9-2023

Effect of 24-h blood pressure dysregulations and reduced ocular perfusion pressure in open-angle glaucoma progression

Jesus D. Melgarejo

Jan V. Eijgen

Dongmei Wei

Gladys E. Maestre

Lama A. Al-Aswad

See next page for additional authors

Authors

Jesus D. Melgarejo, Jan V. Eijgen, Dongmei Wei, Gladys E. Maestre, Lama A. Al-Aswad, Chia-Te Liao, Luis J. Mena, Thomas Vanassche, Stefan Janssens, and Peter Verhamme

Original Article

OPEN

Effect of 24-h blood pressure dysregulations and reduced ocular perfusion pressure in open-angle glaucoma progression

Jesus D. Melgarejo[a,b,c,*], Jan V. Eijgen[d,e,*], Dongmei Wei[a], Gladys E. Maestre[b,c,f], Lama A. Al-Aswad[g], Chia-Te Liao[a], Luis J. Mena[h], Thomas Vanassche[i], Stefan Janssens[j], Peter Verhamme[i], Zhen-Yu Zhang[a], Karel V. Keer[d,e,†], and Ingeborg Stalmans[d,e,†]

Background: Low ocular perfusion pressure (OPP), which depends on the mean arterial pressure (MAP) and intraocular pressure (IOP), is associated with glaucoma. We studied 24-h MAP dysregulations and OPP in relation to the progression of glaucoma damage.

Methods: We retrospectively analyzed 155 normal-tension glaucoma (NTG) and 110 primary open-angle glaucoma (POAG) patients aged 18 years old followed at the University Hospital Leuven with repeated visual field tests ($n = 7000$ measures, including both eyes) who underwent 24-h ambulatory blood pressure monitoring. Twenty-four-hour MAP dysregulations were variability independent of the mean (VIM), and the five lowest dips in MAP readings over 24 h. OPP was the difference between 2/3 of the MAP and IOP. Glaucoma progression was the deterioration of the visual field, expressed as decibel (dB) changes in mean deviation analyzed by applying multivariable linear mixed regression models.

Results: The mean age was 68 years (53% were women). High 24-h VIMmap was associated with glaucoma progression in POAG ($P < 0.001$) independently of the 24-h MAP level. The estimated changes in mean deviation in relation to dip MAP measures ranged from −2.84 dB [95% confidence interval (CI) −4.12 to −1.57] to −2.16 dB (95% CI −3.46 to −0.85) in POAG. Reduced OPP along with high variability and dips in MAP resulted in worse mean deviation deterioration.

Conclusion: The progression of glaucoma damage associates with repetitive and extreme dips in MAP caused by high variability in MAP throughout 24 h. This progression exacerbates if 24-h MAP dysregulations occur along with reduced OPP.

Keywords: ambulatory blood pressure, blood pressure variability, dips in the blood pressure, glaucoma progression, ocular perfusion pressure, primary open-angle glaucoma

Abbreviations: CI, confidence internal; IOP, intraocular pressure; MAP, mean arterial pressure; NTG, normal-tension glaucoma; OPP, ocular perfusion pressure; POAG, primary open-angle glaucoma; VIM, variability independent of the mean

BACKGROUND

Open-angle glaucoma is a chronic and progressive disease characterized by the loss of retinal ganglion cells, resulting in irreversible vision loss and ultimately blindness [1]. The progression of glaucoma is attributed to vascular dysregulations that compromise the oxygen supply of the optic nerve [2]. One pivotal mechanism is reduced ocular perfusion pressure (OPP) [2], which is often studied as the difference between mean arterial pressure (MAP) and intraocular pressure (IOP) [3]. Although glaucoma damage occurs in the presence of reduced OPP because of either low MAP or high IOP, patients with normal IOP still experience glaucoma progression and even more, the majority of cases suffer MAP hypertension [2,4].

The study of variability in the MAP and IOP over 24 h offers an opportunity to understand reduced OPP above and beyond absolute high MAP and low IOP levels. Compared with IOP, the use of 24-h ambulatory blood pressure monitoring in clinical and research settings is feasible and

Journal of Hypertension 2023, 41:000–000

[a]Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium, [b]Institute of Neurosciences, School of Medicine, University of Rio Grande Valley, Harlingen, [c]Rio Grande Valley Alzheimer's Disease Resource Center for Minority Aging Research (RGV AD-RCMAR), University of Texas Rio Grande Valley, Brownsville, Texas, USA, [d]Department of Ophthalmology, UZ Leuven, [e]Department of Neurosciences, Research Group Ophthalmology, KU Leuven, Leuven, Belgium, [f]Department of Human Genetics, School of Medicine, University of Texas Rio Grande Valley, Brownsville, Texas, [g]Scheie Eye Institute, Department of Ophthalmology, University of Pennsylvania, Philadelphia, Pennsylvania, USA, [h]Department of Informatics, Universidad Politécnica de Sinaloa, Mazatlán, México, [i]Centre for Molecular and Vascular Biology, KU Leuven Department of Cardiovascular Sciences, KU Leuven and [j]Division of Cardiology, Department of Internal Medicine, UZ Leuven, Leuven, Belgium

Correspondence to Ingeborg Stalmans, MD, PhD, Department of Ophthalmology, UZ Leuven, Leuven Herestraat 49, 3000 Leuven, Belgium. Tel: +32 16 33 22 11; e-mail: ingeborg.stalmans@mac.com

*J.D.M. and J.V.E. are joint first authors who contributed equally.

†K.V.K. and I.S. are joint last authors who contributed equally.

Received 25 April 2023 **Accepted** 24 July 2023

DOI:10.1097/HJH.0000000000003537

permits the study of reading-to-reading MAP variability [5,6]. This opens the possibility to investigate two potential unexplored mechanisms in open-angle glaucoma that can lead to reduced OPP in the presence of normal or high MAP. First, 24-h blood pressure dysregulations defined as repetitive and extreme drops in MAP because of excessive variability throughout a 24-h period regardless of the absolute MAP level (Figure S1, http://links.lww.com/HJH/C260). Second, combination of 24-h MAP dysregulations with reduced 24-h OPP resulting in worse progression of glaucoma damage [7]. To explore these mechanisms, we aimed this study to investigate the association of 24-h MAP dysregulations and OPP with the progression of normal-tension glaucoma (NTG) and primary open-angle glaucoma (POAG) damage.

METHODS

Cohort study

We retrospectively included patients aged 18 years or older with open-angle glaucoma from the database available at the Glaucoma Department, UZ Leuven, Belgium to conduct an observational retrospective longitudinal cohort study. We identified 476 Caucasian NTG and POAG patients followed at the glaucoma department between 1998 and 2019 who underwent 24-h ambulatory blood pressure monitoring at the glaucoma service of the UZ Leuven (Figure S2, http://links.lww.com/HJH/C260) [8]. Glaucoma specialists determined to perform the 24-h ambulatory blood pressure monitoring in patients who experienced glaucoma progression despite the IOP being within the normal range during follow-up (Figure S3, http://links.lww.com/HJH/C260). Of 476 patients (Figure S2, http://links.lww.com/HJH/C260), a total of 265 patients were included in the present study: 155 NTG and 110 POAG cases. Figure S2, http://links.lww.com/HJH/C260 displays the exclusion criteria. Of these 265 patients, 101 underwent 24-h IOP assessment. The Ethics Committee of the UZ Leuven approved the secondary use of the data from the glaucoma patients (registration numbers, S65245 and B32220083510). All methods were carried out in accordance with relevant guidelines and regulations and adhered to the principles of the Declaration of Helsinki.

Ophthalmological examination

The ophthalmic examination was performed by glaucoma specialists, and included measurement of best corrected visual acuity, biomicroscopy, and fundus examination by slit lamp examination and a 90 diopter lens. The IOP was measured with Goldmann applanation tonometry. The optic nerve head and the retinal fiber layer were examined by Heidelberg Retinal Tomography (HRT3) or optical coherence tomography Spectralis (Heidelberg Engineering GmbH, Heidelberg, Germany). The visual field was tested using the Humphrey Visual Field Analyser HFA3 (Carl Zeiss Meditec AG, Jena, Germany) or the Octopus 300/900 system (Haag-Streit AG, Köniz, Switzerland). Glaucoma was diagnosed following the fifth European Glaucoma Society Guidelines [9], as a significant optic nerve rim and retinal nerve fiber layer thinning with congruent visual field defects. Patients were categorized into NTG ($\leq$ 21 mmHg) and POAG (>21 mmHg) based on their maximal recorded untreated IOP level.

Twenty-four hour blood pressure level and dysregulations

Ambulatory blood pressure was recorded with validated oscillometric recorders (Mobil-O-Graph devices) [10]. The programmed intervals between readings ranged from 15 min during the daytime to 30 min at night (Table S1, http://links.lww.com/HJH/C260). The within-participant 24-h MAP was a time-weighted average, giving a weight to each participant reading proportional to the time interval between readings. 24-h MAP hypertension was a 24 MAP = >92 mmHg [11]. We defined 24-h MAP dysregulations as repetitive and extreme drops in MAP over 24 h because of excessive reading-to-reading variability regardless of the absolute MAP level (Figure S1, http://links.lww.com/HJH/C260). To study 24-h MAP variability, we used variability independent of the mean (VIM) index. We selected VIM instead of other conventional indexes of variability (e.g. standard deviation, coefficient of variation, maximum − minimum) because VIM does not correlate with the level and captures most of the variability information (Figure S4, http://links.lww.com/HJH/C260) – conventional indexes are highly correlated with the level. VIM was calculated as the within-participant standard deviation divided by the mean to the power x and multiplied by the population mean to the power x [12]. The power x was obtained by fitting a curve through a plot of the standard deviation against the mean, using the model: standard deviation = a $\times$ mean^x, where x was derived by non-linear regression analysis. The value of x so obtained was 0.815 for estimating 24-h VIM_{map}. To study extreme and drastic drops in MAP, the five readings with the largest drops compared with the previous reading in individual 24-h recordings were selected – the time elapsed in between was used to quantify the duration of dips/blips.

Ocular perfusion pressure

The OPP was calculated as the difference between 2/3 of the 24-h MAP and 24-h IOP level [3]. The factor 2/3 accounts for the difference in blood pressure between the brachial and ophthalmic artery when individuals are seated and the fact that the orbital arteries are further upstream. Given that we are considering MAP and IOP recordings during awake time, we assume patients were seated or in the supine position when the ambulatory blood pressure monitoring recorded MAP measures – all IOP recordings were taken with the patient seated. Patients were hospitalized to evaluate fluctuations and peaks in the IOP measured at least in the morning, afternoon, before sleeping, and the next day early morning, with Goldmann or Perkins (early morning) applanation tonometry. To investigate changes in OPP, we identified the maximum and minimum OPP levels in 24 h by estimating the difference between the corresponding MAP and IOP during 24 h, that is, we matched the MAP measurements closest to the time when the IOP was measured.

Statistical analysis

For database management and statistical analysis, we used SAS software, version 9.4 (SAS Institute, Cary, North

Carolina, USA), maintenance level 5. We compared means by *t* tests or Wilcoxon–Mann–Whitney, and proportions by Fisher exact test. We identified potential covariables based on their biological relevance to glaucoma or their possible role as confounders [1,13], and additionally accounted models for the time-difference between the baseline visual field test and ambulatory blood pressure monitoring. All analyzes were stratified by NTG and POAG.

To evaluate glaucoma progression, we used the change in mean deviation during follow-up period, expressed as decibels (dB), obtained from the visual field tests. We studied the association of glaucoma progression with 24-h MAP dysregulations, 24-h IOP and 24-h OPP by implementing unadjusted and adjusted linear mixed models. In studies of glaucoma progression, mixed modeling has been suggested as a preferable method to investigate the progression of glaucoma disease as the outcome of interest (e.g. visual field tests) is usually continuously measured multiple times during follow-up visits [14,15]. Mixed models allowed us to introduce a random-effect accounting for clustering of the observations within participants while accounting for correlation between eyes. The introduction of a random-effect takes into account the variation in the baseline mean deviation measurements for each participant as they differ [16,17]. Including follow-up time as an intercept in the random statement allows us to construct longitudinal linear mixed models. Subsequently, we derived from mixed modeling the predicted longitudinal mean deviation to investigate the contribution of 24-h MAP dysregulations and reduced 24-h OPP. As supplementary analysis, we performed cross-sectional analyses by using baseline mean deviation, and applied linear regression models instead of mixed modelling to examine the association of mean deviation with ambulatory MAP variability, 24-h IOP, and OPP. Significance was a two-tailed α level of 0.0 or less5.

RESULTS

Demographics and clinical characteristics

The mean age at the baseline visual field test was 68.3 years, and 53.2% ($n = 141$) patients were women (Table 1). The prevalence of office, 24-h (based on the 24-h SBP and 24-h DBP levels), and 24-h MAP hypertension ranged between 53.6 and 83.6%, and less than 15.5% were on antihypertensive medication. Table S2, http://links.lww.com/HJH/C260 contains the antihypertensive medications registered. Ambulatory blood pressure measures were similar between NTG and POAG ($P \geq 0.122$).

Ophthalmologic characteristics

The following IOP records were significantly ($P \leq 0.045$) higher in POAG than NTG (Table 2); maximum untreated IOP (24 vs. 18 mmHg), IOP at baseline (14 vs. 12 mmHg), visit–to-visit mean IOP (12 vs. 10 mmHg), visit-to-visit VIM_{iop} (1.6 vs 1.1 mmHg), 24-h mean IOP (12 vs. 11 mmHg), 24-h VIM_{iop} (1.70 vs 1.46 mmHg), the maximum IOP value in 24 h (14 vs 12 mmHg). Other ophthalmic characteristics distributed similar between the two groups ($P \geq 0.065$). The median follow-up time was 8 years. The mean deviation at baseline and last follow-up visit was −8 and −11 dB. Table S2, http://links.lww.com/HJH/C260 listed the type and number of medications registered from NTG and POAG patients.

TABLE 1. Baseline characteristics of glaucoma patients

Characteristic	NTG ($n = 155$)	POAG ($n = 110$)	*P* value[a]
Demographics			
Women [*n* (%)]	96 (61.9)	45 (40.9)	<0.001
Age at first visual field test (years)	68.1 ± 10.9	68.5 ± 10.8	0.761
Clinical characteristics			
Current smoking [*n* (%)]	6 (3.9)	3 (2.7)	0.612
Drinking alcohol [*n* (%)]	28 (18.1)	23 (20.9)	0.563
BMI (kg/m^2)	24.8 ± 3.5	25.7 ± 3.4	0.038
Obesity [*n* (%)]	11 (7.1)	14 (12.7)	0.122
Dyslipidemia [*n* (%)]	9 (5.8)	6 (5.4)	0.903
Diabetes mellitus [*n* (%)]	22 (14.2)	14 (12.7)	0.731
Previous cardiovascular diseases [*n* (%)]	11 (7.1)	6 (5.4)	0.591
Office hypertension [*n* (%)][b]	112 (72.3)	92 (83.6)	0.030
Office MAP (mmHg)	97.7 ± 13.6	102.0 ± 10.9	0.007
Antihypertensive treatment [*n* (%)]	24 (15.5)	7 (6.4)	0.023
Ambulatory BP level			
24-h hypertension [*n* (%)][b]	86 (55.5)	59 (53.6)	0.766
24-h MAP hypertension [*n* (%)][c]	97 (62.6)	70 (63.6)	0.861
24-h MAP level (mmHg)	96.3 ± 9.8	96.2 ± 9.4	0.925
24-h MAP VIM (mmHg)	11.6 ± 3.1	11.9 ± 2.9	0.373
Dips[d]			
Duration of extreme dips (min)	105 (90–121)	95 (85–120)	0.091
Extreme dips – 24-h MAP (mmHg)	72.2 ± 13.4	71.7 ± 1.7	0.737
Extreme dips – forgoing reading (mmHg)	−20.9 ± 5.6	−20.5 ± 5.6	0.592
Ratio extreme dip/forgoing reading (mmHg)	0.81 ± 0.04	0.81 ± 0.04	0.386

Values are arithmetic mean ± standard deviation or median (interquartile range). The median of the number of 24-h blood pressure (BP) recordings were the same between NTG and POAG (70 vs. 71; $P = 0.062$). MAP, mean arterial pressure; NTG, normal-tension glaucoma; POAG, primary open-angle glaucoma; VIM, variability independent of the mean.
[a]*P* values denote the significance of the difference in baseline characteristics between NTG and POAG patients.
[b]Office and 24-h hypertension defined based on SBP and DBP. The thresholds were at least 130/80 mmHg and at least 125/75 mmHg for office and 24-h hypertension; respectively.
[c]24-h MAP hypertension defined as an oscillometric calculated 24-h MAP equal or greater than 92 mmHg.
[d]Dips refer to the five readings with the largest drop compared with the previous reading within-in individual 24-h MAP recordings.

TABLE 2. Ophthalmic clinical characteristics of glaucoma patients

Ophthalmologic phenotypes	NTG ($n = 155$)	POAG ($n = 110$)	*P* value[a]
Cup-to-disc ratio	0.85 (0.75–0.93)	0.85 (0.75–0.93)	0.505
Maximum untreated IOP (mmHg)	18 (16–20)	24 (22–28)	<0.001
IOP closest to first visual field test (mmHg)	12 (10–14)	14 (11–18)	<0.001
Visit-to-visit mean IOP (mmHg)	10.5 ± 2.1	12.3 ± 2.5	<0.001
Visit-to-visit VIM IOP (mmHg)	1.14 (0.60–1.70)	1.60 (1.11–2.22)	<0.001
24-h IOP assessment			
Number of IOP recordings (n)	6 (5, 6)	5 (5, 6)	0.386
24-h mean IOP (mmHg)	10.9 ± 1.4	12.2 ± 1.8	<0.001
24-h VIM IOP (mmHg)	1.46 ± 0.51	1.70 ± 0.67	0.045
Maximum IOP in 24 h (mmHg)	12.6 ± 1.9	14.1 ± 2.1	<0.001
24-h ocular perfusion pressure			
24-h mean OPP[b] (mmHg)	53.8 ± 6.2	50.7 ± 4.9	0.009
Maximum OPP in 24 h[†] (mmHg)	56.9 ± 6.7	54.1 ± 6.0	0.041
Minimum OPP in 24 h[†] (mmHg)	48.0 ± 6.4	45.4 ± 5.6	0.044
IOP-lowering treatment			
Eye drops medications [*n* (%)]	63 (40.7)	46 (41.8)	0.848
Surgical intervention [*n* (%)]	40 (25.8)	40 (36.4)	0.065
Outcome variable			
Number of visual field tests (*n*)	10 (6–17)	11 (6, 20)	0.282
Follow-up time (years)	8 (3–11)	9 (4, 12)	0.067
Mean deviation at baseline (dB)	−8 (−12 to −4)	−8 (−14 to −3)	0.850
Mean deviation at last follow-up (dB)	−11 (−16 to −5)	−11 (−16 to −6)	0.728
Absolute change of mean deviation (dB)	−2 (−6 to 1)	−2 (−5 to 1)	0.919

Full description of the IOP-lowering medications is given in Table S2, http://links.lww.com/HJH/C260. The value of *x* to estimated visit-to-visit VIM_{iop} was 1.10. IOP, intraocular pressure; NTG, normal-tension glaucoma; OPP, ocular perfusion pressure; POAG, primary open-angle glaucoma; VIM, variability independent of the mean.
[a]*P* values denote the significance of the difference between NTG and POAG patients.
[b]Maximum OPP in 24 h refers to the highest OPP level estimated from the difference of the corresponding MAP and IOP recordings during 24 h. We matched the MAP closest to the IOP. Minimum was the lowest OPP level estimated using the same approach.

In Figure S2, http://links.lww.com/HJH/C260, we displayed the average IOP during the follow-up period.

Twenty-four hour mean arterial pressure dysregulations

In univariate linear mixed models, a higher variability and extreme dips in the 24-h MAP were associated with glaucoma progression in patients with POAG ($P <= 0.008$, Table 3). After accounting for confounders, every +3 mmHg increase in the 24-h VIM_{map} was associated with a −2.07 dB longitudinal change in the mean deviation ($P < 0.001$). For each +30 min, duration of dips was associated with a −0.84 dB longitudinal change in the mean deviation. For the remaining indexes quantifying dips in the 24-h MAP, a lower change in the mean deviation was associated with extreme dips minus 24-h MAP (−2.84 dB

TABLE 3. Mixed models for the association of longitudinal changes in the mean deviation in relation to variability and dips in the 24-h mean arterial pressure in patients with normal-tension glaucoma and primary open-angle glaucoma

	Longitudinal changes in mean deviation (dB)			
	Unadjusted		Adjusted[b]	
Variability and dips in the MAP	Estimate (95% CI)[a]	*P* value	Estimate (95% CI)[a]	*P* Value
NTG (no patients 155/306 eyes/no observations 3868[c])				
24-h MAP VIM, +3 mmHg	0.25 (−0.56 to 1.06)	0.539	0.43 (−0.45 to 1.31)	0.340
Dips				
Duration of extreme dips, +30 min	0.18 (−0.57 to 0.92)	0.644	0.14 (−0.64 to 0.93)	0.722
Extreme dips minus 24-h MAP, −10 mmHg	0.36 (−0.25 to 0.97)	0.245	0.44 (−0.44 to 1.32)	0.325
Extreme dips minus forgoing reading, −6 mmHg	0.14 (−0.73 to 1.01)	0.750	0.20 (−0.79 to 1.19)	0.691
Ratio extreme dip/forgoing reading, −0.05 mmHg	0.17 (−0.76 to 1.10)	0.723	0.13 (−0.89 to 1.14)	0.804
POAG (No patients 110/210 eyes/no observations 3132[c])				
24-h VIM MAP level, +3 mmHg	−1.67 (−2.73 to −0.60)	0.002	−2.07 (−3.21 to −0.94)	<0.001
Dips				
Duration of extreme dips, +30 min	0.99 (0.26–1.72)	0.008	0.84 (0.07–1.61)	0.033
Extreme dips minus 24-h MAP, −10 mmHg	−1.75 (−2.58 to −0.93)	<0.001	−2.84 (−4.12 to −1.57)	<0.001
Extreme dips minus forgoing reading, −6 mmHg	−1.65 (−2.70 to −0.60)	0.002	−2.16 (−3.46 to −0.85)	0.001
Ratio extreme dip/forgoing reading, −0.05 mmHg	−2.31 (−3.39 to −1.23)	<0.001	−2.18 (−3.48 to −0.88)	0.001

MAP, mean arterial pressure; NTG, normal-tension glaucoma; POAG, primary open-angle glaucoma; VIM, variability independent of the mean.
[a]Estimates are longitudinal changes in the mean deviation expressed in decibels (dB), given with 95% confidence interval (CI). Negative changes indicate worsening in the visual field test.
[b]Mixed models accounted for the within-participant and eye side clustering, and were adjusted for sex, age, BMI, diabetes mellitus, dyslipidemia, smoking habits, in-office intraocular pressure (IOP) closest to the visual field test, past untreated (max) IOP, eye drops and surgical treatment for lowering the IOP, use of antihypertensive medication, follow-up time, and time-difference between the visual field test and the ambulatory BP monitoring.
[c]Number of repeated measurements used to estimate the association between changes in the mean deviation and ambulatory MAP variability.

per −10 mmHg dips; $P < 0.001$), minus (−2.16 dB per −6 mmHg dips; $P = 0.001$) and relative (−2.18 dB per −0.05 mmHg dips; $P = 0.001$) to the forgoing reading. In patients with NTG, indexes of 24-h MAP dysregulations were not related to changes in the mean deviation ($P \geq 0.245$). We observed the same findings using cross-sectional exploratory analyses (Table S3, http://links.lww.com/HJH/C260 and Figure S5, http://links.lww.com/HJH/C260). We did not find significant associations between changes in the mean deviation at baseline and blips in the 24-h MAP (Table S4, http://links.lww.com/HJH/C260).

Reduced ocular perfusion pressure

Overall, patients with POAG had lower OPP than NTG (Table 2; $P \leq 0.044$). The average 24-h OPP was 50.7 vs. 53.8 mmHg; $P = 0.009$), and the maximum and minimum OPP were 54.1 vs. 56.9 mmHg ($P = 0.041$) and 45.4 vs. 48.0 mmHg ($P \leq 0.041$); respectively. In adjusted linear mixed models (Table 4), higher variability in the visit-to-visit and 24-h IOP was associated with worse changes in the mean deviation in POAG (−2.09 and −2.41 dB change per +1 increase in VIM_{iop}: $P \leq 0.047$). Every 5 mmHg decrease in OPP perfusion pressure was associated with a −2.51 dB longitudinal changes in the mean deviation [confidence interval (CI), −3.91 to −1.12 dB; $P < 0.001$). Although non-significant, a higher maximum OPP was associated with a 0.86 dB improvement in the mean deviation ($P = 0.139$) whereas a minimum OPP was associated with −1.02 dB longitudinal changes in the mean deviation ($P = 0.088$). In cross-sectional exploratory analysis, we also observed that reduced OPP was related to lower mean deviation in patients with POAG (Table S5, http://links.lww.com/HJH/C260, $P \leq 0.009$ and Figure S4, http://links.lww.com/HJH/C260, $P \leq 0.024$, and Figure S4, http://links.lww.com/HJH/C260). In patients with NTG, lower OPP was not associated with changes in the mean deviation (Table S5, http://links.lww.com/HJH/C260).

We illustrate in Fig. 1 the contribution of 24-h OPP with variability and dips in the MAP in relation to the predicted longitudinal mean deviation in patients with POAG. In all panels, we observed that lower 24-h OPP was associated with greater predicted longitudinal mean deviation during the follow-up $P \leq 0.035$. Moreover, high variability (panel a, $P = 0.006$) or extreme dips (panels b and c, $P \leq 0.003$) in the MAP also related to worse mean deviation and resulted in worse glaucoma progression in the presence of lower OPP.

DISCUSSION

To the best of our knowledge, this is the first study addressing the association of glaucoma progression in relation to 24-h MAP dysregulations. During a follow-up time of 8 years, the IOP level remained within the normal range, but all IOP measures were significantly higher and varied more in POAG than NTG. The OPP was also more reduced in POAG than NTG (<54 vs. <57 mmHg). Twenty-four hour MAP dysregulations were associated with −2.84 to −2.07 dB longitudinal changes in the mean deviation in patients with POAG ($P \leq 0.001$). Patients with POAG experienced worse progression if reduced OPP was accompanied by 24-h MAP dysregulations. We did not observe significant associations in NTG.

Hypotension and hypertension have been identified as risk factors for glaucoma [6,18–23]. These conflicting findings result in a complex link between blood pressure and glaucoma [24]. In this study, we proposed that above and beyond the absolute level, dysregulations in the 24-h blood pressure defined as repetitive, and extreme drops in MAP due to excessive reading-to-reading MAP variability might be an alternative mechanism involved in open-angle glaucoma. We hypothesize that reduced OPP occurs when MAP extremely and repetitively drops over 24 h in the presence of normal or high MAP level as reported in our study. Moreover, contrary to cumulative evidence focusing on nocturnal hypotension [18–23], we observed that ∼80% of the extreme dips in the MAP occurred during the daytime. Clinicians should be aware that glaucomatous eyes might not be able to adequately autoregulate blood flow in case of extreme and repetitive MAP dips. This is clinically important considering that most glaucoma cases are

TABLE 4. Mixed models for the association of longitudinal changes in the mean deviation in relation to intraocular pressure and ocular perfusion pressure measures in patients with primary open-angle glaucoma

	Longitudinal changes in mean deviation (dB)			
	Unadjusted		Adjusted[b]	
Parameters of IOP and ocular perfusion pressure	Estimate (95% CI)[a]	*P* value	Estimate (95% CI)[a]	*P* value
Office IOP measurements taking during follow-up				
Visits-to-visit mean IOP, +2 mmHg	1.32 (0.52–2.12)	0.001	1.38 (0.57–2.19)	0.001
Visits-to-visit VIM IOP, +1 mmHg	−1.89 (-2.79 to −0.99)	<0.001	−2.09 (-3.03 to −1.16)	<0.001
24-h ocular perfusion pressure[c]				
24-h mean OPP[d], −5 mmHg	−3.00 (−1.56 to −4.44)	<0.001	−2.51 (−3.91 to −1.12)	<0.001
Maximum OPP in 24 h[e], +5 mmHg	2.78 (1.35–4.22)	0.001	0.86 (−0.30 to 2.01)	0.139
Minimum OPP in 24 h[e], −5 mmHg	−1.20 (−2.50 to 0.11)	0.072	−1.02 (−2.19 to 0.15)	0.088

IOP, intraocular pressure; MAP, mean arterial pressure; OPP, ocular perfusion pressure; VIM, variability independent of the mean.
[a]Estimates are longitudinal changes in the mean deviation expressed in decibels (dB), given with 95% confidence interval (CI). Negative changes indicate worsening in the visual field test.
[b]Mixed models accounted for the within-participant and eye side clustering, and were adjusted for sex, age, smoking habits, past (max) IOP registered, eye drops and surgical treatment for lowering the IOP, use of antihypertensive medication, time-difference between the visual field test and the ambulatory BP monitoring, and by the time-difference between the visual field test and the 24-h IOP assessment.
[c]Number of repeated measurements used to generate estimates. The number of patients was 39, 77 eyes, and 1057 observations 1057.
[d]24 h mean OPP is the difference between averaged 24-h MAP and 24-h IOP.
[e]Maximum OPP in 24 h refers to the highest OPP level estimated from the difference of the corresponding MAP and IOP recordings during 24 h. We matched the MAP closest to the IOP. Minimum OPP was the lowest OPP level estimated using the same approach.

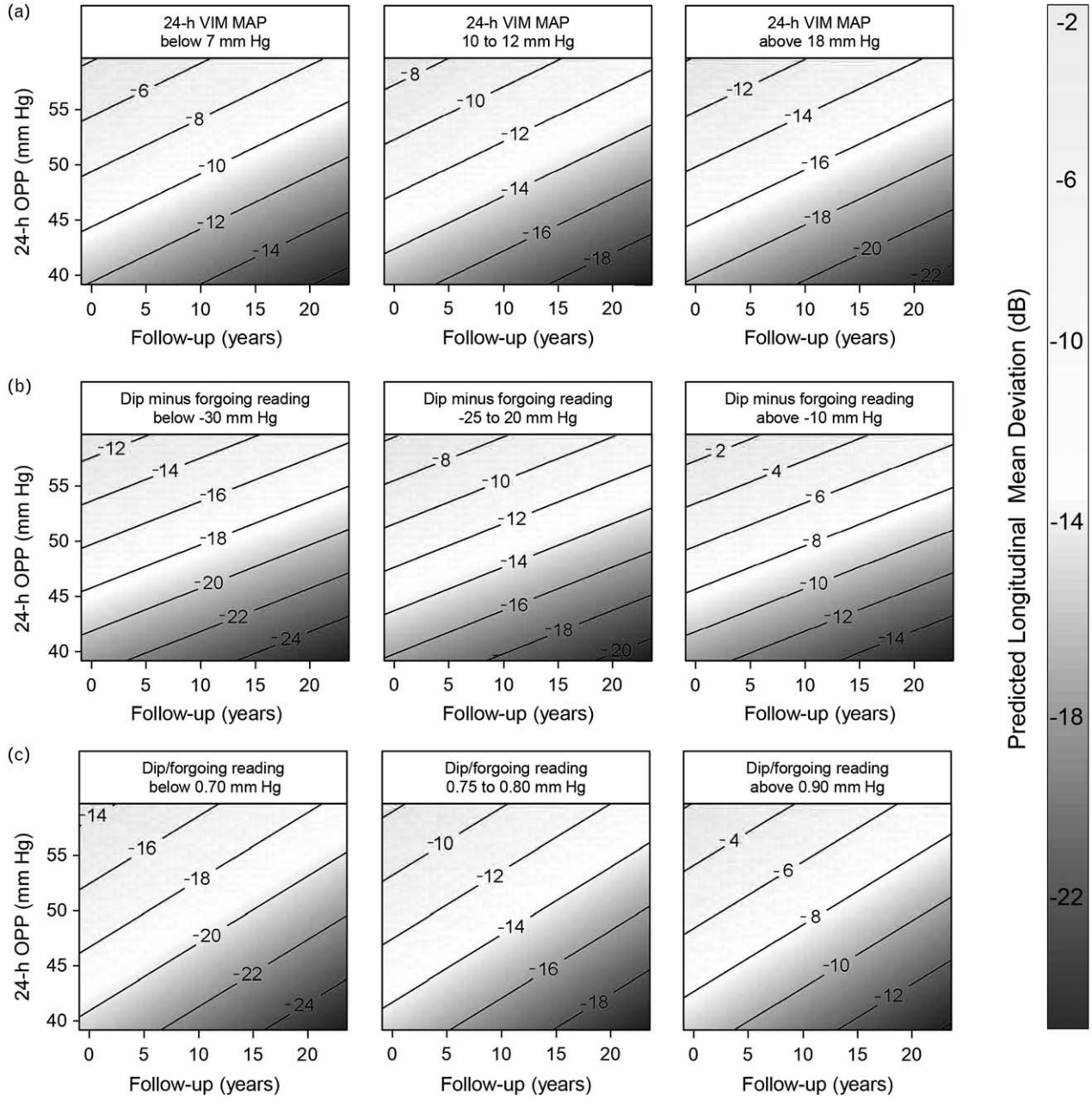

FIGURE 1 Predicted longitudinal mean deviation in patients with primary open-angle glaucoma in relation to ocular perfusion pressure (OPP) level along with variability and dips in the mean arterial pressure. The numbers within the contour graphics represent the predicted longitudinal mean deviation (dB) during follow-up time. The blue–white–red bar indicates the severity of the changes, where blue represents the smaller change and red the largest. We derived the predicted longitudinal mean deviation from mixed modelling while accounting for sex, age, BMI, diabetes mellitus, dyslipidemia, smoking habits, in-office intraocular pressure closest to the visual field test, maximum untreated intraocular pressure registered, eye drops and surgical treatment for lowering the intraocular pressure, use of antihypertensive medication, and time-difference between the visual field test and the ambulatory blood pressure monitoring, and by the time-difference between the visual field test and the 24-h intraocular pressure assessment. Vertical lines represent the 95% confidence interval. For panel a, the *P* values of the contribution of 24-h OPP and 24-h VIM_{map} were 0.031 and 0.067, respectively. The *P* values of 24-h OPP combined with dip measures were 0.004 and 0.003 for panel b, and 0.035 and less than 0.001 in panel c.

individuals with hypertension, potentially experiencing 24-h blood pressure dysregulations. Stabilizing extreme and drastic drops in MAP might provide unique opportunities to prevent open-angle glaucoma damage associated with reduced OPP.

Our second potential mechanism that combination of 24-h MAP dysregulation with reduced OPP results in worse glaucoma damage, should be contextualized to controversies regarding the interpretation of OPP. We estimated OPP as MAP − IOP based on studies documenting that reduced OPP increases glaucoma risk [25]. However, the inclusion of OPP with blood pressure or IOP in the same regression model leads to inaccurate interpretation of estimates [26]. These estimates would not correspond to the association of OPP level with glaucoma risk per se but to IOP and blood pressure levels instead. This has been described as a potential statistical flaw [26], limiting the use of OPP as a risk factor for glaucoma [24]. We did not disentangle such a flaw but we rather examined OPP and MAP using a different perspective, that is, reading-to-reading MAP variability.

In the presence of low, normal, or high level, the extent of 'variability' in MAP over 24 h provides information above the absolute MAP level. In fact, to study the independent association of variability with a given outcome, regression models should account for the level [27]. In our study, we included the 24-h OPP level and 24-h MAP dysregulations in the same mixed regression model which permits investigating the effect of MAP variability and drops occurring over 24 h at different OPP level. This approach is feasible when variability is the focus of study, offering opportunities to investigate novel vascular mechanisms in glaucoma disease.

The nonsignificant findings in NTG in our study might be explained by patients' characteristics and/or less compromised OPP in NTG than in POAG. On one hand, our study was restricted to Caucasian NTG, with lower IOP compared with other studies [19,23,28–39], and at lower risk of glaucoma progression compared with Hispanics, Asian, or African individuals [40–42]. On the other hand, we observed that POAG had lower OPP than NTG – as it has been previously reported [28–31] – driven by higher IOP levels. Therefore, 24-h MAP dysregulations combined with increased IOP should result in lower OPP in POAG than NTG [3,32]. Therefore, we do not rule out the hypothesis that 24-h MAP dysregulations might relate to NTG progression in different settings and cohorts. Moreover, this finding possibly underlies the importance of non-IOP/OPP-related risk factor for disease progression in NTG pointing towards an intrinsic vascular dysfunction, which needs further investigation [8,43–45].

Limitations

Our study should be interpreted in the context of its limitations. First, the study was not prospectively designed to test whether 24-h blood pressure dysregulation related to glaucoma progression. Second, the median number of IOP readings was five recordings between 0700 and 2300 h plus one recording in the morning after patient woke up, and no nocturnal readings were taken. Third, the criteria to perform ambulatory blood pressure monitoring in glaucoma patients was based on disease progression despite the IOP being kept within the normal range. This might result in a biased selection of glaucoma patients. However, we examined severe cases, numerous studies have also associated glaucoma prevalence, incidence, and progression in individuals with ambulatory blood pressure monitoring. Fourth, about 40% of the patients underwent surgical interventions to lower IOP. Although models accounted for these interventions, confounding cannot entirely be ruled out.

In conclusion, we found that 24-h MAP dysregulations defined as extreme and repetitive dips in MAP because of excessive variability in the MAP throughout a 24-h period are associated with worse progression of POAG damage independently of the 24-h MAP level. Stabilization of excessive 24-h MAP variability should result in less pronounced drops in MAP, which could represent a potential therapeutic target in patients with POAG to prevent reduced OPP or abnormal ocular blood flow. Large-scale studies and clinical trials are needed to validate the role of 24-h blood pressure dysregulations.

ACKNOWLEDGEMENTS

We gratefully acknowledge Renilde Wolfs (Research Unit Hypertension and Cardiovascular Epidemiology, Department of Cardiovascular Sciences, University of Leuven) for expert clerical assistance.

Availability of data and materials: the datasets generated and/or analyzed during the current study are not publicly available due to privacy regulations and local data sharing laws but are available from the corresponding author on reasonable request.

Funding: Internal Funds KU Leuven (STG-18-00379) supported the Research Unit Hypertension and Cardiovascular Epidemiology, Department of Cardiovascular Sciences, Leuven.

Conflicts of interest

I.S. is a consultant for: Alcon, AbbVie, EyeD Pharma, MONA, Horus Pharma, Santen, Théa Pharma and is a cofounder and shareholder of MONA. These conflicts of interests were not directly related to the subject or preparation of the submitted work. The other authors have no conflicts of interest.

REFERENCES

1. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma. A review. *JAMA* 2014; 311:1901–1911.
2. Flammer J, Orgül S, Costa VP, Orzalesi N, Krieglstein GK, Serra LM, *et al*. The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res* 2002; 21:359–393.
3. Van Keer K, Breda JB, Pinto LA, Stalmans I, Vandewalle E. Estimating mean ocular perfusion pressure using mean arterial pressure and intraocular pressure. *Invest Ophthalmol Vis Sci* 2016; 57:2260–12260.
4. Asefa NG, Neustaeter A, Jansonius NM, Snieder H. Autonomic dysfunction and blood pressure in glaucoma patients: the Lifelines Cohort Study. *Invest Ophthalmol Vis Sci* 2020; 61:25.
5. Melgarejo JD, Eijgen JV, Maestre GE, Al-Aswad LA, Thijs L, Mena LJ, *et al*. Open-angle glaucomatous optic neuropathy is related to dips rather than increases in the mean arterial pressure over 24-h. *Am J Hypertens* 2022; 35:703–714.
6. Melgarejo JD, Maestre GE, Mena LJ, Lee JH, Petitto M, Chavez CA, *et al*. Normal-tension glaucomatous optic neuropathy is related to blood pressure variability in the Maracaibo Aging Study. *Hypertens Res* 2021; 44:1105–1112.
7. Costa VP, Harris A, Anderson D, Stodtmeister R, Cremasco F, Kergoat H, *et al*. Ocular perfusion pressure in glaucoma. *Acta Ophthalmol* 2014; 92:e252–e266.
8. Pinto LA, Willekens K, Van Keer K, Shibesh A, Molenberghs G, Vandewalle E, Stalmans I. Ocular blood flow in glaucoma - the Leuven Eye Study. *Acta Ophthalmol* 2016; 94:592–598.
9. European Glaucoma Society. Terminology and guidelines for glaucoma. Dogma. 2008.
10. Weiá W, T"lle M, Zidek W, van der Giet M. Validation of the Mobil-O-Graph: 24 h-blood pressure measurement device. *BPM* 2010; 15:225–228.
11. Melgarejo JD, Yang WY, Thijs L, Li Y, Asayama K, Hansen TW, *et al*., International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome Investigators. Association of fatal and nonfatal cardiovascular outcomes with 24-hour mean arterial pressure. *Hypertension* 2021; 77:39–48.
12. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, *et al*. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *The Lancet* 2010; 375:895–905.
13. Melgarejo JD, Lee JH, Petitto M, Yépez JB, Murati FA, Jin Z, *et al*. Glaucomatous optic neuropathy associated with nocturnal dip in blood pressure: findings from the Maracaibo Aging Study. *Ophthalmology* 2018; 125:807–814.
14. Swaminathan SS, Berchuck SI, Jammal AA, Rao JS, Medeiros FA. Rates of glaucoma progression derived from linear mixed models

using varied random effect distributions. *Transl Vis Sci Technol* 2022; 11:16.
15. Jammal AA, Thompson AC, Mariottoni EB, Urata CN, Estrela T, Berchuck SI, *et al*. Rates of glaucomatous structural and functional change from a large clinical population: the Duke Glaucoma Registry Study. *Am J Ophthalmol* 2021; 222:238–247.
16. Fitzmaurice GM, Ravichandran C. A primer in longitudinal data analysis. *Circulation* 2008; 118:2005–2010.
17. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics* 1982; 38:963–974.
18. Graham SL, Fraco MS, Drance SM. Nocturnal hypotension: role in glaucoma progression. *Surv Ophthalmol* 1999; 43 Suppl:S10–S16.
19. Charlson ME, de Moraes CG, Link A, Wells MT, Harmon G, Peterson JC, *et al*. Nocturnal systemic hypotension increases the risk of glaucoma progression. *Ophthalmology* 2014; 121:2004–2012.
20. Plange N, Kaup M, Daneljan L, Predel H, Remky A, Arend O. 24-h blood pressure monitoring in normal tension glaucoma: night-time blood pressure variability. *J Hum Hypertens* 2006; 20:137–142.
21. Tsioufis C, Andrikou I, Thomopoulos C, Syrseloudis D, Stergiou G, Stefanadis C. Increased nighttime blood pressure or nondipping profile for prediction of cardiovascular outcomes. *J Hum Hypertens* 2011; 25:281–293.
22. Bowe A, Grünig M, Schubert J, Demir M, Hoffmann V, Kütting F, *et al*. Circadian variation in arterial blood pressure and glaucomatous optic neuropathy - systematic review and meta-analysis. *Am J Hyperten* 2015; 28:1077–1082.
23. Choi J, Jeong J, Cho H, Kook MS. Effect of nocturnal blood pressure reduction on circadian fluctuation of mean ocular perfusion pressure: a risk factor for normal tension glaucoma. *Invest Ophthalmol Vis Sci* 2006; 47:831–836.
24. Tanna AP. Blood pressure and glaucoma—a complex relationship. *JAMA Ophthalmol* 2023; 141:258–259.
25. Kim KE, Oh S, Baek SU, Ahn SJ, Park KH, Jeoung JW. Ocular perfusion pressure and the risk of open-angle glaucoma: systematic review and meta-analysis. *Sci Rep* 2020; 10:1–12.
26. Khawaja AP, Crabb DP, Jansonius NM. The role of ocular perfusion pressure in glaucoma cannot be studied with multivariable regression analysis applied to surrogates. *Invest Ophthalmol Vis Sci* 2013; 54:4619–4620.
27. Asayama K, Wei FF, Hara A, Hansen TW, Li Y, Staessen JA. Prognosis in relation to blood pressure variability: con side of the argument. *Hypertension* 2015; 65:1170–1179.
28. Sacc SC, Rolando M, Marletta A, Macri A, Cerqueti P, Ciurlo G. Fluctuations of intraocular pressure during the day in open-angle glaucoma, normal-tension glaucoma and normal subjects. *Ophthalmologica* 1998; 212:115–119.
29. Cheng J, Kong X, Xiao M, Sun X. Twenty-four-hour pattern of intraocular pressure in untreated patients with primary open-angle glaucoma. *Acta Ophthalmol* 2016; 94:e460–e467.
30. Tajunisah I, Reddy SC, Fathilah J. Diurnal variation of intraocular pressure in suspected glaucoma patients and their outcome. *Graefes Arch Clin Exp Ophthalmol* 2007; 245:1851–1857.
31. Agnifili L, Mastropasqua R, Frezzotti P, Fasanella V, Motolese I, Pedrotti E, *et al*. Circadian intraocular pressure patterns in healthy subjects, primary open angle and normal tension glaucoma patients with a contact lens sensor. *Acta Ophthalmol* 2015; 93:e14–e21.
32. Jammal AA, Berchuck SI, Mariottoni EB, Tanna AP, Costa VP, Medeiros FA. Blood pressure and glaucomatous progression in a large clinical population. *Ophthalmology* 2022; 129:161–170.
33. Hopf S, Schwantuschke D, Schmidtmann I, Pfeiffer N, Hoffmann EM. Impact of intraocular pressure fluctuations on progression of normal tension glaucoma. *Int J Ophthalmol* 2021; 14:1553-1559.
34. Sakata R, Aihara M, Murata H, Mayama C, Tomidokoro A, Iwase A, Araie M. Contributing factors for progression of visual field loss in normal-tension glaucoma patients with medical treatment. *J Glaucoma* 2013; 22:250–254.
35. El Mallah MK, Walsh MM, Stinnett SS, Asrani SG. Selective laser trabeculoplasty reduces mean IOP and IOP variation in normal tension glaucoma patients. *Clin Ophthalmol* 2010; 4:889–893.
36. Ramli N, Nurull BS, Hairi NN, Mimiwati Z. Low nocturnal ocular perfusion pressure as a risk factor for normal tension glaucoma. *Prevent Med* 2013; 57 Suppl:S47–S49.
37. Tokunaga T, Kashiwagi K, Tsumura T, Taguchi K, Tsukahara S. Association between nocturnal blood pressure reduction and progression of visual field defect in patients with primary open-angle glaucoma or normal-tension glaucoma. *Jpn J Ophthalmol* 2004; 48:380–385.
38. Lee K, Yang H, Kim JY, Seong GJ, Kim CY, Bae HW. Risk factors associated with structural progression in normal-tension glaucoma: Intraocular pressure, systemic blood pressure, and myopia. *Invest Ophthalmol Vis Sci* 2020; 61:35–135.
39. Sung KR, Lee S, Park SB, Choi J, Kim ST, Yun SC, *et al*. Twenty-four hour ocular perfusion pressure fluctuation and risk of normal-tension glaucoma progression. *Invest Ophthalmol Vis Sci* 2009; 50:5266–5274.
40. Broman AT, Quigley HA, West SK, Katz J, Munoz B, Bandeen-Roche K, *et al*. Estimating the rate of progressive visual field damage in those with open-angle glaucoma, from cross-sectional data. *Invest Ophthalmol Vis Sci* 2008; 49:66–76.
41. Wadhwa SD, Higginbotham EJ. Ethnic differences in glaucoma: prevalence, management, and outcome. *Curr Opin Ophthalmol* 2005; 16:101–106.
42. Wurster P, Harris A, Gonzalez AC, Adjei S, Verticchio Vercellin A, Mathew S, *et al*. Risk factors for open-angle glaucoma in persons of Latin American descent. *J Glaucoma* 2020; 29:217–225.
43. Lee SH, Kim GA, Lee W, Bae HW, Seong GJ, Kim CY. Vascular and metabolic comorbidities in open-angle glaucoma with low-and high-teen intraocular pressure: a cross-sectional study from South Korea. *Acta Ophthalmol* 2017; 95:e564–e574.
44. Kim JH, Lee TY, Lee JW, Lee KW. Comparison of the thickness of the lamina cribrosa and vascular factors in early normal-tension glaucoma with low and high intraocular pressures. *Korean J Ophthalmol* 2014; 28:473–478.
45. Barbosa-Breda J, Van Keer K, Abegão-Pinto L, Nassiri V, Molenberghs G, Willekens K, *et al*. Improved discrimination between normal-tension and primary open-angle glaucoma with advanced vascular examinations–the Leuven Eye Study. *Acta Ophthalmol* 2019; 97:e50–e56.