

# Circadian Fluctuation of Mean Ocular Perfusion Pressure Is a Consistent Risk Factor for Normal-Tension Glaucoma

Jaewan Choi, Kyung Hoon Kim, Jinbo Jeong, Hyun-soo Cho, Chang Hwan Lee, and Michael S. Kook

**PURPOSE.** To investigate systemic and ocular hemodynamic risk factors for glaucomatous damage in eyes with normal tension glaucoma (NTG).

**METHODS.** Each patient with diagnosed NTG underwent 24-hour monitoring of intraocular pressure (IOP) and blood pressure (BP), scanning laser polarimetry (GDx-VCC), and a Humphrey visual field (HVF) examination. Multivariate regression models were used to evaluate potential risk factors: age, spherical equivalent, central corneal thickness (CCT), mean/peak in-hospital IOP, circadian IOP fluctuation, average mean arterial pressure (MAP), circadian MAP fluctuation, and circadian fluctuation of mean ocular perfusion pressure (MOPP). Functional outcome variables for glaucomatous damage were mean deviation (MD), pattern SD (PSD), and Advanced Glaucoma Intervention Study (AGIS) score. Anatomic outcome variables were TSNIT (temporal, superior, nasal, inferior, and temporal) average, superior average, inferior average, and nerve fiber indicator (NFI) on GDx-VCC.

**RESULTS.** One hundred thirteen eyes of 113 patients met the inclusion criteria. In the multivariate regression models, larger circadian MOPP fluctuation was significantly associated with decreased MD, increased PSD, and increased AGIS score among functional outcome variables and with reduced TSNIT average, reduced inferior average, and increased NFI among anatomic outcome variables. Larger MAP fluctuation was associated with decreased MD, increased PSD, reduced TSNIT average, reduced inferior average, and increased NFI. CCT was not associated with any outcome variable.

**CONCLUSIONS.** Of the functional and anatomic outcome variables, circadian MOPP fluctuation was the most consistent clinical risk factor for glaucoma severity in eyes with NTG. This finding may suggest an etiology of NTG as a chronic ischemic end organ disease. (*Invest Ophthalmol Vis Sci.* 2007;48:104-111) DOI:10.1167/iovs.06-0615

Hypotheses associated with the development of normal-tension glaucoma (NTG) include those involving vascular factors,<sup>1-8</sup> and those involving intraocular pressure (IOP).<sup>9-11</sup> Patients with NTG have been reported to show significantly

greater reductions in nocturnal blood pressure (BP) than have healthy people,<sup>12</sup> and greater reduction in nocturnal BP is thought to lead to a more rapid progression of glaucoma.<sup>13,14</sup> In contrast, the Beaver Dam Eye Study showed that reduced systemic BP is associated with reduced IOP, suggesting that in these individuals, there is a decreased risk of open-angle glaucoma.<sup>15</sup> Diurnal IOP variation is also thought to be involved in the progression of glaucoma.<sup>16-19</sup> Although large fluctuations in diurnal IOP have been reported to be an independent risk factor for the progression of glaucoma,<sup>16</sup> recent studies have found that the range of diurnal IOP variation was proportional to the level of IOP, indicating that diurnal variation in IOP itself was not an independent risk factor for the progression of glaucoma.<sup>20,21</sup>

Recently, central corneal thickness (CCT) has been recognized as a clinical risk factor in determining glaucoma severity at initial presentation.<sup>22-24</sup> In contrast, CCT has been found to correlate significantly and positively with the area of the neuroretinal rim and negatively with the loss of visual fields at initial presentation, but it does not correlate with the progression of glaucomatous optic nerve neuropathy.<sup>25</sup> This finding suggests that the relationship between CCT and the amount of glaucomatous optic nerve damage at initial presentation to a glaucoma specialist may be a selection artifact associated with delayed detection of glaucoma by the referring ophthalmologist.

Many studies have suggested that loss of autoregulation in ocular blood flow (OBF) may be present in primary open-angle glaucoma (POAG).<sup>26-28</sup> If autoregulatory mechanisms were defective in eyes with glaucoma, the ocular perfusion pressure would be directly affected by arterial perfusion pressure and IOP. Indeed, significantly greater increases in neuroretinal rim blood flow were observed in patients with POAG than in patients with ocular hypertension, when both had similar reductions in IOP.<sup>28</sup> If OBF autoregulation is defective, the calculated mean ocular perfusion pressure (MOPP) may reflect, at least in part, the true OBF. It has also been suggested that relative diurnal or circadian change in MOPP may be a risk factor for POAG.<sup>29,30</sup>

To elucidate the mechanism of glaucomatous damage in eyes with NTG at initial diagnosis, we investigated the systemic and ocular hemodynamic risk factors for advanced glaucomatous damage, as detected by functional and anatomic outcome variables.

## METHODS

### Patients

We performed a retrospective chart review of 113 eyes of 113 consecutive patients (54 men and 59 women) with diagnosed NTG (mean age  $\pm$  SD: 55.0  $\pm$  15.1 years), each of whom was seen by a glaucoma specialist (MSK) during the period from November 2004 to June 2006. Patients were eligible for the study if the optic nerve had a glaucomatous appearance, including diffuse or focal neural rim thinning, hem-

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orrhage, enlarged cupping, or nerve fiber layer defects indicative of glaucoma, in addition to corresponding visual field loss; best corrected visual acuity greater than 20/40; maximum IOP < 22 mm Hg on multiple measurements with Goldmann applanation tonometry (GAT); normal anterior chamber and open angle on slit lamp and gonioscopic examination; and glaucomatous visual field damage. Patients with evidence of intracranial or otolaryngologic lesions, history of a massive hemorrhage or hemodynamic crisis, previous or current use of anti-glaucoma medications, any other ophthalmic disease including noticeable cataract that could result in visual field defects, or a history of diabetes mellitus were excluded. Patients on antihypertension or other hemodynamically active medications, however, were not excluded. The CCT of each patient was measured three times by ultrasonic pachymetry (DGH-550; DGH Technology Inc., Exton, PA) at first visit and the average was calculated. Visual field examination was performed with the Humphrey field analyzer (HFA; Carl-Zeiss Meditec, Dublin, CA) and scanning laser polarimetry (SLP) was performed with a variable corneal compensation system (GDx-VCC software version 5.5.0; Carl Zeiss Meditec, Dublin, CA) at the initial visit. All patients with NTG diagnosed on the basis of clinical evaluation and visual field examination at our glaucoma clinic routinely undergo in-hospital 24-hour monitoring of IOP and BP, as described later. The affected eye was selected in patients with unilateral disease; if both eyes of a patient showed NTG and met the inclusion criteria, one eye was randomly selected. All procedures conformed to the Declaration of Helsinki and the study was approved by the ethics committee of the Asan Medical Center at the University of Ulsan, Korea.

### Visual Field Examination

Visual field examinations were performed with the 24-2 full-threshold (FT) program or 24-2 Swedish Interactive Threshold Algorithm (SITA) standard program on the HFA. Eyes with glaucomatous visual field defects were defined as those that met all the following criteria: (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) Glaucoma Hemifield Test (GHT) results outside 99% of age-specific normal limits; and (3) PSD outside 95% of the normal limit. We included only those patients who, within 1 month of initial evaluation, had a reliable visual field test, defined as a false-positive error less than 15%, a false-negative error less than 15%, and a fixation loss less than 20%. Visual field data for analysis included mean deviation (MD), PSD and the Advanced Glaucoma Intervention Study (AGIS) score. The AGIS score has been described in detail previously.<sup>31</sup> In brief, the visual fields are graded on a scale of 0 to 20 based on the degree of damage shown on the total deviation printout; a higher score reflects advanced glaucomatous visual field damage.

### Scanning Laser Polarimetry of the Retinal Nerve Fiber Layer

SLP imaging was performed in a standardized fashion (GDx-VCC software version 5.5.0; Carl Zeiss Meditec) with a circular scan (3.2-mm diameter) centered on the optic disc, as described.<sup>32</sup> The general principles of SLP with variable corneal polarization compensation (VCC) have been described in detail elsewhere.<sup>33,34</sup> Only eyes with a scan quality score of 8 or better were analyzed. Images with atypical retardation pattern (ARP) were excluded. An atypical scan was defined as one that contained atypical and flowerlike patterns of elevated retardation values that did not match the expected retardation distribution based on retinal nerve fiber layer (RNFL) anatomy and could generate spurious RNFL thickness measurements. The SLP parameters examined were TSNIT (temporal, superior, nasal, inferior, and temporal) average, superior average, inferior average, and nerve fiber indicator (NFI).

TABLE 1. Patient Demographic and Background Variables

Age (y)	55.0 ± 15.1 (range 19–82)
Gender	
Male	54 (47.8)
Female	59 (52.2)
Hypertension	23 (20.4)
Visual field test	
Right eyes	60 (53.1)
FT	36 (60.0)
SITA	24 (40.0)
Left eyes	53 (46.9)
FT	28 (52.8)
SITA	25 (47.2)

Data are expressed as number (percentage) of subject, except for age: mean ± SD (range); *N* = 113.

### Measurement of IOP and Systemic Hemodynamic Parameters

IOP and BP of each patient were evaluated in-hospital over 24 hours, with measurements taken every 2 hours between 12 PM and 10 AM the following day, except for the period between 12 AM and 6 AM, during which measurements were taken every 3 hours. IOP was measured with a slit lamp-mounted GAT with the patient in the sitting position, after the subject had been seated for at least 3 minutes. IOP fluctuation was defined as the difference between the highest and lowest IOPs recorded during the 24-hour period. Systolic and diastolic BPs (SBP, DBP) were measured with a brachial Riva-Rocci sphygmomanometer on the upper left arm after the subject had been seated for at least 3 minutes. Patients were asked to refrain from any physical activities that could affect BP. Meals were provided at 6:30 PM and 7:30 AM and did not include any alcohol or caffeine. SBP and DBP fluctuations were defined as the difference between the highest and lowest SBP and DBP recorded during the 24-hour period.

Mean arterial pressure (MAP) was calculated as:  $MAP = DBP + [\frac{1}{3}(SBP - DBP)]$ . MAP fluctuation was defined as the difference between the highest and lowest MAPs recorded during the 24-hour period. MOPP was calculated at a specified time from the difference between MAP and IOP substituted for venous pressure as:  $MOPP = \frac{2}{3}(MAP - IOP)$ . Circadian MOPP fluctuation (CMF) was defined as the difference between the highest and lowest MOPP values recorded during the 24-hour phasing.

### Statistical Analyses

Descriptive statistics (number and percentage for categorical variables, and mean ± SD for continuous variables) were initially evaluated. Subsequently, each variable was assessed individually for its relationship to the degree of damage from glaucoma. Predictor variables for analysis were age, spherical equivalent (SE), CCT, mean in-hospital IOP, peak in-hospital IOP, IOP fluctuation, average MAP, MAP fluctuation, and CMF. Functional outcome variables were MD, PSD, and AGIS score. Anatomic outcome variables were TSNIT average, superior average, inferior average, and NFI obtained by GDx-VCC. Initially, the relationships between predictor variables and outcome variables were assessed by univariate linear regression models. All predictor variables were subsequently combined in a single regression model to assess their joint effects on the outcome variables by multivariate modeling. The model for each outcome variable was reduced by using backward elimination until it contained only significant predictors. Differences reaching *P* < 0.05 were considered statistically significant.

### RESULTS

Table 1 presents descriptive statistics for demographic and background variables. All 113 patients were Asian; 54 (47.8%) were men and 59 (52.2%) were women. Mean age was 55.0 ±

TABLE 2. Systemic and Ophthalmic Measurements

	Mean $\pm$ SD	Range
Best corrected visual acuity (Snellen acuity)	0.81 $\pm$ 0.20	0.5-1.2
Spherical equivalent (D)	-0.81 $\pm$ 2.35	-10.0-5.25
CCT ( $\mu$ m)	533.9 $\pm$ 29.4	459.3-611.7
IOP parameters (mm Hg, measured by Goldmann applanation tonometry)		
Mean in-hospital IOP	14.2 $\pm$ 2.3	9.0-24.4
Peak in-hospital IOP	16.9 $\pm$ 3.0	11.0-30.0
IOP fluctuation	5.3 $\pm$ 2.3	1.0-15.0
BP parameters (mm Hg)		
Average SBP	123.9 $\pm$ 14.9	95.4-163.9
Average DBP	76.0 $\pm$ 8.4	57.5-107.4
Average MAP	92.0 $\pm$ 10.0	71.2-126.2
SBP fluctuation	32.5 $\pm$ 11.4	12.0-63.0
DBP fluctuation	20.8 $\pm$ 7.4	5.0-43.0
MAP fluctuation	22.8 $\pm$ 7.8	7.0-46.7
Circadian fluctuation of MOPP	15.9 $\pm$ 5.5	5.7-34.1
Visual field parameters (functional outcome variables)		
MD (dB)	-6.1 $\pm$ 5.8	-28.3-2.3
PSD (dB)	5.8 $\pm$ 3.8	1.4-17.4
AGIS score	4.6 $\pm$ 4.6	0-20
SLP-VCC parameters (anatomical outcome variables)		
TSNIT average	45.0 $\pm$ 7.0	27.8-70.0
Superior average	53.4 $\pm$ 9.5	25.4-78.0
Inferior average	49.0 $\pm$ 11.2	26.5-81.0
NFI	47.7 $\pm$ 20.4	5-98

*N* = 113.

15.1 years (range, 19-82), and 23 (20.4%) of the patients had a history of hypertension. Five (4.4%) patients had IOP >21 mm Hg during the 24-hour IOP monitoring and were not excluded from the analysis. Four of these five patients had a single record of IOP >21 mm Hg during the phasing. Only one patient showed consistently high IOP (>21 mm Hg) at night, whereas IOP was below 21 mm Hg during the day. Of the 113 eyes selected for analysis, 60 (53.1%) were right eyes, 36 (60.0%) of which had undergone the 24-2 FT program test on the HFA. The remaining 53 (46.9%) eyes were left eyes, 28 (52.8%) of which had undergone the 24-2 FT program test on the HFA. All remaining eyes underwent the 24-2 SITA standard program test on the HFA.

Table 2 shows descriptive statistics for the systemic and ophthalmic measurements of the study eyes. Average Snellen visual acuity was 0.81  $\pm$  0.20, average SE was -0.81  $\pm$  2.35 D, and their average CCT was 533.9  $\pm$  29.4  $\mu$ m. Mean in-hospital IOP was 14.2  $\pm$  2.3 mm Hg, peak in-hospital IOP was 16.9  $\pm$  3.0 mm Hg, and IOP fluctuation was 5.3  $\pm$  2.3 mm Hg. Average SBP was 123.9  $\pm$  14.9 mm Hg, average DBP was 76.0  $\pm$  8.4 mm Hg, and average MAP was 92.0  $\pm$  10.0 mm Hg. Circadian

fluctuation of MAP and MOPP were 22.8  $\pm$  7.8 and 15.9  $\pm$  5.5 mm Hg, respectively. The average MD and PSD on HFA were -6.1  $\pm$  5.8 dB and 5.8  $\pm$  3.8 dB, respectively. The average AGIS score was 4.6  $\pm$  4.6. The average TSNIT average, superior average, and inferior average on SLP examination were 45.0  $\pm$  7.0, 53.4  $\pm$  9.5, 49.0  $\pm$  11.2, and 47.7  $\pm$  20.4, respectively.

Table 3 presents the result of linear regression between independent predictor variables and outcome variables in a univariate model. When considered alone, only age and circadian MOPP fluctuation (CMF) showed significant associations with some outcome variables (*P* < 0.05). Increased age was significantly associated with decreased inferior average (*P* = 0.023) on GDx-VCC, whereas increased CMF was significantly associated with worsened PSD (*P* = 0.035) and AGIS score (*P* = 0.014) on HVF. SE, CCT, mean in-hospital IOP, peak in-hospital IOP, IOP fluctuation, average MAP, and MAP fluctuation were not associated with any of the outcome variables (*P* > 0.05).

Table 4 presents the result of linear regression between independent predictor variables and outcome variables in a multivariate model. When all variables were considered simul-

TABLE 3. Significance of Independent Variables in Predicting Outcome of Glaucoma: Univariate Models

Predictor Variables	Functional Outcome Variables			Anatomical Outcome Variables			
	MD	PSD	AGIS Score	TSNIT Average	Superior Average	Inferior Average	NFI
Age	0.32	0.12	0.09	0.064	0.40	0.023*	0.96
SE	0.79	0.09	0.31	0.30	0.78	0.25	0.52
CCT	0.50	0.26	0.59	0.60	0.40	0.74	0.62
Mean in-hospital IOP	0.32	0.67	0.51	0.21	0.40	0.15	0.28
Peak in-hospital IOP	0.69	0.22	0.91	0.23	0.26	0.26	0.24
IOP fluctuation	0.48	0.18	0.42	0.75	0.76	0.83	0.54
Average MAP	0.64	0.63	0.68	0.62	0.53	0.63	0.90
MAP fluctuation	0.64	0.55	0.14	0.87	0.86	0.96	0.83
MOPP fluctuation	0.10	0.035*	0.014*	0.35	0.34	0.33	0.43

\* *P* < 0.05.

TABLE 4. Significance of Independent Variables in Predicting Outcome of Glaucoma: Multivariate Models

Predictor Variables	Functional Outcome Variables			Anatomical Outcome Variables			
	MD	PSD	AGIS Score	TSNIT Average	Superior Average	Inferior Average	NFI
Age	—	—	—	0.036*	—	0.013*	—
SE	—	0.036*	—	—	—	—	—
CCT	—	—	—	—	—	—	—
Mean in-hospital IOP	—	—	—	—	—	—	—
Peak in-hospital IOP	—	—	—	—	—	—	—
IOP fluctuation	—	—	—	—	—	—	—
Average MAP	—	—	—	—	—	—	—
MAP fluctuation	0.025*	0.025*	—	0.012*	—	0.018*	0.041*
MOPP fluctuation	0.006*	0.007*	0.014*	0.010*	—	0.016*	0.030*

\*  $P < 0.05$ ; —, not applicable ( $P > 0.05$ ).

taneously, age, SE, MAP fluctuation, and CMF were significantly associated with outcome variables ( $P < 0.05$ ). Significant predictor variables of MD were MAP fluctuation ( $P = 0.025$ ) and CMF ( $P = 0.006$ ). An increased MAP fluctuation of 1 mm Hg was associated with a decreased MD of 0.46 dB, and an increased CMF of 1 mm Hg was associated with a decreased MD of 0.57 dB.

The significant predictor variable of PSD was SE ( $P = 0.036$ ), MAP fluctuation ( $P = 0.025$ ), and CMF ( $P = 0.007$ ). An increased SE of 1 D was associated with an increased PSD of 0.20 dB. An increased MAP fluctuation of 1 mm Hg was associated with an increased PSD of 0.47 dB, and an increased CMF of 1 mm Hg was associated with an increased PSD of 0.57 dB.

Significant predictor variables of the AGIS score were CMF ( $P = 0.014$ ). An increased CMF of 1 mm Hg was associated with an increased AGIS score of 0.23.

Significant predictor variables of TSNIT average were age ( $P = 0.036$ ), MAP fluctuation ( $P = 0.012$ ), and CMF ( $P = 0.010$ ). A 10-year increase in age was associated with a decreased TSNIT average of 2.0, an increased MAP fluctuation of 1 mm Hg was associated with a decreased TSNIT average of 0.52, and an increased CMF of 1 mm Hg was associated with a decreased TSNIT average of 0.53.

None of the predictor variables was associated with the superior average.

Significant predictor variables of the inferior average were age ( $P = 0.013$ ), MAP fluctuation ( $P = 0.018$ ), and CMF ( $P = 0.016$ ). A 10-year increase in age was associated with a decreased inferior average of 2.3, an increased MAP fluctuation of 1 mm Hg was associated with a decreased inferior average of 0.49, and an increased CMF of 1 mm Hg was associated with a decreased inferior average of 0.50.

Significant predictor variables of NFI were MAP fluctuation ( $P = 0.041$ ) and CMF ( $P = 0.030$ ). An increased MAP fluctuation of 1 mm Hg was associated with an increased NFI of 0.43, and an increased CMF of 1 mm Hg was associated with an increased NFI of 0.45.

Figure 1 illustrates two representative cases that may reflect the association of CMF with the structural and functional glaucomatous damage at initial evaluation. Patient 1 had lower mean in-hospital IOP, larger IOP fluctuation, larger MAP fluctuation and larger CMF compared with Patient 2, whereas visual field indices and GDx-VCC parameters in patient 1 revealed more advanced glaucomatous damage.

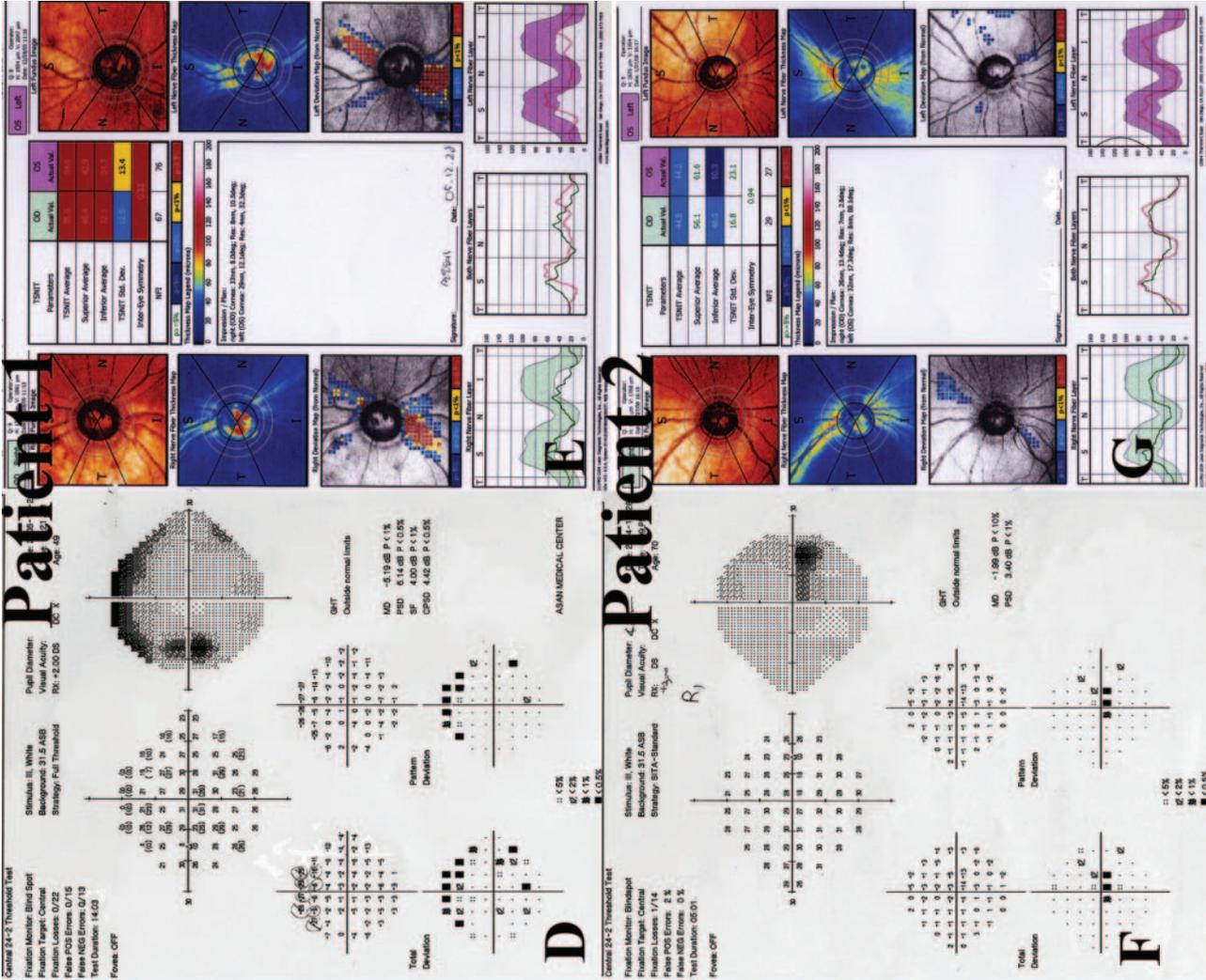
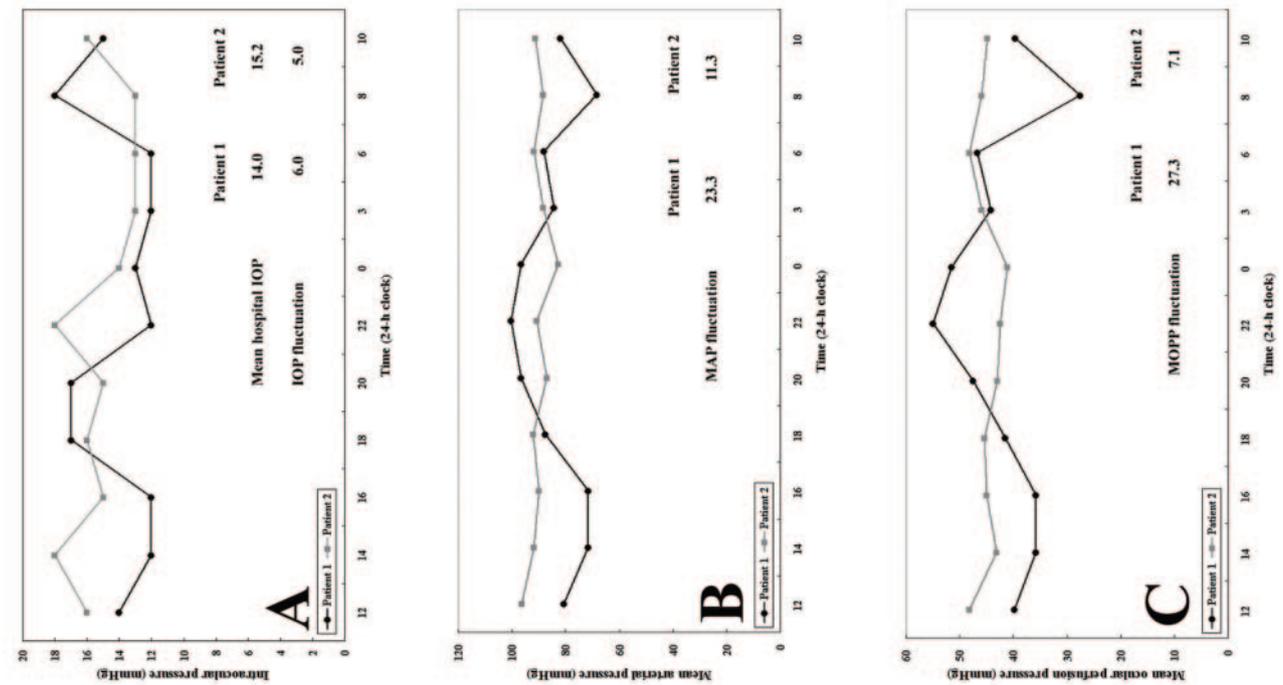
## DISCUSSION

The percentage decrease in diurnal MOPP was found to be significantly larger in patients with untreated POAG than in

normal subjects, suggesting that relative diurnal change in MOPP may be a risk factor for POAG.<sup>29</sup> We have shown that CMF is positively associated with visual field indices (MD, CPSD) at initial diagnosis of NTG.<sup>30</sup> In that study, however, we simply compared biometric parameters between the study and control groups or based our results on a univariate linear regression model, but we did not consider interactions between each systemic and ophthalmic measurement. Using multivariate regression models, we investigated the clinical risk factors that are consistently important in determining the severity of glaucomatous damage in patients with NTG, as determined by functional and anatomic outcomes at initial evaluation, based on results derived from HVF tests and SLP examination on RNFL. To our knowledge, this report is the first to show that circadian MOPP fluctuation is the most consistent risk factor for advanced glaucomatous damage.

There have been several studies for investigating risk factors for open-angle glaucoma, including NTG. Although several studies have reported that CCT is a risk factor for advanced glaucomatous damage,<sup>22-24</sup> other studies have shown that CCT may not be a risk factor for glaucoma progression.<sup>25,35,36</sup> These findings that CCT was not a risk factor for glaucoma progression may be explained by the artifacts in the initial evaluation of glaucoma, including a selection bias caused by late referral of patients with glaucoma who have lower CCT,<sup>25</sup> or higher IOP, which may result in worse visual field results, when compensating for lower CCT. As CCT could affect measured IOP by GAT, CCT, and IOP should be considered together for risk factor analysis. As for IOP fluctuation in glaucoma, we found a similar refutation of previous studies. In contrast to the idea that IOP fluctuation is a risk factor for glaucoma progression,<sup>16</sup> Bengtsson and Heijl<sup>21</sup> revealed that the association of IOP fluctuation with glaucoma progression becomes insignificant when IOP fluctuation is separated from IOP level by multivariate analysis. Recently, we reported that increased CMF is associated with worsened visual field indices in univariate regression analysis.<sup>30</sup> Still, it is necessary to evaluate the conjoined effect of the biometric parameters by multivariate modeling to show that CMF is an independent risk factor for advanced glaucomatous damage.

When univariate and multivariate regression analyses were performed to determine the association between independent risk factors and glaucomatous damage in a previous study, CCT was found to be the most consistent risk factor for advanced glaucomatous damage.<sup>24</sup> The independent variables included in that study were age, SE, sex, race, family history of glaucoma, IOP, and CCT. IOP was measured in the clinic during the daytime and neither circadian IOP fluctuation nor peak IOP measured during 24-hour phasing was considered. In the



present study, based on 24-hour monitoring of IOP and BP, we obtained biometric parameters associated with IOP and BP, which were mean in-hospital IOP, peak in-hospital IOP and IOP fluctuation, average MAP, and MAP fluctuation.

We sorted our outcome variables into two groups, functional and anatomic variables. The functional outcome variables included visual field indices (MD, PSD) on HVF printouts and AGIS score, whereas the anatomic outcome variables included SLP-VCC parameters. The latter may reflect the real global and regional RNFL thickness and detect RNFL loss in advance of the development of visual field deficits.<sup>37,38</sup> In addition, intra- and interoperator reproducibility of SLP-VCC measurements has been shown to be high.<sup>39,40</sup>

We found that age and CMF were associated with some outcome variables by univariate modeling. Increased age was associated with decreased inferior average on SLP-VCC, whereas increased CMF was associated with increased PSD and AGIS score on HVF. The association of age and inferior average may reflect the progressive loss of RNFL with aging in normal subjects.<sup>41,42</sup> Our study group, however, mostly consisted of elderly patients with NTG (mean age: 55.0 years), not revealing the significant association between age and the other GDx-VCC parameters. The finding that there was no association between SE and RNFL parameters on GDx-VCC was consistent with a recent report with examinations performed by optical coherence tomography.<sup>43</sup>

The significant negative association between MD and CMF shown in our previous report<sup>30</sup> was in disagreement with the lack of association shown here. This may be explained by the relatively smaller sample size compared with that of our previous study ( $n = 113$  versus  $n = 132$ ). However, there was a significant association between PSD and CMF. For reference, PSD reflects localized visual field defects, whereas MD primarily reflect diffuse visual field changes (i.e., lens opacity or refractive errors).<sup>44</sup> The AGIS score, which has been shown to be effective in interpreting glaucomatous visual field,<sup>31</sup> also correlated significantly with CMF in our study. Thus, the association of CMF and PSD with AGIS score may strengthen the relationship between CMF and the development of glaucomatous visual field deficit.

In contrast to earlier findings that described a correlation between CCT and glaucoma severity,<sup>24</sup> we did not observe these correlations in our study. This may have been due to differences in the patient population, in that 99% of patients had high-tension glaucoma HTG, and only 1% had NTG in the previous study. In contrast, our population purely consisted of patients with NTG. Our results are consistent with recent findings indicating a lack of association between CCT and baseline visual field test by univariate and multivariate analyses.<sup>35,45</sup>

Of note, we did not exclude the patients with IOP >21 mm Hg during the 24-hour phasing from the study group, since NTG diagnosis in the present study was based on the IOP measurements at clinic hours. Although five patients had IOP >21 mm Hg during the 24-hour phasing, they were included in the analysis, as NTG is traditionally defined by IOP levels measured during clinic hours. Moreover, four of five patients who had IOP >21 mm Hg had a single record of IOP >21 mm Hg during the phasing. In addition, it has been suggested that segregation of persons with OAG based on a single arbitrary

IOP criterion of 21 mm Hg may increase the chance of missing the real association that is sought.<sup>46</sup>

When we considered all independent variables together by multivariate modeling, we found that CMF was the most consistent risk factor for outcome variables. Increased CMF was mostly associated with worsened structural and functional parameters that reflect glaucoma severity. The lack of significant association between CMF and superior average in our study may be due to the relatively modest visual field damage (MD = -6.1, AGIS score = 4.6), since rim loss is usually most pronounced in the inferotemporal disc region of eyes with modest glaucomatous damage.<sup>47</sup> These results indicate that CMF may play the most important role among the risk factors for glaucoma. In addition to being important in patients with NTG with nocturnal hypotension,<sup>30</sup> CMF may be also have a role in the development of glaucoma, regardless of nocturnal BP reduction.

We also found that MAP fluctuation was associated with MD, PSD, TSNIT average, inferior average, and NFI, findings consistent with those of previous studies suggesting that nocturnal hypotension may be involved in the development and progression of glaucoma.<sup>13,48,49</sup> The findings that age and SE were associated with some of the dependent variables may reflect the increased risk of OAG in old age and in myopic subjects.

Recently, a high percentage of patients with NTG were found to exhibit an Alzheimer's disease (AD)-like perfusion pattern in brain magnetic resonance imaging, although none was clinically diagnosed with AD, and those with this AD-like pattern showed a more rapid progression of visual field defects than those with a normal pattern.<sup>50</sup> These findings suggest that NTG and AD may have a common pathologic mechanism. There have also been several studies that indicate the relationship between blood flow variation and end-organ damages. Altered circadian BP rhythm has been associated with cerebral blood flow change, resulting in cerebrovascular damage,<sup>51-54</sup> and patients with nocturnal hypotension may also be at increased risk for development of left ventricular hypertrophy or myocardial infarction.<sup>55,56</sup> Excess free radicals derived from ischemia and reperfusion may contribute to reversible or irreversible manifestations of cell injury.<sup>57,58</sup> From these, we can hypothesize that chronic repetitive circadian ocular blood flow variations could result in accumulative ischemia and reperfusion effects, manifested in the form of RNFL damage and corresponding visual field loss.

Our study has several limitations, including the relatively small sample size for multivariate regression analysis. However, our finding, that CMF affects most outcome variables in functional and anatomic terms, was consistent and thus supports our hypothesis. A second limitation of our study is the inability to generalize our findings to all types of primary open-angle glaucoma classified by IOP level, since 24-hour IOP and BP monitoring was performed only in patients with IOP ≤21 mm Hg. Third, our calculation of MOPP, based on the theoretical formula, may not reflect the real physiological status of ocular perfusion. Direct measurement of ocular blood flow could result in different outcome. Autoregulation of blood flow or locally compromised vascular status (i.e., atherosclerosis) may also play a role in the ocular blood flow. Fourth, there may have been some selection bias in our patient population, be-

**FIGURE 1.** Example cases: (A-C) 24-hour monitored IOP, MAP and MOPP data from a 50-year-old man with NTG (patient 1) revealed that lower mean hospital IOP, larger IOP fluctuation, larger MAP fluctuation, and larger MOPP fluctuation compared with that of a 72-year-old woman with NTG (patient 2). Circadian MOPP fluctuations were 27.3 mm Hg in patient 1 and 7.1 mm Hg in patient 2. (D, F) HVF test revealed worse visual field indices (MD, -5.2 dB versus -2.0 dB; PSD, 6.14 dB versus 3.40 dB) and increased AGIS score (7 vs. 0) in patient 1 than in patient 2. (E, G) GDx-VCC examination revealed more widespread attenuation of RNFL thickness in the right eye of patient 1 than in patient 2.

cause patients referred to a tertiary hospital may have more advanced glaucomatous damage. However, our series of patients included in the present study are the whole patients who initially visited our clinic during the period from November 2004 to June 2006 and met the inclusion criteria. Thus, we believe that our patients could represent a consecutive series. Fifth, the AGIS scores were calculated not only from the 24-2 FT program, but also from the 24-2 SITA standard program in our study. As this scoring system was originally designed for the 24-2 FT program, there may be some deviation with the 24-2 SITA standard program. Sixth, measuring BP and IOP with patients the sitting position during nocturnal samplings may not reflect the best possible physiological status. Somewhat different results may have been obtained if we had measured BP and IOP in a seamless physiological manner at these hours. Feke et al. (*IOVS* 2002;43:ARVO E-Abstract 841) showed that, however, there is no significant change in retinal blood flow from the baseline during postural change, when measured by laser Doppler flowmetry, in a group of healthy women. This implies that increased IOP in the supine position may not affect the ocular blood flow, as there may be proportionally increased blood flow to the eye due to postural change, and it could be a supplementary supporting explanation for our methods.

In conclusion, we found that circadian MOPP fluctuation was the most consistent clinical risk factor in determining glaucoma severity in patients with NTG. These findings may suggest that relatively large reductions in ocular perfusion pressure may lead to daily repetitive ischemic insult, followed by reperfusion damage. These accumulative injuries to ocular tissue may be manifested as glaucoma severity in terms of functional and anatomic outcome variables. Our results suggest that NTG may have a common pathologic mechanism with other chronic ischemic end organ diseases.

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