. *Am J Ophthalmol.* 2014;158:615–627.e9.
15. Bae HW, Lee N, Lee HS, Hong S, Seong GJ, Kim CY. Systemic hypertension as a risk factor for open-angle glaucoma: a meta-analysis of population-based studies. *PLoS One.* 2014;9(9):e108226.
16. Grzybowski A, Och M, Kanclerz P, Leffler C, Moraes CG. Primary open angle glaucoma and vascular risk factors: a review of population based studies from 1990 to 2019. *J Clin Med.* 2020;9(3):761.

17. Nislawati R, Taufik Fadillah Zainal A, Ismail A, Waspodo N, Kasim F, Gunawan AMAK. Role of hypertension as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. *BMJ Open Ophthalmol.* 2021;6:e000798.
18. He Z, Vingrys AJ, Armitage JA, Bui BV. The role of blood pressure in glaucoma. *Clin Exp Optom.* 2011;94:133–149.
19. Chung HJ, Hwang HB, Lee NY. The Association between primary open-angle glaucoma and blood pressure: two aspects of hypertension and hypotension. *Biomed Res. Int.* 2015;2015:827516.
20. Schwartz CL, McManus RJ. What is the evidence base for diagnosing hypertension and for subsequent blood pressure treatment targets in the prevention of cardiovascular disease? *BMC Med.* 2015;13:256.
21. Bowe A, Grünig M, Schubert J, et al. Circadian variation in arterial blood pressure and glaucomatous optic neuropathy—a systematic review and meta-analysis. *Am J Hypertens.* 2015;28:1077–1082.
22. Werne A, Harris A, Moore D, BenZion I, Siesky B. The circadian variations in systemic blood pressure, ocular perfusion pressure, and ocular blood flow: risk factors for glaucoma? *Surv Ophthalmol.* 2008;53:559–567.
23. Anderson DR, Patella VM. *Automated Static Perimetry.* 2nd ed. St. Louis: Mosby; 1999.
24. Lee J, Jeong D, Kwon J, Kook MS, Choi J. Association between nocturnal blood pressure dips and optic disc hemorrhage in patients with normal-tension glaucoma. *Am J Ophthalmol.* 2017;176:87–101.
25. Mansouri K, Weinreb RN, Liu JH. Efficacy of a contact lens sensor for monitoring 24-h intraocular pressure related patterns. *PLoS One.* 2015;10(5):e0125530.
26. Beltran-Agulló L, Buys YM, Jahan F, et al. Twenty-four hour intraocular pressure monitoring with the SENSIMED Triggerfish contact lens: effect of body posture during sleep. *Br J Ophthalmol*. 2017;101:1323–1328.
27. Freiberg F J, Lindell J, Thederan L A, Leippi S, Shen Y, Klink T. Corneal thickness after overnight wear of an intraocular pressure fluctuation contact lens sensor. *Acta Ophthalmol.* 2012;90(7):e534–e539.
28. Holló G, Kóthy P, Vargha P. Evaluation of continuous 24-hour intraocular pressure monitoring for assessment of prostaglandin-induced pressure reduction in glaucoma. J Glaucoma. 2014;23(1):e6–e12
29. Tojo N, Hayashi A. Influence of ocular dimensional change on 24-hour intraocular pressure measurement with contact lens sensor. *J Glaucoma*. 2019;28:808–810.
30. Hubanova R, Aptel F, Chiquet C, Mottet B, Romanet J P.Effect of overnight wear of the Triggerfish sensor on corneal thickness measured by Visante anterior segment optical coherence tomography. *Acta Ophthalmol*. 2014;92(2):e119–e123.
31. Mansouri K, Liu JH, Weinreb RN, Tafreshi A, Medeiros FA. Analysis of continuous 24-hour intraocular pressure patterns in glaucoma. *Invest Ophthalmol Vis Sci.* 2012;53:8050–8056.
32. Alm A, Bill A. Ocular and optic nerve blood flow at normal and increased intraocular pressures in monkeys (Macaca irus): a study with radioactively labelled microspheres including flow determinations in brain and some other tissues. *Exp Eye Res.* 1973;15:15–29.
33. Sayah DN, Mazzaferri J, Ghesquière P, et al. Non-invasive in vivo measurement of ocular rigidity: Clinical validation, repeatability and method improvement. *Exp Eye Res.* 2020;190:107831.
34. Tan CS, Ouyang Y, Ruiz H, Sadda SR. Diurnal variation of choroidal thickness in normal, healthy subjects measured by spectral domain optical coherence tomography. *Invest Ophthalmol Vis Sci.* 2012;53:261–266.
35. Mori F, Konno S, Hikichi T, Yamaguchi Y, Ishiko S, Yoshida A. Factors affecting pulsatile ocular blood flow in normal subjects. *Br J Ophthalmol.* 2001;85:529–530.
36. Lam AK, Chan ST, Chan B, Chan H. The effect of axial length on ocular blood flow assessment in anisometropes. *Ophthalmic Physiol Opt.* 2003;23:315–320.
37. Lam AK, Chan ST, Chan H, Chan B. The effect of age on ocular blood supply determined by pulsatile ocular blood flow and color Doppler ultrasonography. *Optom Vis Sci*. 2003;80:305–311.
38. Medeiros FA, Meira-Freitas D, Lisboa R, Kuang TM, Zangwill LM, Weinreb RN. Corneal hysteresis as a risk factor for glaucoma progression: a prospective longitudinal study. *Ophthalmology*. 2013;120:1533–1540.
39. Kaufmann C, Bachmann LM, Robert YC, Thiel MA. Ocular pulse amplitude in healthy subjects as measured by dynamic contour tonometry. *Arch Ophthalmol.* 2006;124:1104–1108.
40. Demirok G, Topalak Y, Başaran M M, Ataç G A, Öztürk S, Sengün A. Correlation of ocular pulse amplitude, choroidal thickness, and internal carotid artery Doppler ultrasound findings in normal eyes. *Semin Ophthalmol*. 2017;32:620–624.