Relationship Between 24-Hour Mean Ocular Perfusion Pressure Fluctuation and Rate of Paracentral Visual Field Progression in Normal-Tension Glaucoma

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Purpose. To investigate the relationship between unstable mean ocular perfusion pressure (MOPP) and the rate of paracentral visual field (PVF) progression in patients with medically treated normal-tension glaucoma (NTG).

Methods. The data of 157 eyes of 122 patients with NTG who were followed for more than 6 years (mean follow-up, 8.7 years ± 12.6 months) and had more than 5 reliable standard visual field (VF) tests were analyzed retrospectively. Groups in the highest, middle, and lowest tertiles of 24-hour MOPP fluctuation (HMF, MMF, and LMF, respectively) were compared in terms of rates of change of mean thresholds in the central 10° (PVF), 10° to 24°, and global areas by using a linear mixed model. Clinical factors associated with rapid PVF progression were also investigated.

Results. The LMF and HMF groups did not differ significantly in the mean global rate of VF changes (−0.52 vs. −0.71 dB/y; $P = 0.07$). The HMF group had a significantly faster progression of VF defects in the central 10° area than the LMF group (−1.02 vs. −0.54 dB/y; $P < 0.001$) but did not differ in terms of progression of VF defects in the peripheral 10° to 24° area (−0.39 vs. −0.495 dB/y; $P = 0.425$). PVF progression was significantly associated with 24-hour MOPP fluctuation ($\beta = -0.31$, $P < 0.001$) and VF damage severity at initial presentation ($\beta = 0.134$, $P = 0.011$).

Conclusions. Medically treated NTG eyes with greater 24-hour MOPP fluctuations (HMF) had faster PVF defect progression than eyes with stable 24-hour MOPP (LMF). Twenty-four hour MOPP fluctuation associated significantly with PVF progression velocity.

Keywords: open-angle glaucoma, ocular perfusion pressure, mean ocular perfusion pressure fluctuation, paracentral visual field progression rate

The paracentral visual field (PVF), which includes the central 10° visual field (VF) area, is of paramount importance if a glaucoma patient is to enjoy normal daily activities. Several reports have shown that patients with glaucoma assign the greatest importance to tasks that use the PVF, such as reading.[1,2] Therefore, PVF preservation is a key concern in glaucoma management. Recently, Park et al.[3] showed that in patients with early glaucoma, parafoveal scotoma associates with disc hemorrhages and systemic risk factors, such as hypotension, migraine, Raynaud's phenomenon, and sleep apnea. In addition, Park et al.[3] reported that patients with normal-tension glaucoma (NTG) who have systemic autonomic dysfunction or abnormal nail capillaroscopy as a result of systemic vascular dysregulation, often present with an initial PVF defect.[4] This suggests that in NTG with PVF defects, the primary glaucoma pathogenesis might involve a vascular mechanism.

Previously, we reported that 24-hour mean ocular perfusion pressure (MOPP) instability correlates with glaucomatous VF damage at the initial presentation of NTG and is the most consistent risk factor for glaucoma.[5,6] In subsequent studies of NTG, large fluctuations of 24-hour MOPP due to excessive nocturnal dips of systemic blood pressure (BP) were found to associate strongly with a greater risk of glaucomatous VF progression, particularly in the PVF area.[7,8]

We hypothesized that NTG eyes with unstable 24-hour MOPP would experience faster VF progression in the PVF area than those with relatively stable 24-hour MOPP when followed over a long-term period. Therefore, the goal of the present study was to examine the velocity of both global and regional PVF progression in the same cohort of NTG patients with unstable 24-hour MOPP. The velocity of PVF progression in those patients was compared with that in patients with stable 24-hour MOPP. Finally, the relationship between various clinical risk factors and the rate of PVF progression was assessed.

Methods

Subjects

This was a retrospective study approved by the Asan Medical Center Institutional Review Board. The design of this study followed the principles of the Declaration of Helsinki. The medical records of 420 consecutive patients with NTG who were seen by a glaucoma specialist (MSK) between March 1996 and June 2011 at the glaucoma service of the Asan Medical Center, Seoul, Korea, were reviewed retrospectively. At the initial glaucoma workup, each patient underwent a comprehensive ophthalmological examination that included a review of his or her medical history, measurement of the best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, Goldmann applanation tonometry (GAT), gonioscopy, dilated funduscopic examination using a 90- or 78-diopter (D) lens, stereoscopic optic disc photography, and VF examination using standard automated perimetry (SAP). SAP testing was performed by using the full-threshold strategy of program 24-2 (Carl Zeiss Meditec, Dublin, CA). The central corneal thickness (CCT) of each patient was also obtained during initial presentation or follow-up by a trained technician who was masked to the patient status and examination data. For each patient, CCT was calculated as the average of three measurements obtained during the same visit by using ultrasound pachymetry (DGH-550 instrument; DGH Technology Inc., Exton, PA).

To diagnose NTG, all open-angle glaucoma (OAG) patients with bilateral IOP less than 22 mm Hg in the office hours underwent 24-hour IOP, BP, and MOPP evaluations. NTG patients had to have an optic disc of glaucomatous appearance, including diffuse or focal neural rim thinning; hemorrhage; enlarged cupping or nerve fiber layer defects indicative of glaucoma along with compatible glaucomatous VF loss, both confirmed and agreed on by two glaucoma specialists (YL, MSK); a BCVA better than 20/30; maximum bilateral IOP less than 22 mm Hg during in-hospital 24-hour IOP monitoring, as well as in the outpatient clinic using GAT; a normal anterior chamber; and an open angle on gonioscopic examination. Patients with evidence of intracranial or otolaryngeal lesions, histories of massive hemorrhage or hemodynamic crisis, previous use of antiglaucoma medication, presentation with any other ophthalmic disease that could result in VF defects, or histories of diabetes mellitus or eye surgery/laser treatment were excluded from the study. Eyes were defined as having glaucomatous VF defects if they met two of the following criteria, as confirmed by more than two reliable consecutive tests, in addition to compatibility with optic nerve appearance: (1) a cluster of three points with a probability of less than 5% on a pattern deviation (PD) map in at least one hemifield, and including at least one point with a probability of less than 1% or a cluster of two points with a probability of less than 1%; (2) a glaucoma hemifield test result outside 99% of the age-specific normal limit; and (3) a pattern SD (PSD) outside 95% of the normal limit. Reliable VF assessment was defined as a VF test with a false-positive error of less than 15%, a false-negative error of less than 15%, and a fixation loss of less than 20%. The first perimetric result was excluded from analysis to obviate learning effects. The second VF was performed within 2 to 4 weeks from the first perimetric analysis.

All patients had to meet the following additional inclusion criteria to enter the current retrospective study: newly diagnosed NTG without previous treatment, age older than 40 years, in-hospital 24-hour monitoring of IOP and BP, follow-up at our clinic for at least 6 years with visits at 6- to 12-month intervals, and adherence to antihypertensive glaucoma treatment (prostaglandin analogues, 67%; dorzolamide/timolol fixed combination, 22%; beta-blocker, 11%; and alpha-adrenergic agonist, 23%). Adherence was assessed based on a patient's response to the follow-up questionnaires filled out during return visits, and availability of at least five reliable VF datasets (after exclusion of the first reliable perimetry dataset) during follow-up whose mean deviation (MD) exceeded −20.00 dB without threat to fixation, as measured by a Humphrey field analyzer (HFA; Carl Zeiss Meditec). If surgical or laser treatment was considered due to VF progression, the eyes were excluded from the analysis. Patients with progressive lens opacity and BCVA less than 20/30 and other ocular diseases that could affect VF during follow-up were excluded from the study. The affected eye was selected in patients with unilateral disease. If both eyes of a patient had NTG and met inclusion criteria, both eyes were included in the analyses. Subjects on systemic antihypertensive or other hemodynamically active medications were not excluded.

Twenty-Four–Hour In-Hospital Monitoring of IOP and BP

All participants were admitted and went through in-hospital 24-hour monitoring of IOP and BP at the initial workup. The method has been described in detail elsewhere.[7,8] Briefly, the BP and IOP of each patient were evaluated in the hospital over 24 hours, with measurements being taken every 2 hours between 12 PM and 10 AM the following day, except for the period between midnight and 6 AM, during which time measurements were taken every 3 hours. When a patient was awake, a BP measurement was first obtained in the sitting position, followed by IOP measurements using a slit-lamp–mounted GAT, again in the sitting position. Systolic and diastolic BPs (SBP and DBP, respectively) were measured with a brachial sphygmomanometer (DS48-11CB; Welch Allyn, Skaneateles Falls, NY) on the upper left arm after the patient had been seated and rested for at least 5 minutes. IOP was next measured after the subject had been seated in the slit-lamp chair for at least 5 minutes. During the sleep period (midnight to 6 AM), patients were awakened and seated for at least 5 minutes before BP measurements were taken. Each patient was then asked to move to the slit-lamp chair for IOP measurement, which was performed after 5 minutes of rest in the sitting position. Patients were asked to refrain from any physical activity that could affect BP during admission. Meals were provided at 6:30 PM and 7:30 AM and did not include any alcohol or caffeine. During follow-up, each patient with VF progression as determined by a glaucoma specialist (MSK) was invited to undergo a repeat 24-hour in-hospital monitoring of IOP and BP to document any changes in 24-hour IOP and BP pattern.

MOPP Estimation

To calculate MOPP, mean arterial pressure (MAP) was calculated as follows: $MAP = DBP + [1/3 \times (SBP - DBP)]$.[9,10] It was thus possible to calculate MOPP at any specified time from the difference between MAP and IOP (substituting for venous pressure) as follows: $MOPP = 2/3 \times MAP - IOP$.[11–13]

Division of Patients Into Three Groups According to 24-Hour MOPP Fluctuation: The Highest, Middle, and Lowest Tertiles

The study patients were categorized into three groups on the basis of the degree of MOPP fluctuation during the initial 24-hour in-hospital IOP and BP measurements; namely, those in the highest, middle, and lowest tertiles of MOPP fluctuation

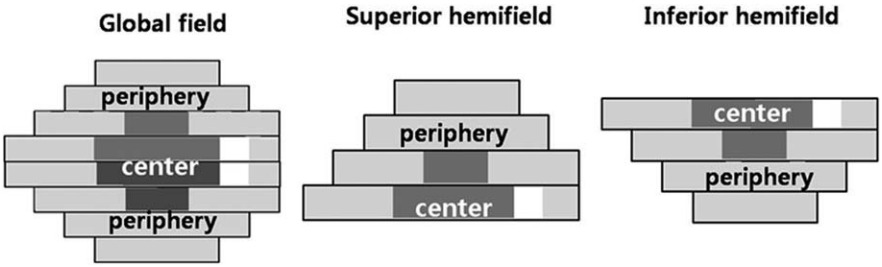

FIGURE 1. The central 10° (*center*) and 10° to 24° region (*periphery*) of the Humphrey 24-2 visual field was defined as illustrated. Two test locations within the blind spot (*white area*) were excluded.

(denoted as HMF, MMF, and LMF, respectively). Twenty-four hour MOPP fluctuation was defined as the amplitude of the 24-hour MOPP variation. It was calculated as SD of 11 MOPP values obtained during 24 hours, as SD is considered the robust estimate of IOP fluctuation and less subject to outlier values of IOP and BP.[7,14,15] In total, 157 eyes of 122 patients with NTG who met the inclusion criteria were analyzed. Therefore, the HMF, MMF, and LMF groups contained 52, 52, and 53 patients, respectively.

Location of VF Defects

To determine the location of VF defects and their progression, the HFA 24-2 field was divided into two areas, namely the central 10° and peripheral 10° to 24° areas. Two test locations within the blind spot were excluded. The central 10° and 10° to 24° regions were each further divided into superior and inferior hemifields to investigate the incidence and rate of VF progression (Fig. 1). The rationale for analyzing superior and inferior hemifields separately was that VF progression in NTG patients might show different rates depending on the hemifield location.[16,17] The VF defect clusters at baseline and the final VF test were categorized according to their location in the central 10° or 10° to 24° regions. Central VF defects were defined as clusters of three significant points in the central 10° with a probability of less than 5% on the PD map or two significant points in the central 10° with a probability of less than 1% on the PD map. Peripheral VF defects were defined by clusters in the 10° to 24° region. If the single cluster of three adjacent points overlapped both the central 10° and the peripheral 10° to 24° region (based on the PD plot), the area containing two points was considered to bear the VF defect.

Estimation of VF Progression Rate

All individual values at each test location of the total deviation (TD) plot within the central 10° arc and outside the 10° arc were averaged to yield the central mean threshold (MT) and peripheral MT, respectively. From each follow-up VF of the 157 eligible patients, the MT of the global, central 10°, peripheral 10° to 24°, superior central 10°, inferior central 10°, peripheral superior 10° to 24°, and peripheral inferior 10° to 24° regions of VF based on TD were collected. The change in MT from the baseline MT (second VF test) of each area from the same eye was used to calculate the progression rate.

Definition of VF Progression

The probability levels considered to be statistically significant for VF progression were *P* less than 0.0125 for the slope of the superior and inferior central and peripheral zones, *P* less than 0.025 for the slope of the central 10° and peripheral 10° to 24° zones, and *P* less than 0.05 for the slope of the global 24-2 zone (MT of total deviation).[18,19]

Statistical Analysis

Sample size calculation was based on the assumption that a 20% difference in PVF progression (central 10°) between the control (eyes in the LMF) and study group (eyes in the HMF) was clinically relevant. Approximately 33 patients were required in each group, given an alpha of 0.05 and 1-beta of 0.80. A statistical power of 80% was chosen to decrease the risk of a false-negative result. A total sample size of at least 99 eyes was needed to meet the condition described above.

Categorical variables are presented as numbers and percentages, and the χ^2 test was used to compare the HMF, MMF, and LMF groups in terms of clinical characteristics. Continuous variables are expressed as means ± SDs, or as medians ± interquartile ranges, as appropriate. One-way ANOVA was used for comparisons. The post hoc test with the Scheffe method was used for multiple comparisons. Bonferroni correction was used for multiple comparisons. The groups were compared in terms of the frequencies of VF defects in each region by using the χ^2 test.

To calculate the progression rate, which is the slope of the MT of each zone, and the factors associated with VF progression in the central 10° zone, a linear mixed model was used to account for the correlated nature of the outcomes within an individual's eye.[20] Models were fitted with fixed coefficients (fixed effects) of follow-up time (years), patient's age (years), spherical equivalent (D), baseline IOP, mean follow-up IOP, baseline MD, and baseline PSD, with random intercepts and coefficients (random effects) of patient and eye (each eye nested within subject) for the effect of time. The HMF, MMF, and LMF groups were classified on the basis of the degree of MOPP fluctuation derived from the initial 24-hour in-hospital IOP and BP measurements without taking follow-up IOP data into account and compared in terms of their VF progression rates in each region. The probability levels considered to be statistically significant were *P* less than 0.0125 for the comparison of the superior and inferior central 10° and peripheral 10° to 24° zones, *P* less than 0.025 for the comparison of the central 10° and peripheral 10° to 24° zones, and *P* less than 0.05 for the comparison of the global 24-2 area.[18,19]

Finally, linear mixed models were constructed to predict the PVF (central 10° area) progression rate based on spherical error, age, sex, baseline IOP, follow-up mean IOP, 24-hour mean IOP, 24-hour IOP fluctuation, baseline MD, baseline PSD, 24-hour mean SBP, 24-hour mean DBP, 24-hour mean MOPP, 24-hour SBP fluctuation, 24-hour DBP fluctuation, and 24-hour MOPP fluctuation. *P* value less than 0.05 was considered to be statistically significant. All statistical analyses were performed by using SAS software version 9.1.3 (SAS, Inc., Cary, NC) and SPSS software version 17.0 (SPSS, Inc., Chicago, IL).

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Table 1. Comparison of the Demographics of the Three Groups Classified on the Basis of 24-Hour MOPP Fluctuation (LMF, MMF, and HMF)

	LMF, $n = 53$	MMF, $n = 52$	HMF, $n = 52$	*P* Value
Age, y	54.2 ± 11.4	55.8 ± 12.6	56.1 ± 11.2	0.481
Sex, M/F, n	24/18	20/20	13/27	0.741
SE, diopters	−0.81 ± 2.50	−0.64 ± 2.30	−0.95 ± 2.10	0.388
CCT, μm	530.2 ± 34.8	538.7 ± 28.5	528.4 ± 30.8	0.150
VF MD, dB	−5.42 ± 5.28	−4.90 ± 5.60	−5.35 ± 5.64	0.770
Center 10° VF MD, dB	−3.08 ± 3.12	−3.12 ± 2.85	−4.21 ± 3.81	0.0547
Sup center 10° VF MD, dB	−3.67 ± 3.95	−4.24 ± 3.75	−6.21 ± 5.21	0.031
Inf center 10° VF MD, dB	−2.50 ± 2.01	−2.02 ± 1.98	−2.86 ± 1.92	0.687
Pph 10°–24° VF MD, dB	−6.85 ± 5.01	−6.42 ± 5.24	−5.44 ± 4.85	0.745
Sup Pph 10°–24° VF MD, dB	−8.85 ± 6.12	−8.85 ± 6.12	−8.85 ± 6.12	0.680
Inf Pph 10°–24° VF MD, dB	−4.85 ± 4.01	−4.19 ± 3.82	−5.98 ± 4.01	0.890
VF PSD, dB	5.88 ± 3.95	6.22 ± 4.82	5.88 ± 4.21	0.870
24-hour mean SBP, mm Hg	124.2 ± 12.4	124.6 ± 12.7	129.6 ± 16.2	0.380
24-hour mean DBP, mm Hg	74.80 ± 9.01	75.10 ± 9.26	76.20 ± 9.45	0.840
24-hour mean MOPP, mm Hg	46.40 ± 6.21	46.80 ± 6.71	47.90 ± 6.35	0.510
24-hour SBP fluctuation, mm Hg	3.01 ± 2.05	8.80 ± 3.28	14.20 ± 4.89	<0.001*
24-hour DBP fluctuation, mm Hg	2.63 ± 2.82	8.20 ± 3.89	12.90 ± 4.90	<0.001*
24-hour MOPP fluctuation, MOPP SD (range)	3.55 ± 0.41 (2.28–4.68)	7.93 ± 0.68 (6.35–9.0)	13.10 ± 1.06 (11.15–14.96)	<0.001*
Mean baseline IOP, mm Hg	15.40 ± 2.71	16.20 ± 2.71	15.00 ± 2.11	0.870
24-hour mean IOP, mm Hg	14.70 ± 2.51	14.20 ± 2.22	13.90 ± 2.01	0.740
24-hour IOP fluctuation, mm Hg	1.88 ± 0.43	1.68 ± 0.61	1.77 ± 0.66	0.380
Mean follow-up IOP, mm Hg	13.10 ± 1.65	13.20 ± 1.65	12.8 ± 1.55	0.520

Pph, peripheral; Sup, superior; Inf, inferior; SE, spherical equivalent.
* Statistically significant.

Results

Demographics and Characteristics of Three Groups

In total, 157 eyes of 122 patients with NTG who met the inclusion criteria were analyzed. Of the 122 patients, 60 (49.2%) were men, 62 (50.8%) were women, and all were Koreans. Female sex was more common in the HMF group: 65%, 49%, and 45% were female in the HMF, MMF, and LMF groups, respectively. However, this trend did not achieve statistical significance ($P = 0.741$, ANOVA, Table 1). The average age at initial presentation was 55.2 ± 11.4 years. The three groups did not differ significantly in terms of baseline age ($P = 0.481$, ANOVA, Table 1).

The average number of VF examinations was 9.7 ± 2.5 (range, 5–15 after excluding the first VF examination) and the mean follow-up period was 8.7 years ± 12.6 months (76–156 months). The three groups did not differ significantly in terms of the number of VF tests and the average follow-up period ($P = 0.723$ and 0.662, respectively, ANOVA). The initial MD of all eyes was −5.22 ± 5.38 dB, and the PSD was 5.94 ± 4.53 dB. The three groups did not differ significantly in terms of initial MD and PSD ($P = 0.77$ and 0.87, respectively, ANOVA).

The three groups differed significantly in terms of 24-hour SBP, DBP, and MOPP fluctuation (all $P < 0.001$). Comparisons of the three groups in terms of other variables are summarized in Table 1.

Validation of classification (LMF, MMF, and HMF) was performed in those patients who underwent second 24-hour MOPP evaluations at various follow-up points (6 months to 4 years). Validation group consisted of 82 eyes of 64 NTG subjects (HMF: 40 eyes, MMF: 20 eyes, and LMF: 22 eyes from 17 bilateral patients and 48 unilateral patients). After random selection of 20 eyes from the HMF group, all 20 eyes that initially belonged to the HMF group remained HMF on repeat examination (MOPP SD range, 9.44–13.76 mm Hg). Eighteen eyes from the MMF group at baseline were categorized in the MMF group (MOPP SD range, 5.20–8.05 mm Hg), whereas two eyes became LMF on repeat examination. Likewise, 18 eyes from 20 LMF eyes at baseline belonged to the LMF group (MOPP SD range, 1.95–4.35) on repeat examination, whereas 2 LMF eyes were reclassified in the MMF group with increased 24-hour MOPP SDs (5.8 and 6.2 mm Hg).

Table 2. Change in the Number of VF Defects in the Central 10° or the Peripheral 10° to 24° at the Last Follow-up Relative to Baseline in the Three Groups Classified on the Basis of 24-Hour MOPP Fluctuation (LMF, MMF, and HMF)

	Baseline	Last Follow-up	*P* Value
Total, 157 eyes, *n* (%)			
Center	64 (40.8)	97 (61.8)	0.023*
Pph	93 (59.2)	123 (78.3)	0.102
LMF, 53 eyes, *n* (%)			
Center	16 (30.2)	20 (37.7)	0.623
Pph	33 (62.3)	46 (86.8)	0.031*
MMF, 52 eyes, *n* (%)			
Center	21 (40.4)	27 (51.9)	0.410
Pph	34 (65.4)	43 (82.7)	0.145
HMF, 52 eyes, *n* (%)			
Center	27 (51.9)	50 (96.1)	0.011*
Pph	26 (50.0)	34 (65.4)	0.34

* Statistically signficant.

Frequency of Central 10° VF Defects in the Three Groups

The whole cohort showed a significant increase in VF defect from baseline to the last follow-up in the center ($P = 0.023$) but

Table 3. Comparison of the Three Groups Classified on the Basis of 24-Hour MOPP Fluctuation (LMF, MMF, and HMF) in Terms of the Frequencies of VF Defects in the Central 10° or the Peripheral 10° to 24° at Baseline or the Last Follow-up

	LMF, 53 Eyes, *n* (%)	MMF, 52 Eyes, *n* (%)	HMF, 52 Eyes, *n* (%)	*P* Value*	*P* Value†	*P* Value‡
Baseline						
Center 10°	16 (30.2)	21 (40.4)	27 (51.9)	0.008§	0.055	0.067
Pph 10°–24°	33 (62.3)	34 (65.4)	26 (50.0)	0.041§	0.040§	0.78
Last follow-up						
Center 10°	20 (37.7)	27 (51.9)	50 (96.1)	0.001§	0.012§	0.085
Pph 10°–24°	46 (86.8)	43 (82.7)	34 (65.4)	0.035§	0.053	0.75

* LMF versus HMF.
† MMF versus HMF.
‡ LMF versus MMF.
§ Statistically significant.

not in the periphery ($P = 0.102$). This pattern was also observed for the HMF group ($P = 0.011$ and 0.34, respectively). The LMF or MMF groups did not differ in terms of VF frequencies over time in either VF region (Table 2).

Sixteen (30.2%), 21 (40.4%), and 27 (51.9%) of the eyes of the LMF, MMF, and HMF groups, respectively, had VF defects within the central 10° at the baseline VF examination (Table 3). These between-group differences were significant (LMF versus HMF; $P = 0.008$). At the last follow-up VF examination, these numbers had risen to 20 (37.7%), 27 (51.9%), and 50 (96.1%), respectively (Table 3). These between-group differences were also statistically significant (LMF versus HMF, $P = 0.001$; MMF versus HMF, $P = 0.012$, respectively).

Incidence of Central 10° VF Defect Progression in the Three Groups

In terms of progression of the VF defects in the central 10°, 7 (13.2%), 8 (15.3%), and 27 (51.2%) eyes of the LMF, MMF, and HMF groups, respectively, showed negative slopes (as shown by regression coefficients [RCs] of the MT) with *P* values below 0.025. The between-group differences in incidence were also significant ($P = 0.011$) (Table 4). The central 10° area was then divided into superior and inferior sectors. The between-group difference in incidence was also significant in both the superior and inferior central 10° areas ($P = 0.008$ and 0.012, respectively) (Table 4).

Rates of Central 10° VF Progression in the Three Groups

Table 5 shows the RCs of the global area (central 10° + 10°–24° areas), the entire 10° and 10° to 24° areas, and the superior and inferior central 10° and peripheral 10° to 24° areas. The three groups did not differ significantly in terms of the global area. However, the HMF group showed significantly greater progression in the entire central 10°, the superior central 10°, and the inferior central 10° areas than the MMF and LMF groups ($P < 0.0125$ for all combined comparisons, Figs. 2a-d).

Predictors of Fast PVF Progression

In the linear mixed model, the coefficients of the interaction between VF progression rate in the central 10° area and the degree of 24-hour MOPP fluctuation were negative and statistically significant ($P < 0.001$). A lower baseline MD value also associated significantly with a faster rate of central 10° VF progression ($P = 0.011$) (Table 6). No significant association was found between the rate of VF change and any other clinical factors including 24-hour SBP and DBP fluctuation.

Discussion

To our knowledge, this is the first report regarding the effect of unstable 24-hour MOPP on the velocity of PVF progression in NTG patients followed for up to 13 years (mean follow-up: 8.7 years). Such NTG cases constitute the predominant form of glaucoma in our part of Asia. The current study showed that HMF and LMF patients differed in terms of the incidence of VF defects within the central 10° at baseline. Moreover, at the final follow-up, the eyes of the HMF group were more likely to have central VF defects than the eyes from the other groups. This finding was further validated by the results of the linear mixed model after controlling for various covariates: more eyes in the HMF group showed PVF progression than those in the LMF group (Tables 2–4).

With respect to PVF progression rate, the present study showed that patients with unstable 24-hour MOPP (HMF

Table 4. Comparison of the Three Groups Classified on the Basis of 24-Hour MOPP Fluctuation (LMF, MMF, and HMF) in Terms of Incidence of Significant VF Defect Progression in the Central 10° Area and Peripheral 10° to 24° Area, in the Superior and Inferior Central 10° Areas, and in the Superior and Inferior Peripheral 10° to 24° Areas

Linear Mixed Model	LMF, 53 Eyes, *n* (%)	MMF, 52 Eyes, *n* (%)	HMF, 52 Eyes, *n* (%)	*P* Value
Central 10°	7 (13.2)	8 (15.3)	27 (51.9)	0.011*
Pph 10°–24°	14 (26.4)	11 (21.2)	10 (19.2)	0.550
Superior Central 10°	6 (11.3)	8 (15.3)	28 (53.8)	0.008*
Inferior Central 10°	7 (13.2)	7 (13.5)	24 (46.2)	0.012*
Superior Pph 10°–24°	10 (18.9)	7 (13.5)	8 (15.4)	0.775
Inferior Pph 10°–24°	11 (20.7)	7 (13.5)	9 (17.3)	0.75

* Statistically significant.

Table 5. Comparison of the Three Groups Classified on the Basis of 24-Hour MOPP Fluctuation (LMF, MMF, and HMF) in Terms of VF Defect Progression Rate (dB/y) in Global and Regional Areas

	LMF, 53 Eyes	MMF, 52 Eyes	HMF, 52 Eyes	*P* Value*	*P* Value†	*P* Value‡
Global	−0.52	−0.58	−0.71	0.07	0.24	0.65
Center 10°	−0.54	−0.678	−1.02	<0.001§	0.01§	0.08
Pph 10°–24°	−0.495	−0.473	−0.39	0.425	0.78	0.75
Sup Cent 10°	−0.64	−0.69	−1.28	<0.001§	<0.001§	0.77
Inf Cent 10°	−0.44	−0.401	−0.75	0.003§	<0.001§	0.765
Sup Pph 10°–24°	−0.592	−0.510	−0.42	0.520	0.588	0.582
Inf Pph 10°–24°	−0.402	−0.44	−0.36	0.723	0.685	0.81

Cent, center.
* LMF versus HMF.
† MMF versus HMF.
‡ LMF versus MMF.
§ Statistically significant.

group) progressed significantly faster than patients with stable 24-hour MOPP (LMF group), as indicated by the RCs that were derived from the linear mixed model analyses. The HMF group showed greater speed of PVF progression than the LMF group in the central 10° and both the superior and inferior central 10°. Similar findings were also obtained when the HMF group was compared with the MMF group in terms of PVF progression rates at various central locations.

Previous studies have shown that VF progression occurs more rapidly in the superior hemifield than the inferior hemifield in OAG.[16,17,21,22] Cho and Kee[17] recently reported that the VF progression rate of the superior central 10° (–0.911 dB/y) in NTG eyes with initial superior hemifield defects differed significantly from the VF progression rate of the inferior central 10° (–0.16 dB/y) in NTG eyes with initial inferior hemifield defects. Although it is difficult to compare studies owing to variations in the study populations and the research design, our results are in line with those of Cho and Kee[17] in that the superior 10° zone in the HMF group (–1.28 dB/y) showed more rapid VF progression than the inferior 10° zone (–0.75 dB/y, $P < 0.0125$). Notably, we found that the rate of PVF progression in the inferior 10° zone of the HMF group (–0.75 dB/y) was much higher than the rate recorded by Cho and Kee[17] (–0.16 dB/y). Our findings suggest that OAG eyes with unstable 24-hour MOPP (HMF) have a relatively fast rate of PVF progression in even the inferior 10° zone.

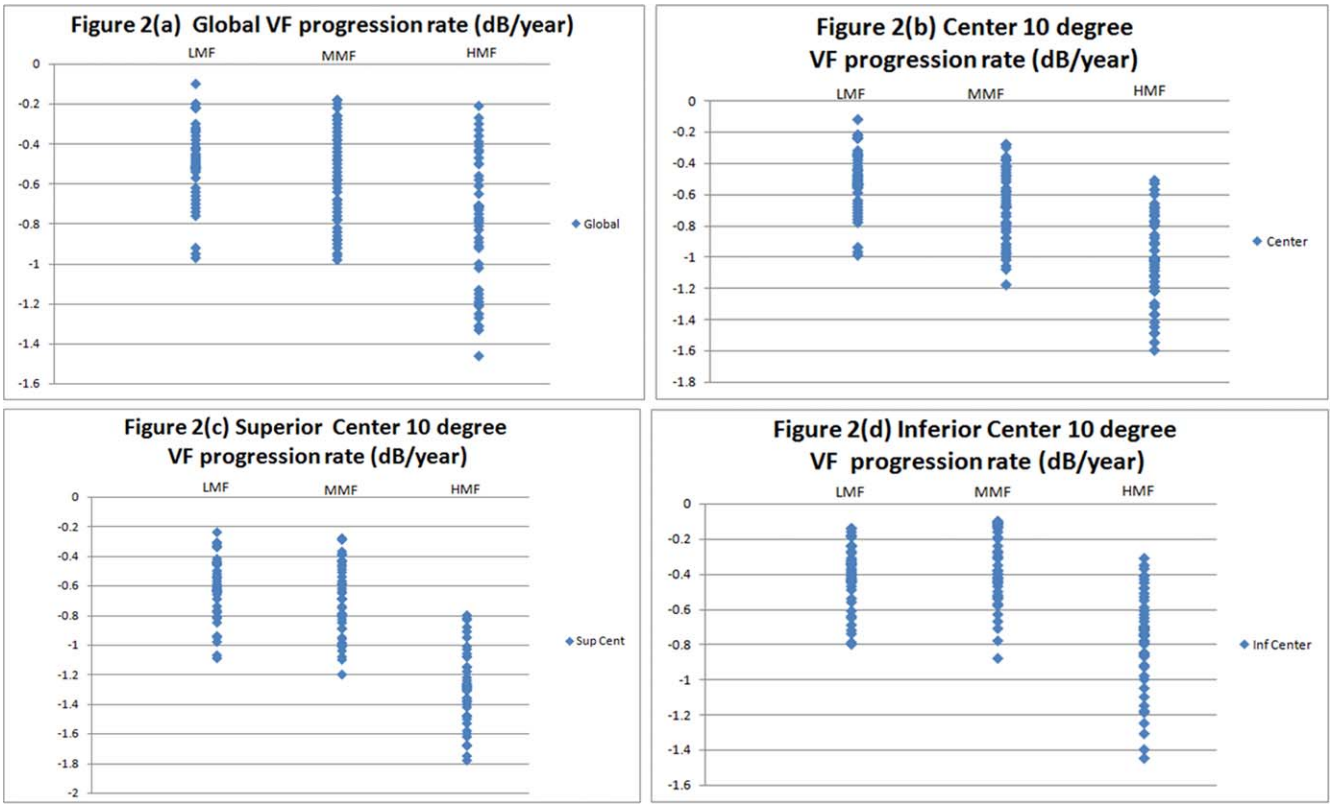

Figure 2. (**a**) Scatterplot showing VF progression slopes (rates) for each group in global region. *y*-axis, dB/y. (**b**) Scatterplot showing VF progression slopes (rates) for each group in center 10 degree region. (**c**) Scatterplot showing VF progression slopes (rates) for each group in the superior center 10° region. (**d**) Scatterplot showing VF progression slopes (rates) for each group in the inferior center 10° region.

Table 6. Regression Coefficient Estimates of the Linear Mixed Model for Rate of Paracentral (Central 10°) VF Defect Progression

	Coefficient Estimate, β	*P*
Age	−0.018	0.543
Sex, reference: female	0.381	0.082
Spherical error, D	0.014	0.810
Baseline IOP	0.121	0.315
Follow-up mean IOP	−0.082	0.667
24-hour mean IOP	−0.071	0.595
24-hour IOP fluctuation	0.104	0.125
Baseline MD	0.134	0.011*
Baseline PSD	−0.032	0.770
24-hour mean SBP	0.016	0.812
24-hour mean DBP	0.025	0.760
24-hour mean MOPP	0.032	0.601
24-hour SBP fluctuation	−0.088	0.14
24-hour DBP fluctuation	−0.092	0.11
24-hour MOPP fluctuation	−0.31	<0.001*

* Statistically significant.

There are a number of explanations for why eyes with unstable 24-hour MOPP exhibit a faster rate of VF progression in the central 10° area than the eyes in the LMF group. When Hayreh and colleagues[23] measured hourly averaged BP, they found that patients with NTG and patients with nonarteritic anterior ischemic optic neuropathy (NAAION) had significantly larger decreases in mean diastolic BP than healthy subjects. Therefore, disturbances of the retrobulbar hemodynamics in patients with NTG and NAAION, especially in the short posterior ciliary arteries, may lead to similar patterns of VF loss and/or progression. Although the common pattern of a VF defect may be a combination of an inferior altitudinal defect with an inferior nasal defect,[24,25] Ellenberger and Netsky[26] reported three cases of NAAION eyes with both inferior and superior altitudinal and superior nasal sectoral defects involving the PVF area. Compared with patients with NAAION, which is episodic, patients with NTG and unstable 24-hour MOPP may continue to experience repeated ischemic injuries on a daily basis throughout their lifetimes, which could increase the rate of progressive VF damage in the initially affected PVF location relative to the peripheral zone. Another explanation is that the most common pattern of VF progression in glaucoma is the deepening of an existing scotoma, followed by expansion.[27,28] Therefore, in the HMF group, the PVF progression rate is likely to be greater than the VF progression rate in the peripheral 10° to 24° zone because the progression reflects the deepening or expansion of preexisting initial PVF defects.

Another important finding in the present study was that the rate of PVF progression was linked to the degree of MOPP fluctuation over 24 hours: more profound 24-hour MOPP fluctuation due to an abnormal dip in nocturnal BP associated with an increased rate of PVF progression. Likewise, a poorer baseline VF was also a significant predictor of PVF progression in the present glaucoma population. This indicates that PVF progression may be more rapid in more advanced disease than in early disease. This notion is supported by several studies that assessed the VF: they showed that advanced glaucoma associates with a higher risk of progression.[29–31] This also may be true for NTG eyes with initial PVF defects. Although there were significant differences in systemic 24-hour BP fluctuation (SBP, DBP, and MOPP) among the three groups, only 24-hour MOPP fluctuation emerged as a significant predictor of rapid PVF progression. This may be because 24-hour MOPP fluctuation was the most strongly associated with PVF progression rate and three BP fluctuation variables (SBP, DBP, and MOPP) were highly correlated with each other.

Several limitations of the present study must be acknowledged. One important limitation of this study is that the measurements of BP and IOP, and the estimation of MOPP, were based on data from the sitting position obtained in single 24-hour measurements. In 2003, Liu and coworkers[32] reported that in the habitual position at the sleep laboratory, untreated OAG patients had nocturnal (supine) IOP that was significantly higher than diurnal (seated) IOP. More recent studies, including ours, have reported similar findings in NTG patients.[33,34] Likewise, BP can be measured simultaneously to the 24-hour IOP measurement using an automated BP monitor device in the supine position at nighttime to better reflect habitual 24-hour BP. Unfortunately, our study design in 1996 did not take into account the effect of nocturnal habitual position on IOP and BP measurements. Nevertheless, our study limitation is minimized by the condition that all three tested groups (HMF, MMF, and LMF) were subject to an identical study design and measurements of IOP, BP, and MOPP. Although three MOPP groups were classified based on single baseline 24-hour IOP and BP measurements, follow-up estimation of 24-hour MOPP fluctuations in the same cohort revealed consistent levels of 24-hour MOPP fluctuations on repeat 24-hour monitoring. The design of the study was retrospective and a number of patients with NTG were excluded from the patient pool due to lack of required data (e.g., CCT, refractive error, VF data, 24-hour IOP and BP measurements), which may have introduced some selection bias and led to misleading conclusions after the analysis. Moreover, the central 10° points have lower test-retest variability than the peripheral zone points.[35–37] Therefore, it is easier to detect PVF progression in the central 10°, which may explain why the rate of PVF progression in the HMF group was faster than VF progression in the 10° to 24° zone. Another limitation of the present study is that it will not be possible to generalize its findings to all types of OAG classified by IOP level, or to non-Asian individuals, since the present study only involved Koreans with 24-hour IOP less than 22 mm Hg. The calculation of MOPP and variations thereof, which was based on a theoretical formula, may not reflect the real physiological status of MOPP or the blood flow to the optic nerve or retina.

In conclusion, the present study showed that unstable 24-hour MOPP in NTG eyes was associated with an increased incidence of glaucomatous VF progression and that the location of progression was often near the central fixation point. The velocity of VF progression was significantly faster in the central 10° than in the peripheral 10° to 24° zone. These findings suggest that NTG eyes with unstable 24-hour MOPP may require more frequent and careful monitoring of PVF change and more aggressive treatment.

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References

1. Burr JM, Kilonzo M, Vale L, Ryan M. Developing a preference-based Glaucoma Utility Index using a discrete choice experiment. *Optom Vis Sci*. 2007;84:797–808.
2. Aspinall PA, Johnson ZK, Azuara-Blanco A, Montarzino A, Brice R, Vickers A. Evaluation of quality of life and priorities of patients with glaucoma. *Invest Ophthalmol Vis Sci*. 2008;49:1907–1915.
3. Park SC, De Moraes CG, Teng CCW, et al. Initial parafoveal versus peripheral scotomas in glaucoma: risk factors and visual field characteristics. *Ophthalmology*. 2011;118:1782–1789.
4. Park HYL, Jung KI, Na KS, et al. Visual field characteristics in normal-tension glaucoma patients with autonomic dysfunction and abnormal peripheral microcirculation. *Am J Ophthalmol*. 2012;154:466–475.
5. Choi J, Jeong J, Cho HS, et al. 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.
6. Choi J, Kim KH, Jeong J, et al. Circadian fluctuation of mean ocular perfusion pressure is a consistent risk factor for normal-tension glaucoma. *Invest Ophthalmol Vis Sci*. 2007;48:104–111.
7. Sung KR, Lee S, Park SB, et al. Twenty-four hour ocular perfusion pressure fluctuation and risk of normal-tension glaucoma progression. *Invest Ophthalmol Vis Sci*. 2009;50:5266–5274.
8. Sung KR, Cho JW, Lee S, et al. Characteristics of visual field progression in medically treated normal-tension glaucoma patients with unstable ocular perfusion pressure. *Invest Ophthalmol Vis Sci*. 2011;52:737–743.
9. Anderson DR. Introductory comments on blood flow autoregulation in the optic nerve head and vascular risk factors in glaucoma. *Surv Ophthalmol*. 2004;43:S5–S9.
10. Sherwood L. *Human Physiology: From Cells to Systems*. 5th ed. Pacific Grove, CA: Brooks Cole; 2004.
11. Gherghel D, Orgul S, Gugleta K, et al. Relationship between ocular perfusion pressure and retrobulbar blood flow in patients with glaucoma with progressive damage. *Am J Ophthalmol*. 2000;130:597–605.
12. Hayreh SS. The blood supply of the optic nerve head and the evaluation of it: myth and reality. *Prog Retin Eye Res*. 2001;20:563–593.
13. Bisantis C. Ocular blood flow and its autoregulation. In: Bucci MG ed. *Glaucoma: Decision Making in Therapy*. Milan: Springer-Verlag; 1996:37–40.
14. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Predictive factors for glaucomatous visual field progression in the advanced glaucoma intervention study. *Ophthalmology*. 2004;111:1627–1635.
15. Caprioli J. Intraocular pressure fluctuation: an independent risk factor for glaucoma? *Arch Ophthalmology*. 2007;125:1124–1125.
16. De Moraes CG, Prata TS, Tello C, Ritch R, Liebmann JM. Glaucoma with early visual field loss affecting both hemi-fields and the risk of disease progression. *Arch Ophthalmol*. 2009;127:1129–1134.
17. Cho HK, Kee C. Comparison of the progression rates of the superior, inferior, and both hemifield defects in normal-tension glaucoma patients. *Am J Ophthalmol*. 2012;154:958–968.
18. Smith SD, Katz J, Quigley HA. Analysis of progressive change in automated visual fields in glaucoma. *Invest Ophthalmol Vis Sci*. 1996;37:1419–1428.
19. Katz J, Gilbert D, Quigley HA, Sommer A. Estimation progression of visual field loss in glaucoma. *Ophthalmology*. 1997;1104:1017–1025.
20. Shigeeda T, Tomidokoro A, Araie M, et al. Long-term follow-up of visual field progression after trabeculectomy in progressive normal-tension glaucoma. *Ophthalmology*. 2002;109:766–770.
21. Fukuchi T, Yoshino T, Sawada H, et al. Progression rate of total, and upper and lower visual field defects in open-angle glaucoma patients. *Clin Ophthalmol*. 2010;4:1315–1323.
22. Teng CC, De Moraes CG, Prata TS, et al. The region of largest beta-zone parapapillary atrophy area predicts the location of most rapid visual field progression. *Ophthalmology*. 2011;118:2409–2413.
23. Hayreh SS, Podhajsky P, Zimmerman MB. Role of nocturnal arterial hypotension in optic nerve head ischemic disorders. *Ophthalmologica*. 1999;213:76–96.
24. Hayreh SS, Zimmerman B. Visual field abnormalities in nonarteritic anterior ischemic optic neuropathy: their pattern and prevalence at initial examination. *Arch Ophthalmol*. 2005;123:1554–1562.
25. Gerling J, Meyer JH, Kommerell G. Visual field defects in optic neuritis and anterior ischemic optic neuropathy: distinctive features. *Graefes Arch Clin Exp Ophthalmol*. 1998;236:188–192.
26. Ellenberger C Jr, Netsky MG. Infarction in the optic nerve. *J Neurol Neurosurg Psychiatry*. 1968;31:606–611.
27. Mikelberg FS, Drance SM. The mode of progression of visual field defects in glaucoma. *Am J Ophthalmol*. 1984;98:443–445.
28. Boden C, Blumenthal EZ, Pascual J, et al. Patterns of glaucomatous visual field progression identified by three progression criteria. *Am J Ophthalmol*. 2004;138:1029–1036.
29. Chen PP. Correlation of visual field progression between eyes in patients with open-angle glaucoma. *Ophthalmology*. 2002;109:2093–2099.
30. Leske MC, Heijl A, Hyman L, et al. Predictors of long-term progression in the Early Manifest Glaucoma Trial. *Ophthalmology*. 2007;114:1965–1972.
31. Chen PP, Park RJ. Visual field progression in patients with initially unilateral visual field loss from chronic open-angle glaucoma. *Ophthalmology*. 2000;107:1688–1692.
32. Liu JH, Zhang X, Kripke DF, Weinreb RN. Twenty-four-hour intraocular pressure pattern associated with early glaucomatous changes. *Invest Ophthalmol Vis Sci*. 2003;44:1586–1590.
33. Hara T, Tsuru T. Increase of peak intraocular pressure during sleep in reproduced diurnal changes by posture. *Arch Ophthalmol*. 2006;124:165–168.
34. Lee YR, Kook MS, Joe SG, et al. Circadian (24-hour) pattern of intraocular pressure and visual field damage in eyes with normal-tension glaucoma. *Invest Ophthalmol Vis Sci*. 2012;53:881–887.
35. Heijl A, Lindgren G, Olsson J. Normal variability of static perimetric threshold values across the central visual field. *Arch Ophthalmol*. 1987;105:1544–1549.
36. Heijl A, Lindgren A, Lindgren G. Test-retest variability in glaucomatous visual fields. *Am J Ophthalmol*. 1989;108:130–135.
37. Katz J, Sommer A. A longitudinal study of the age-adjusted variability of automated visual fields. *Arch Ophthalmol*. 1987;105:1083–1086.

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