Twenty-four Hour Ocular Perfusion Pressure Fluctuation and Risk of Normal-Tension Glaucoma Progression

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Purpose. To investigate the relationship between clinical factors including 24-hour mean ocular perfusion pressure (MOPP, ⅔ × mean arterial pressure [MAP] − intraocular pressure [IOP]) and visual field (VF) progression in eyes with medically treated normal-tension glaucoma (NTG).

Methods. One hundred one eyes of 101 NTG patients followed up for more than 4 years (mean follow-up, 6.2 years ± 12.1 months) were included after retrospective chart review. Several clinical factors including demographic, systemic, ocular risk factors, and 24-hour MOPP were explored for associations with decreasing VF. Kaplan-Meier analyses were performed to compare outcomes with reference to four risk factors (age, myopia, and elevated MAP and MOPP fluctuation) for VF deterioration. Hazard ratios (HRs) for the association between potential risk factors and glaucoma progression were obtained using Cox proportional hazards models.

Results. Overall VF progression was detected in 29 (28.7%) eyes. There were significant differences between progressors and nonprogressors in nocturnal MAP and MOPP fluctuations (both $P < 0.0001$), 24-hour MAP, and MOPP fluctuations (both $P < 0.0001$), initial mean deviation ($P = 0.0034$), and pattern standard deviation (PSD) score ($P < 0.0001$). Both elevated 24-hour MAP and MOPP fluctuations were associated with greater VF progression probabilities based on Kaplan-Meier analyses. Among all risk factors investigated, the Cox proportional hazards model indicated that VF progression was significantly associated with 24-hour MOPP fluctuation and initial PSD score.

Conclusions. Clinical factors other than IOP were associated with VF progression in our series of medically treated NTG eyes. Twenty-four-hour MOPP fluctuation was the most consistent prognostic factor for glaucoma progression. (*Invest Ophthalmol Vis Sci.* 2009;50:5266–5274) DOI:10.1167/iovs.09-3716

Normal-tension glaucoma (NTG) is believed to be multifactorial in pathogenesis, although the mechanism of optic nerve damage has not been fully elucidated. Several risk factors have been found to be associated with NTG progression. The most frequently reported are intraocular pressure (IOP) level, initial visual field (VF) defect, disc hemorrhages, migraine history, and the sex of the individual.[1–6]

According to the Collaborative Normal Tension Glaucoma (CNTG) study reports, 20% of NTG subjects showed VF progression despite a lowering of IOP of more than 30% from baseline.[7] Thus, non-IOP-related elements have been sought as possible risk factors for NTG progression. There is growing evidence from clinical studies that circulatory abnormalities, including low blood pressure (BP), nocturnal hypotension, and unstable mean ocular perfusion pressure (MOPP), may be involved in the pathogenesis and progression of glaucomatous optic nerve disease.[8–15] Previous population-based studies consistently found that lower diastolic ocular perfusion pressure (DOPP) was a glaucoma risk factor.[16–21] A recent study on glaucoma incidence showed that both systolic ocular perfusion pressure (SOPP) and mean ocular perfusion pressure (MOPP) may also be important in the development of glaucoma.[21] Tokunaga et al.[22] reported that nonphysiologic nocturnal BP reduction was related to glaucoma progression in a 4-year follow-up study with 38 subjects with NTG or primary open-angle glaucoma (POAG). This longitudinal study emphasized the importance of hemodynamic parameters as possible risk factors for NTG progression.

We have reported in prior studies that 24-hour MOPP instability is positively associated with the degree of glaucomatous VF damage at initial NTG presentation.[14,15] Furthermore, among various ocular and perfusion pressure risk variables studied, 24-hour MOPP fluctuation was found to be the most consistent clinical risk factor for determining glaucoma severity in patients with NTG although both age and myopia also played roles.[15] These cross-sectional findings suggest that long-standing OPP instability may lead to chronic optic disc circulation insufficiency which would, in turn, induce deterioration of glaucomatous VF defects. Similar findings have also been reported in past studies.[23–32] Therefore, we sought to test this hypothesis by identifying clinically relevant factors associated with glaucoma progression or that might affect, or at least predict, such progression in our consecutive series of medically treated NTG eyes. Based on our previous findings,[14,15] we paid particular attention to both OPP parameters and demographic factors known to affect glaucomatous damage outcomes, to ascertain whether such parameters also influence NTG progression. We report our findings in a cohort of patients with a minimum follow-up time of 4 years.

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Materials and Methods

Subjects

We retrospectively reviewed the records of 330 consecutive patients with NTG seen by a glaucoma specialist (MSK) from March 1996 to June 2003 in the glaucoma service of the Asan Medical Center, Seoul, Korea. At initial NTG diagnosis, each patient received a comprehensive ophthalmic examination including a review of medical history, measurement of best-corrected visual acuity (BCVA) to confirm that VA was adequate for automated perimetry performance, slit-lamp biomicroscopy, Goldmann applanation tonometry (GAT), gonioscopy, dilated funduscopic examination with 90- or 78-D lens stereoscopic optic disc photography, VF examination with standard automated perimetry (SAP), and 24-hour in-hospital IOP measurement. SAP testing was performed by using the full-threshold 24-2 strategy (Carl Zeiss Meditec, Dublin, CA). The central corneal thickness (CCT) of each patient was also obtained during initial presentation by a trained technician who was masked to the patient's 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 (model DGH-550; DGH Technology Inc., Exton, PA).

For NTG diagnosis, 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 (KRS, MSK); a BCVA better than 20/30; maximum IOP less than 22 mm Hg during in-hospital 24-hour IOP monitoring as well as at the outpatient clinic by GAT; 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 NTG diagnosis. Eyes with glaucomatous VF defects were defined as those that 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 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 (GHT) result outside 99% of the age-specific normal limit; and (3) a pattern standard deviation (PSD) outside 95% of the normal limit. Reliable VF assessment was defined as a VF test with a false-positive error $< 15\%$, a false-negative error $< 15\%$, and a fixation loss $< 20\%$. The first perimetric result was excluded from analysis to obviate learning effects.

All patients had to meet the following inclusion criteria to enter into the current retrospective study: newly diagnosed NTG without previous treatment, age > 40 years; in-hospital 24-hour monitoring of IOP and BP; follow-up at our clinic of at least 4 years with visits at 4- to 6-month intervals; adherence to antihypertensive glaucoma treatment (prostaglandin analogues, 78%; dorzolamide/timolol fixed combination with prostaglandin analogues 11%; dorzolamide/timolol fixed combination, 8%; and timolol, 3%); availability of at least five reliable VF datasets (Humphrey field analyzer; Carl Zeiss Meditec) performed with the central 24-2 program during the follow-up periods, thus excluding the first perimetry dataset; and mean deviation (MD) better than -20.00 dB without threat to fixation, by the field analyzer. If surgical or laser treatment was performed during the follow-up, only the data obtained in the period before the treatment were analyzed. The affected eye was selected in patients with unilateral disease, and if both eyes of a patient had NTG and met the inclusion criteria, one eye was randomly selected and included in the analyses. Subjects on systemic antihypertensive or other hemodynamically active medications were not excluded. Institutional Review Board approval was obtained from the Asan Medical Center. The design of this study adhered to the principles of the Declaration of Helsinki.

In-hospital 24-hour Monitoring of IOP and BP

BP and IOP were evaluated in-hospital over 24 hours in each patient, with measurements taken every 2 hours between 12 PM and 10 AM the following day, except for the period between midnight and 6 AM, during which measurements were taken every 3 hours. When a patient was awake, a BP measurement was first taken 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 Riva-Rocci sphygmomanometer on the upper left arm after the patient had been seated for at least 5 minutes. IOP was then 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), the patients were awakened and seated for at least 5 minutes before BP measurements were taken (all measurements were completed within a few minutes). 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. The 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.

Mean arterial pressure (MAP) was calculated as follows: $\text{MAP} = \text{DBP} + [\frac{1}{3}(\text{SBP} - \text{DBP})]$.[33,34] It was thus possible to calculate MOPP at any specified time from the difference between MAP and IOP (substituted for venous pressure) as follows: $\text{MOPP} = \frac{2}{3}(\text{MAP} - \text{IOP})$.[29,35,36] To calculate SOPP (DOPP) at any specific time, the difference between SBP (or DBP) and IOP was calculated as follows: $\text{SOPP (DOPP)} = \frac{2}{3}(\text{SBP [or DBP]} - \text{IOP})$.[29,35,36] Nocturnal MAP was calculated as the average of MAP values taken from 8 PM to 6 AM the following day, and diurnal MAP was calculated as the average of MAP measurements at all other times.[37,38] Nocturnal MAP and diurnal MAP fluctuation were calculated as the highest minus the lowest MAP value within each period. Nocturnal and diurnal MOPP fluctuations were calculated in the same manner. Twenty-four-hour MAP fluctuation was previously defined as the amplitude of nocturnal BP decline and calculated as diurnal average MAP minus nocturnal lowest MAP.[14,15,39,40] Twenty-four-hour MOPP fluctuation was also defined as the amplitude of the nocturnal OPP decrease and calculated in the same way (diurnal average MOPP minus nocturnal lowest MOPP).[14,15,39,40] Twenty-four-hour SOPP and DOPP fluctuations were calculated in the same manner. Each IOP fluctuation during 24-hour admission and at follow-up visits were calculated as the standard deviation (SD) of all IOPs measured during the relevant assessments. The rationale was that IOP fluctuation expressed as SD considered the number of measurements taken and might thus be less sensitive to outliers.[41]

Determination of Glaucoma Progression

Modified Anderson criteria for the VF progression were used to determine glaucoma progression throughout follow-up.[42] First, Advanced Glaucoma Intervention Study (AGIS) scores were calculated for all patients with NTG from second baseline VFs and were considered to reflect the baseline VF severity because advanced VF defects are more vulnerable to fluctuation.[43] VF progression in our study required an MD deterioration of >3 dB compared with two baseline values, demonstrated at least twice during the follow-up period; and deterioration of three adjacent points in the total deviation plot by 5 dB or more from the baseline value of each test location, with at least one point depressed by 10 dB, in the early stage of NTG (baseline AGIS score 5 or less). If the baseline AGIS score was over 5, the three adjacent points had to deteriorate 10 dB or more from the baseline value. Such changes were required to be confirmed in two consecutive perimetric examinations, compared with two baseline values. The time of the first VF progression detection was defined as the end point in a patient showing progression. VF progression was confirmed and agreed on by two experienced glaucoma specialists (KRS, MSK), each of whom was

masked with regard to the subject's identity and to all other test results, including IOP levels.

Statistical Analyses

Sample size calculation was based on the assumption that a 20% difference in VF progression between control eyes (those with stable MAP or MOPP fluctuation) and eyes at risk (those with high MAP or MOPP fluctuation) was clinically relevant. Approximately 33 patients were required in each group, given an α of 0.05 and a $1 - \beta$ 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 these conditions. Because of the retrospective study design and the explorative nature of the work, however, our statistical assumptions may have innate limitations and should be interpreted with caution.

Categorical variables are presented as numbers and percentages, and the χ^2 test was used to compare clinical characteristics between the two groups (nonprogressors and progressors). Continuous variables are expressed as means ± SD or medians ± interquartile ranges whenever appropriate, and Student's unpaired *t*-test or the Mann-Whitney *U* test was used for comparisons. Analyses included all follow-up measurements from baseline to time of progression or last follow-up visit. Kaplan-Meier life table analyses were performed to compare the survival experience (time to confirmed VF progression) in the presence or absence of each potential risk factor for VF deterioration within four categories: age (young, ≤55 years, versus old, >55 years), myopia (SE: ≥ −3 D versus < −3 D), and MAP and MOPP fluctuations (unstable, highest tertile range versus stable, lowest tertile range).

Hazard ratios (HRs) for the associations between potential predictive factors and glaucoma progression were obtained with Cox proportional hazards models. Univariate analyses were performed separately for each variable. Variables with $P \leq 0.20$ in univariate analyses were included in the multivariable Cox proportional hazards models. A backward elimination process was used to develop the final multivariable model, and adjusted HRs with 95% confidence intervals (CIs) were calculated. Schoenfeld residuals and the log [−log (survival rate)] test were used to verify that the proportional hazards assumptions were not violated. Model fit was assessed using residual analyses. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with commercial software (SAS ver. 9.1; SAS Institute Inc., Cary, NC, and SPSS ver. 15.0; SPSS Inc., Chicago, IL).

Results

A total of 101 eyes of 101 patients with NTG met inclusion criteria. Among the 101 patients, 48 were men, 53 were women, and all were Asians. Mean age was 54.2 ± 11.9 years, and mean MD and PSD at baseline were −4.82 ± 5.50 dB and 5.22 ± 4.03 dB, respectively. Patient demographics and baseline characteristics are shown in Table 1. The number of perimetric examinations analyzed ranged from 5 to 16 (mean, 7.6 ± 2.4) after excluding the first set of perimetry data, to minimize any learning effect. The follow-up duration range was 49 to 120 months (mean, 74.8 ± 12.1 months). Average total follow-up periods were 73.1 ± 11.2 months for progressors and 76.6 ± 12.4 months for nonprogressors, with no statistically significant between-group difference ($P = 0.34$).

Table 1. Baseline Demographics and Characteristics of Study Participants

Mean age (range), y	54.2 ± 11.9 (41–81)
Sex	
Male, *n*	48
Female, *n*	53
Visual field, dB	
Right eye ($n = 53$)	
MD	−5.00 ± 6.14
PSD	5.46 ± 4.27
Left eye ($n = 48$)	
MD	−4.63 ± 4.74
PSD	4.94 ± 3.77

Among the 101 eyes, 29 (28.7%) showed VF progression, and 72 (71.3%) were stable. Mean progression onset time was 56.3 ± 17.0 months. Baseline MD and PSD, nocturnal MAP and MOPP, and 24-hour MAP, SOPP, DOPP, and MOPP fluctuations differed significantly between VF progressors and nonprogressors. The difference in 24-hour MOPP fluctuation between VF progressors and nonprogressors was approximately 7 mm Hg (progressors; 9.88 mm Hg versus nonprogressors; 3.18 mm Hg). Between-group analyses of variables are summarized in Table 2.

Figures 1 to 4 describe risk factors showing apparent relationships to initial glaucomatous damage in our previous studies.[14,15] The Kaplan-Meier life table method was used to estimate the probability of non-progression of VF loss at 10-year follow-up visits. There was no statistically significant difference between patients in the two age groups (younger, ≤55 years versus older, >55 years; $P = 0.307$, Fig. 1), or those in the two different myopic groups (SE: ≥ −3D vs. < −3D; $P = 0.492$, Fig. 2). However, eyes with higher levels of 24-hour MAP fluctuation ($P = 0.006$, Fig. 3) and 24-hour MOPP fluctuation ($P < 0.0001$, Fig. 4) showed greater VF progression cumulative probabilities, based on the log-rank tests. The cumulative probability of nonprogression of VF loss was 38.7% at the 80 month follow-up visits for patients with high MAP fluctuation and 79.5% for those with low fluctuation. This between-group difference was highly significant ($P = 0.006$, log-rank test). The cumulative probability of nonprogression of VF loss was 20.6% at 80 months in patients with high MOPP fluctuations and 82.1% in those with low MOPP fluctuations. This between-group difference was again highly significant ($P < 0.0001$, log-rank test).

Table 3 and 4 show univariate and multivariate HRs for each putative glaucoma progression risk factor. Baseline PSD; nocturnal MAP, SOPP and MOPP fluctuations; and 24-hour MAP, SOPP, DOPP, and MOPP fluctuations were found to be significantly predictive of VF progression by univariate analysis (Table 3). In multivariate analysis employing a backward elimination method, baseline PSD and 24-hour MOPP fluctuation were significantly associated with VF progression (Table 4). In this model, MOPP fluctuation was significantly associated with VF progression outcome (HR, 1.272; 95% CI, 1.137–1.422; $P < 0.0001$). Each 1 mm Hg increase in MOPP fluctuation was associated with a 27.2% greater chance of glaucoma progression during follow-up.

Discussion

Of the suspected risk factors identified in our previous studies to be associated with the initial extent of glaucomatous damage (i.e., old age, myopia, unstable MAP, and MOPP),[14,15] we were able to show that patients with NTG in the highest tertiles of MAP and MOPP fluctuation over 24 hours were at greater risk of progressive VF loss than patients in the lowest fluctuation tertiles ($P = 0.006$, $P < 0.0001$; respectively, log-rank test: Figs. 3, 4).

When we considered all independent variables together using the Cox regression model, we found that unstable MOPP was the most consistent hemodynamic prognostic factor for VF progression in both univariate and multivariate analyses (for both, $P < 0.0001$). In other words, increased 24-hour MOPP fluctuation was a significant risk factor for glaucoma progres-

TABLE 2. Comparisons between VF Progressors and Nonprogressors

Variable	Nonprogressors	Progressors	*P*
Age, y	53.5 ± 11.6	55.9 ± 12.7	0.37
Sex (M/F), *n*	13/16	35/37	0.83
SE, D	−0.68 ± 1.88	−0.45 ± 1.98	0.65
CCT, μm	473.7 ± 165.6	479.5 ± 139.5	0.87
VF MD, dB	−4.18 ± 5.52	−6.41 ± 5.18	0.0034*
VF PSD, dB	4.17 ± 3.35	7.82 ± 4.44	<0.0001*
24-hour mean SBP, mm Hg	122.9 ± 14.7	127.3 ± 12.7	0.16
24-hour mean DBP, mm Hg	75.1 ± 9.59	76.8 ± 8.75	0.40
24-hour mean MAP, mm Hg	91.1 ± 10.9	93.7 ± 9.52	0.26
24-hour peak MAP, mm Hg	102.4 ± 12.4	105.4 ± 11.2	0.25
24-hour trough MAP, mm Hg	81.6 ± 10.1	82.1 ± 8.96	0.84
Diurnal MAP fluctuation, mm Hg	16.6 ± 5.60	16.6 ± 6.27	0.99
Nocturnal MAP fluctuation, mm Hg	13.1 ± 6.93	20.5 ± 9.89	<0.0001*
24-hour MAP fluctuation, mm Hg	6.03 ± 4.24	13.5 ± 5.73	<0.0001*
24-hourS OPP fluctuation, mm Hg	7.18 ± 5.47	12.9 ± 5.91	<0.0001*
24-hour DOPP fluctuation, mm Hg	4.30 ± 4.67	8.25 ± 3.85	<0.0001*
24-hour mean MOPP, mm Hg	46.3 ± 6.63	48.7 ± 6.21	0.096
24-hour peak MOPP, mm Hg	54.6 ± 7.87	57.3 ± 7.47	0.11
24-hour trough MOPP, mm Hg	40.0 ± 6.86	40.2 ± 5.79	0.89
Diurnal MOPP fluctuation, mm Hg	11.7 ± 4.29	11.8 ± 4.66	0.92
Nocturnal MOPP fluctuation, mm Hg	9.74 ± 4.81	15.2 ± 6.71	<0.0001*
24-hour MOPP fluctuation, mm Hg	3.18 ± 2.06	9.88 ± 3.41	<0.0001*
Mean baseline IOP, mm Hg	16.3 ± 2.38	15.9 ± 1.87	0.40
24-hour mean IOP, mm Hg	15.5 ± 2.72	14.8 ± 1.70	0.25
24-hour peak IOP, mm Hg	17.1 ± 3.50	16.7 ± 2.64	0.54
24-hour trough IOP, mm Hg	11.8 ± 2.45	11.2 ± 1.98	0.32
24-hour IOP fluctuation, mm Hg	4.76 ± 0.79	4.72 ± 0.57	0.84
Mean follow-up IOP, mm Hg	13.6 ± 1.94	13.5 ± 1.65	0.71
Follow-up IOP fluctuation, mm Hg	1.93 ± 0.57	1.83 ± 0.76	0.19

* $P < 0.05$.

sion, with a 27.2% increase in the HR for every 1 mm Hg increment (HR, 1.272; 95% CI, 1.137–1.422; $P < 0.0001$). These results may support our earlier conclusions on the effect of unstable MOPP on glaucoma prognosis. The associations between nocturnal MAP, SOPP, and MOPP fluctuations; 24-hour MAP, SOPP, and DOPP fluctuation; and glaucoma progression, were significant in univariate analyses but disappeared on multivariate analysis. This was probably because the influences of IOP and BP as well as joint effects among various perfusion pressures were corrected in the multivariate analysis. However, in our univariate analysis, 24-hour SOPP and DOPP fluctuations were also important in predicting glaucoma progression. This finding is in line with a recent population-based study that all lower ocular perfusion pressures (SOPP, DOPP, and MOPP) were positively related to the risk of open-angle glaucoma.[21]

Previous studies exploring a role for perfusion pressure in glaucoma incidence and severity found that reduced SOPP and/or MOPP, together with lowered DOPP may be glaucoma risk factors.[16–21] However, the cited studies and other cross-sectional works measured these hemodynamic parameters only on particular occasions (during the initial interview or on follow-up visits). To reflect the general ocular perfusion health over 24 hours, it may be more appropriate to consider both multiple MOPP values and 24-hour MOPP variation. As these parameters integrate IOP, SBP, and DBP over 24 hours, MOPP fluctuation may serve as a better surrogate of ocular perfusion status than either SBP or DBP measured at any particular time.

Recently, emerging evidences have pointed to a role for ischemia in glaucoma pathogenesis. It has been suggested that the perfusion parameters of the lamina cribrosa and neuroretinal rim in glaucoma patients might be significantly correlated with VF defects as measured using scanning laser Doppler flowmetry.[44,45] Oku et al.[46] showed that optic nerve head ischemia could contribute to the enlargement and excavation of the disc cup, independent of IOP level. Furthermore, Satilmis et al.[47] found that, independent of glaucomatous damage extent and IOP, the progression rate of glaucomatous VF damage correlates with retrobulbar hemodynamic variables. These reports raise an interesting question. What causes optic nerve head ischemia in association with glaucoma development and progression? Reduced perfusion pressure may play a role in ocular structure ischemia. Based on our findings, we hypothesize that 24-hour MOPP fluctuation may contribute to the pathogenesis and progression of glaucomatous optic neuropathy. To the best of our knowledge, the present study is the first to address the association between glaucomatous progression and unstable MOPP.

Several studies have indicated a relationship, relevant to our findings, between blood flow variation and end-organ damage. Altered circadian BP rhythm has been associated with cerebral blood flow changes, resulting in cerebrovascular damage and progression,[48–51] and patients with nocturnal hypotension may also be at increased risk for development of left ventricular hypertrophy or silent myocardial infarction.[37,52] Excess free radicals derived from ischemia and reperfusion may contribute to reversible or irreversible manifestations of cell injury.[53,54] A recent report showed that a large diurnal fluctuation in ocular blood flow may be related to POAG pathogenesis.[55] Thus, chronic repetitive 24-hour ocular blood flow variations could result in accumulative ischemia and reperfusion effects, manifested in the progression of retinal nerve fiber layer (RNFL) damage and corresponding VF loss.

In this study, patients on antihypertensive or other hemodynamically active medications were not excluded from entry or follow-up. We are aware that inclusion of patients on antihypertensive medication could bias BP and MOPP estimations and is thus a limitation of the present study. Such systemic medications can influence both ocular vascular resistance and autoregulation. Thus, the drugs can contribute to VF progres-

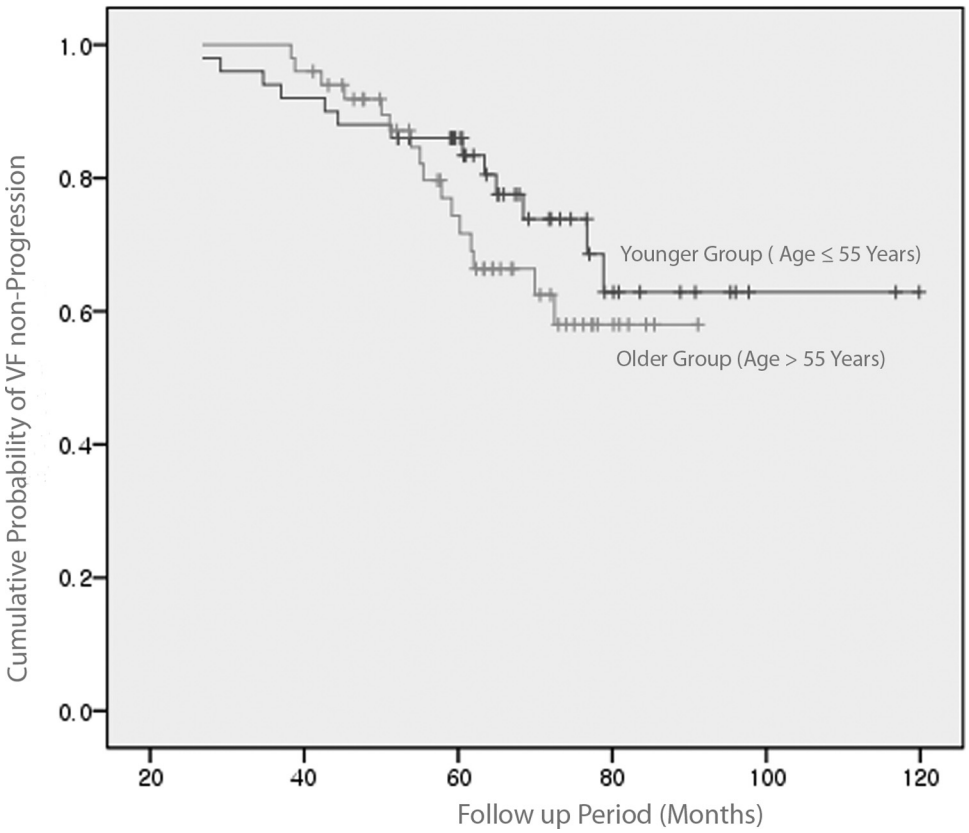

Figure 1. Kaplan-Meier survival analysis comparing patients in different age groups.

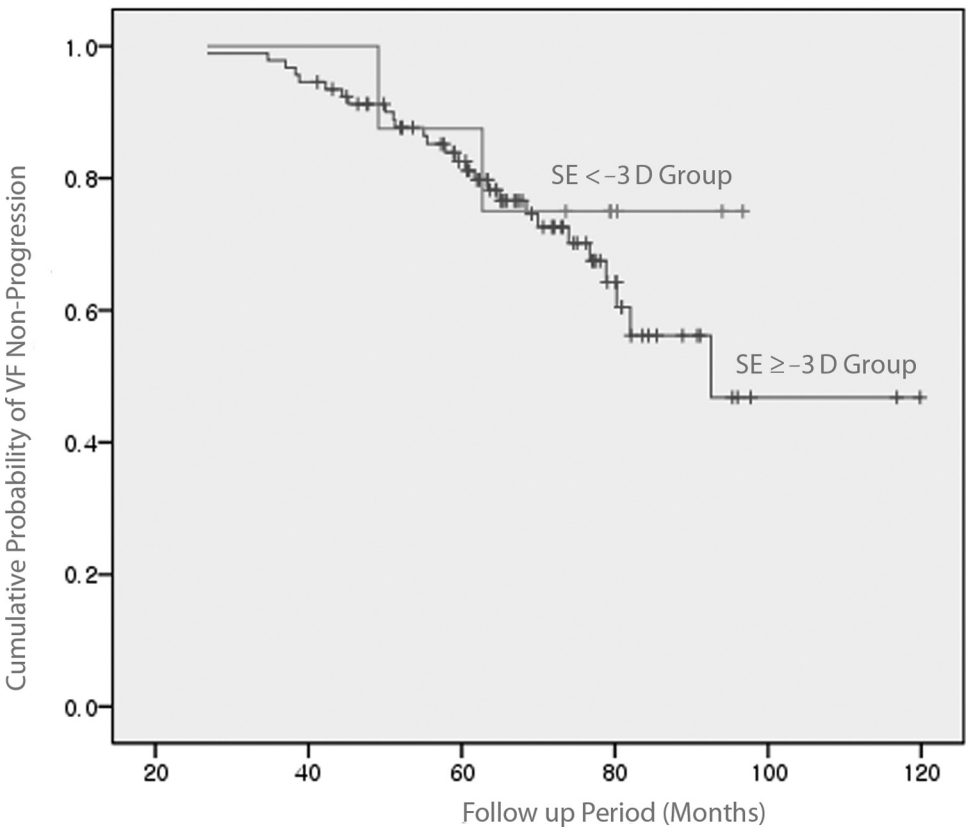

Figure 2. Kaplan-Meier survival analysis comparing patients with myopia with those with low to no myopia.

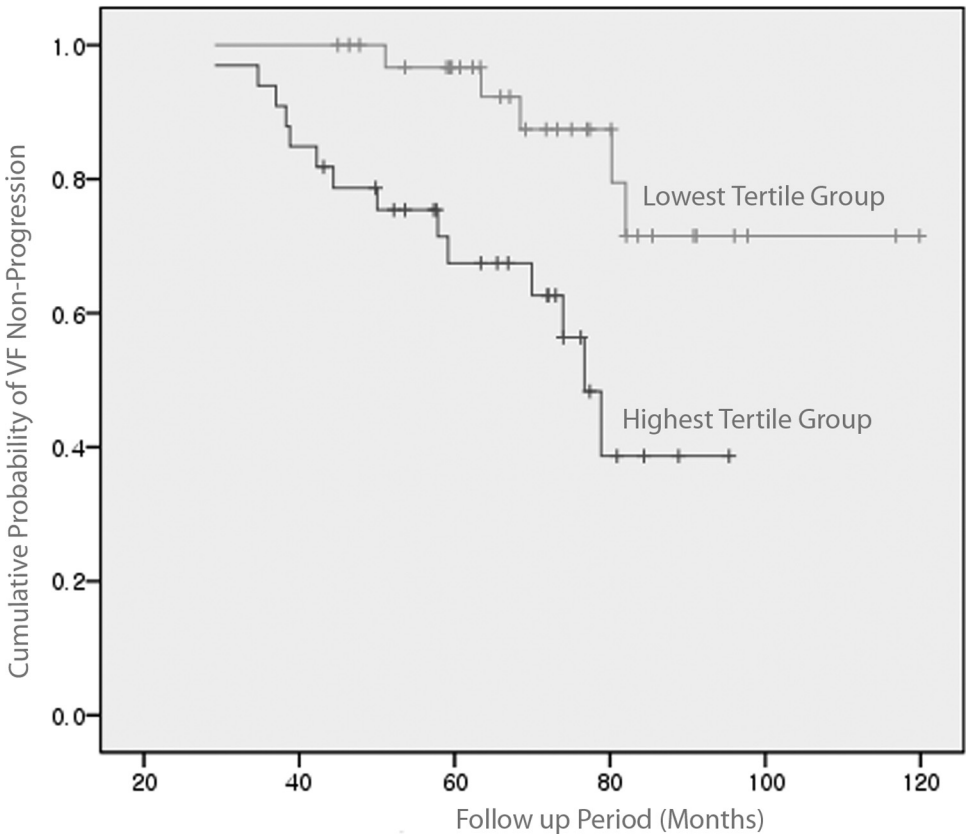

FIGURE 3. Kaplan-Meier survival analysis of MAP fluctuation.

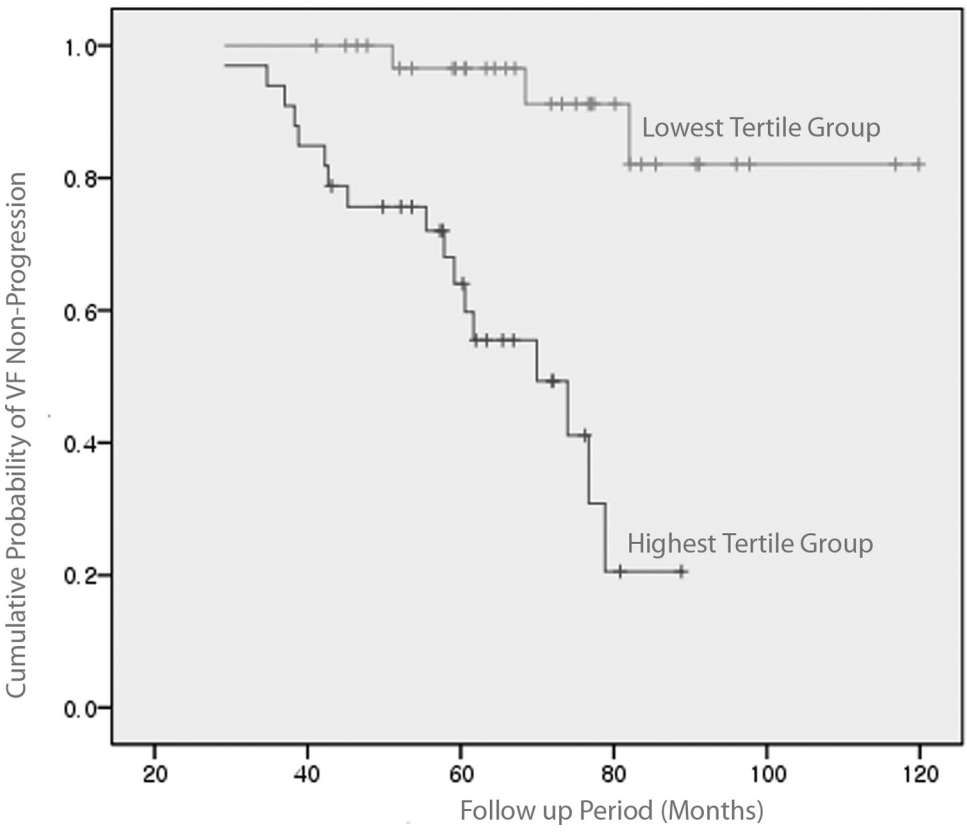

FIGURE 4. Kaplan-Meier survival analysis of MOPP fluctuation.

TABLE 3. Univariate Cox Proportional Hazards Model for Prediction of Glaucoma Progression

Variable	HR	95% CI	*P*
Age	1.020	0.988–1.054	0.2224
Sex	0.686	0.327–1.435	0.3166
SE	1.018	0.796–1.301	0.8900
CCT	1.001	0.999–1.003	0.4340
VF MD	0.965	0.918–1.014	0.1560
VF PSD	1.158	1.075–1.248	<0.0001*
24-hour mean SBP	1.018	0.992–1.004	0.1853
24-hour mean DBP	1.011	0.972–1.051	0.5861
24-hour mean MAP	1.017	0.981–1.053	0.3592
24-hour peak MAP	1.014	0.983–1.046	0.3704
24-hour trough MAP	1.002	0.965–1.040	0.9364
Diurnal MAP fluctuation	0.981	0.920–1.046	0.563
Nocturnal MAP fluctuation	1.064	1.029–1.099	<0.0001*
24-hour MAP fluctuation	1.078	1.023–1.136	0.0048*
24-hour mean MOPP	1.046	0.989–1.106	0.1182
24-hour peak MOPP	1.033	0.987–1.081	0.1581
24-hour trough MOPP	1.007	0.955–1.063	0.7881
Diurnal MOPP fluctuation	0.984	0.909–1.066	0.695
Nocturnal MOPP fluctuation	1.099	1.048–1.153	<0.0001*
24-hour MOPP fluctuation	1.087	1.044–1.132	<0.0001*
Nocturnal SOPP fluctuation	1.007	0.928–1.177	0.013*
24-hour SOPP fluctuation	1.063	1.001–1.151	<0.0001*
Nocturnal DOPP fluctuation	1.002	0.873–1.053	0.893
24-hour DOPP fluctuation	1.043	0.999–1.122	<0.0001*
Mean baseline IOP	0.887	0.747–1.053	0.1696
24-hour mean IOP	0.871	0.738–1.028	0.1031
24-hour peak IOP	0.929	0.822–1.049	0.2360
24-hour trough IOP	0.912	0.772–1.076	0.2730
24-hour mean IOP fluctuation	0.794	0.467–1.351	0.3950
Mean follow-up IOP	0.915	0.738–1.135	0.4207
Follow-up IOP fluctuation	0.672	0.331–1.362	0.2702

* $P < 0.05$.

sion and could have affected our study outcomes by influencing ocular blood flow independent of MOPP readings.

The use of topical antiglaucoma therapy may also influence ocular blood flow. Martinez et al.[56] found that most blood flow parameters of intraocular and periocular vessels improved after application of topical dorzolamide in both normal and glaucomatous eyes, although in the cited studies, the investigators took measurements 2 hours after the instillation. Approximately 20% of the patients with NTG in the present study were prescribed topical dorzolamide in a fixed combination with timolol. Therefore, we cannot completely rule out the effects of this combination on ocular blood flow or MOPP.

Notably, poorer VF baseline function was a significant glaucoma progression predictor in our study population. We found an association between the level of glaucomatous VF damage and VF progression (HR, 1.183; 95% CI, 1.096–1.262; $P < 0.0001$ with increased PSD; Table 4). Wilson et al.[57] noted that both initial IOP and advanced glaucomatous VF defects were associated with progression.

Both older age and myopia were found to be important clinical risk factors for glaucoma severity in NTG eyes.[15] Age was an important risk factor for glaucoma prevalence in several population-based studies, as was myopia.[58–63] However, we did not find in the present study that age was related to further glaucoma progression. This finding may be in line with results of the CNTG study in which analysis of natural NTG progression revealed a variable glaucoma progression rate.[6,64] Therefore, analysis of a mixture of rapid and slow progressors may result in the average rate of progression being constant at all ages.

TABLE 4. Multivariate Cox Proportional Hazards Model with Backward Elimination for Prediction of Glaucoma Progression

Variable	HR	95% CI	*P*
PSD	1.183	1.096–1.262	<0.0001
24-hour MOPP fluctuation	1.272	1.137–1.422	<0.0001

A number of population-based studies suggested that myopia was a risk for POAG development.[65–70] However, as with age, myopia also did not seem to affect VF progression rate in the present study. Future longitudinal studies evaluating the effect of myopia on glaucoma progression would clarify any possible association between these conditions.

No IOP-related parameters, including baseline, mean 24-hour admission value, or follow-up average, were found to be significantly related to the VF progression. Our results may appear to differ from previous findings on the effect of IOP on NTG progression.[7,71,72] A recent follow-up report from the EMGT study, which included a significant number of eyes with NTG, found that IOP level at follow-up was an important risk factor for glaucoma progression, with HR increasing by 12% to 13% for every 1 mm Hg of higher IOP.[72] These seemingly differing findings may be explained by variations in patient populations under study and IOP levels seen during follow-up. All our patients were medically treated and maintained a relatively low mean follow-up IOP of 13.5 mm Hg. In fact, neither in-hospital mean nor follow-up average IOP differed between the two groups (nonprogressors versus progressors, Table 2). We continue to believe that lowering of IOP is important in NTG treatment to help prevent long-term glaucomatous progression. Lowering of IOP was not uniformly effective, however, in stopping NTG progression in every individual, as noted in the present study.

Our study had several limitations, including a relatively small sample size for multivariate analysis. However, our finding that unstable MOPP over the course of 24 hours might be related to glaucoma progression based on rather rigid VF criteria and relatively long follow-up times is in line with our previous data and may thus support our hypothesis. A second limitation was our inability to generalize findings to all types of open-angle glaucoma classified by IOP level, because our study required 24-hour and outpatient IOP values less than 22 mm Hg before patient inclusion. Third, our calculation of MOPP, based on a theoretical formula, may not reflect the real physiological status of ocular perfusion. Direct measurement of ocular blood flow could result in a different outcome. Autoregulation of blood flow or locally compromised vascular status (i.e., atherosclerosis) may also play a role in ocular blood flow dynamics. However, direct measurement of ocular blood flow using imaging devices suffers from limitations including relative lack of reproducibility, operator dependency, and high cost. MOPP is simple to measure and may be a better surrogate for general ocular blood flow than is systemic BP or pulse pressure. Fourth, BP and IOP measurements, and MOPP calculations, using data from sitting patients during 3-hour nocturnal samplings and single 24-hour measurements, may not be the best way to predict associations between these parameters and long-term disease progression. Somewhat different results might have been obtained had we measured BP and IOP in a seamless physiological manner over 24-hour periods on multiple occasions, using 24-hour automated ambulatory BP monitoring. However, such a limitation is intrinsic to this type of retrospective study. Nonetheless, we believe that MOPP calculation based on 24-hour IOP and BP measurement is a useful practical measure and may provide important clues for long-term prognoses of patients with NTG.

In conclusion, in our study unstable 24-hour MOPP was associated with glaucomatous VF progression. This result suggests that compromised nocturnal OPP reductions may lead to repetitive daily ischemic insults, followed by reperfusion damage. These cumulative ocular tissue injuries may manifest as progressive glaucomatous VF deterioration.

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