Effect of Nocturnal Blood Pressure Reduction on Circadian Fluctuation of Mean Ocular Perfusion Pressure: A Risk Factor for Normal Tension Glaucoma

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Purpose. To study blood pressure (BP), intraocular pressure (IOP), and mean ocular perfusion pressure (MOPP) in patients with untreated normal tension glaucoma (NTG), and to investigate the relationship between circadian MOPP fluctuation and visual field status at initial presentation.

Methods. IOP and BP were evaluated in hospital over 24 hours in 132 patients with NTG, with measurements taken every 2 hours between 12 PM and 10 AM the following day, except for the period between 12 and 6 AM, during which measurements were taken every 3 hours. MOPP was calculated from the 24-hour IOP and BP data. Patients were classified into three groups—nondippers, dippers, and overdippers— corresponding to the degree of reduction in their nocturnal mean arterial pressure (MAP) compared with their diurnal MAP. IOP and systemic and ocular hemodynamic parameters were compared among the groups. The correlations between circadian MOPP fluctuation and visual field scores (mean deviation [MD] and corrected pattern standard deviation [CPSD]) at initial presentation were analyzed.

Results. Forty-one (31.1%) of the patients with NTGs were classified into the nondipper group, 36 (27.2%) into the dipper group, and 55 (41.7%) into the overdipper group. Marked circadian MOPP fluctuation was noted in the overdipper group ($P < 0.05$). Circadian MOPP fluctuation showed positive associations with visual field indices at initial diagnosis of NTG ($P < 0.05$, $R^2 = 0.056$ with MD, $R^2 = 0.038$ with CPSD).

Conclusions. Marked circadian MOPP fluctuation was associated with nocturnal BP reduction. Circadian MOPP fluctuation may be a risk factor for the development of NTG. (*Invest Ophthalmol Vis Sci.* 2006;47:831–836) DOI:10.1167/iovs.05-1053

Numerous studies of patients with normal tension glaucoma (NTG) support the hypothesis that vascular factors are significantly involved in the development of the disease.[1–8] Vascular risk factors include migraine, blood transfusion, Raynaud's phenomenon, and nocturnal blood pressure (BP) reduction.[9–12] Nocturnal BP reduction is caused by a reduction in sympathetic activity during the night with a reduced amount of circulating catecholamine hormones, which can in turn lead to a decrease in heart rate, cardiac input, and peripheral resistance. Therefore, in patients with sympathetic dysfunction, the nocturnal reduction in BP can be increased (e.g., in patients with atherosclerosis, vasospastic disorders, or inadequate antihypertensive treatment) or absent (e.g., in patients with diabetes mellitus, orthostatic hypotension, or corticosteroid treatment).[13] Studies have been conducted to investigate the relationship between nocturnal hypotension and glaucomatous optic neuropathy. In the general population, approximately two thirds of individuals exhibit a 5% to 10% physiological nocturnal BP reduction. The remaining individuals are classified as either nondippers or overdippers.[14,15] Patients were divided into dippers or nondippers based on the criteria that the mean daytime BP falls by more than 10% at night in a published article.[16] There is, however, some controversy in the definition of nocturnal BP "dip" between the previous studies on the normal range of nocturnal BP reduction in healthy people. The two main reasons for this controversy between studies appear to be the different method of monitoring BP and the time intervals used to define daytime and nighttime.[14] In the present study, we modified the standard for classification of nondippers, dippers, and overdippers, which was adopted in a previous study.[15]

Both nondippers and overdippers may be at increased cardiovascular risk for development of end-organ damage, such as left ventricular hypertrophy, silent cerebrovascular disease, or myocardial infarction.[13,17,18] Patients with NTG have been reported to show significantly greater nocturnal BP decreases than have healthy people.[19] It has been reported that greater reduction in nocturnal BP leads to greater progression of glaucoma.[15,16]

The role of diurnal IOP variation in the development of glaucoma has been debated.[20–23] Asrani et al.[20] reported that a large fluctuation in diurnal IOP was an independent risk factor for the development of glaucoma, whereas some recent reports showed that the ranges of diurnal IOP variation were proportional to the level of IOP and concluded that diurnal variation in IOP itself was not an independent risk factor for the development of glaucoma.[24,25]

Harris et al.[26] demonstrated the presence of a reversible vasospasm specifically within the ocular vasculature of patients with NTG compared with the normal control, using color Doppler imaging and hypercapnia. It could be speculated from this work that blood flow change may be a contributing factor in the pathogenesis of NTG. Sehi et al.[27] demonstrated that relative diurnal change in IOP did not differ between patients with untreated primary open-angle glaucoma (POAG) and age-matched normal subjects. They also found that the percentage decrease in diurnal mean ocular perfusion pressure (MOPP) was 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. We selected patients with NTG instead of patients with POAG for this study, because there is some evidence that vascular factor may play a more important role in the pathogenesis of glaucomatous optic neuropathy in NTG than in POAG. Relatively few studies, however, have addressed the fluctuation of MOPP and its role as a risk factor for glaucomatous optic neuropathy.[22,27,28]

The purpose of the present study was to classify patients with untreated NTG by the degree of nocturnal BP reduction;

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to study BP, IOP, and MOPP parameters in each classification; and to investigate predictor variables of circadian MOPP fluctuation (CMF). We also evaluated the relationships between CMF and the severity of glaucoma at initial presentation.

METHODS

Patients

We evaluated 132 eyes of 132 consecutive patients (67 men and 65 women) with NTG (mean age ± SD, 60.4 ± 14.4 years) in a retrospective chart review. We reviewed the medical records of each patient with NTG who was seen by a glaucoma specialist (MSK) during the period from April 2000 to December 2004. All patients with diagnosed NTG based on clinical evaluation and visual field examination had undergone in-hospital 24-hour monitoring of IOP and BP, by a method described later in the article. Patients were eligible if they a had glaucomatous optic nerve appearance, including diffuse or focal neural rim thinning, hemorrhage, enlarged cupping, or nerve fiber layer defects indicative of glaucoma in addition to corresponding visual field loss, best-corrected visual acuity more than 20/40, maximum IOP less than 22 mm Hg on multiple measurements (at least three independent results) using Goldmann applanation tonometry (GAT), normal anterior chamber, and an open-angle on slit-lamp and gonioscopic examination, and glaucomatous visual field damage. Patients with evidence of intracranial or otolaryngeal lesion, history of massive hemorrhage or hemodynamic crisis, previous or current use of antiglaucoma medication, any other ophthalmic disease that could result in visual field defects, or a history of diabetes mellitus were not eligible for this study. Patients on antihypertensive or other hemodynamically active medications were not excluded. Patients with IOP greater than 21 mm Hg during in-hospital 24-hour monitoring were also excluded from the study. Central corneal thickness (CCT) was measured three times by ultrasonic pachymetry (DGH-550; DGH Technology Inc., Exton, PA) in all patients on the first visit, and the average in each patient was calculated. The affected eye was selected in patients with unilateral disease, and if both eyes of a patient showed NTG and met the inclusion criteria, one eye was randomly selected for entry. All procedures conformed to the Declaration of Helsinki, and the study was approved by the institutional review board 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 program on the Humphrey field analyzer (HFA; Carl Zeiss Meditec, Inc., Dublin, CA). The criteria for glaucomatous visual field defects were defined as follows: (1) a cluster of three points (except rim area) 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%, (2) a cluster of two points with a probability of less than 1%, (3) GHT outside 99% of age-specific normal limits, (4) or corrected pattern SD (CPSD) outside 95% of the normal limit. Only patients who had a reliable visual field within 1 month of their initial evaluation were included in the study. Reliable visual field was defined as having a false-positive error less than 33%, a false-negative error less than 33%, and a fixation loss less than 20%. Visual field data for analysis included mean deviation (MD) and CPSD.

Measurement of IOP and Systemic Hemodynamic Parameters

IOP and BP were evaluated in the 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 12 and 6 AM, during which measurements were taken every 3 hours. All IOP measurements were taken with a slit-lamp mounted GAT with the patient in the sitting position. IOP was measured after the subject had been seated for at least 3 minutes and was adjusted by 3 mm Hg for every 50 μm that the CCT deviated from 530 μm.[29] Systolic and diastolic BPs (SBP and DBP, respectively) 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.

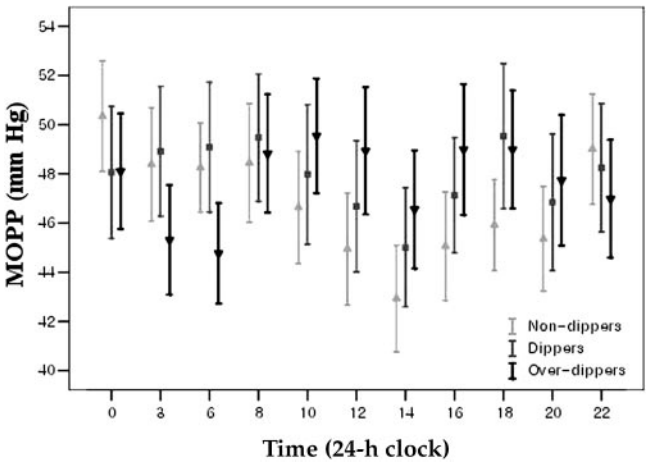

FIGURE 1. Twenty-four-hour phasing curves of circadian variation in MOPP levels in three groups of subjects. Overdippers showed different ranges of nocturnal MOPP that did dippers and nondippers, with statistical significances among groups at 3 AM (one-way ANOVA, $P = 0.048$) and 6 AM ($P = 0.009$). Error bars, 95% confidence interval.

Mean arterial pressure (MAP) was calculated as follows: MAP = DBP + [⅓ × (SBP − DBP)]. It was thus possible to calculate MOPP at a specified time from the difference between MAP and IOP substituted for venous pressure as follows: MOPP = ⅔ × MAP − IOP. Nocturnal MOPP was calculated as the average MOPP from 8 PM to 6 AM the following day, and diurnal MOPP was calculated as the average MOPP at all other times.[17,30] CMF was defined as the difference between the highest and lowest MOPPs recorded during the 24-hour period.

Definitions of Nondippers, Dippers, and Overdippers

Nocturnal BP reduction was calculated as [(diurnal average BP − nocturnal lowest BP)/diurnal average BP] × 100. Patients were then classified into three groups based on the degree of nocturnal BP reduction as follows: nondippers, <5% nocturnal BP reduction (or higher nocturnal BP than diurnal BP; $n = 41$); dippers, ≥5% but <10% reduction ($n = 36$); and overdippers, ≥10% reduction ($n = 55$).[15]

Statistical Analyses

Descriptive statistics (number and percentage for categorical variables and mean ± SD for continuous variables) were initially evaluated. Subsequently, 2 × 3 contingency χ^2 tests were used to detect the differences among groups for categorical variables (gender and hypertension). For analyzing continuous variables, one-way ANOVAs were performed to detect differences among groups, and Dunnett tests were performed for post hoc comparisons. The relationships between each continuous predictor variable (IOP and BP) and the outcome variable (CMF) were first assessed with linear regression by univariate modeling. Finally, all predictor variables were combined in a single regression model, to assess their joint effects on the outcome variables by multivariate modeling. The relationships between CMF and visual field parameters (MD and CPSD) were assessed by using linear regression. Differences reaching $P < 0.05$ were considered statistically significant.

RESULTS

Figure 1 presents the circadian MOPP profiles (error bars, 95% confidence interval) calculated for each group from data ob-

TABLE 1. Patient Demographics and Parameters of IOP, BP, and MOPP

	Nondippers (n = 41)	Dippers (n = 36)	Overdippers (n = 55)	P
Demographics				
Age	59.5 ± 15.3	60.6 ± 14.6	60.7 ± 13.6	0.915
Sex (M:F)	25:16	15:21	26:29	NS
Hypertension	14 (34.1%)	7 (19.4%)	16 (29.1%)	NS
IOP parameters				
Mean Office IOP	14.3 ± 2.7	15.5 ± 2.0	14.7 ± 2.4	0.097
Mean in-hospital IOP	13.7 ± 2.2	14.8 ± 1.8	13.9 ± 2.1	0.055
Peak in-hospital IOP	16.4 ± 3.1	17.7 ± 2.5	16.6 ± 2.4	0.085
IOP fluctuation	5.1 ± 2.5	5.6 ± 2.5	5.4 ± 1.7	0.585
BP parameters				
Mean SBP	123.5 ± 11.5	127.8 ± 13.7	126.7 ± 17.1	0.403
Mean DBP	74.5 ± 8.4	77.2 ± 9.4	75.2 ± 8.6	0.399
SBP fluctuation	33.0 ± 17.3	31.0 ± 9.1	37.4 ± 16.1	0.114
DBP fluctuation	19.7 ± 6.3	20.0 ± 6.6	25.1 ± 7.9	< 0.001†
MOPP parameters				
Mean MOPP	46.8 ± 5.5	47.9 ± 6.2	47.7 ± 6.3	0.725
Diurnal MOPP	45.6 ± 5.2	47.5 ± 6.2	48.5 ± 7.7	0.108
Nocturnal MOPP	49.0 ± 6.2	48.6 ± 6.6	46.3 ± 6.6	0.091
Circadian MOPP Fluctuation	15.1 ± 4.9	15.6 ± 5.0	18.3 ± 5.8	0.007†
HFA indices				
MD	−7.8 ± 7.0	−7.2 ± 6.7	−7.0 ± 5.9	0.853
CPSD	6.3 ± 4.0	4.7 ± 3.4	5.5 ± 4.2	0.317

Data are expressed as the mean ± SD, and all data were recorded over a 24-hour period. Mean office/in-hospital IOP was calculated as the mean IOP measured at the clinic. Peak in-hospital IOP was the highest IOP. IOP fluctuation was defined as (peak IOP − trough IOP). SBP/DBP fluctuation was defined as (peak SBP/DBP − trough SBP/DBP). Diurnal/nocturnal MOPP was calculated as the mean of the daytime (8 AM to 6 PM)/nighttime (8 PM to 6 AM) MOPP. Circadian MOPP fluctuation was defined as (peak MOPP − trough MOPP).

* One-way ANOVA was performed to detect differences among groups, except for categorical variables (gender and hypertension), for which 2 × 3 contingency χ^2 tests were used.

† $P < 0.05$.

tained over the 24-hour period. Overdippers showed a different range of the nocturnal MOPP phasing compared with dippers and nondippers, with statistically significant differences among groups at 3 AM ($P = 0.048$, one-way ANOVA) and 6 AM ($P = 0.009$).

Table 1 presents patient demographics and mean IOP, BP, and MOPP. The distribution of gender and the presence or absence of hypertension were not different among groups ($P > 0.05$, χ^2 test). Similarly, mean office IOP, mean in-hospital IOP, peak in-hospital IOP and IOP fluctuation were not different among the groups, nor were there differences in mean SBP or DBP ($P > 0.05$, one-way ANOVA). There were no remarkable tendencies found in these parameters. DBP fluctuations for each group were 19.7 ± 6.3 mm Hg for nondippers, 20.0 ± 6.6 mm Hg for dippers, and 25.1 ± 7.9 mm Hg for overdippers, respectively. There was a statistical significance in DBP fluctuation ($P < 0.001$). Post hoc comparison revealed that overdippers had a significantly larger DBP fluctuation than did the other two groups ($P < 0.05$, Dunnett test). There was, however, no significant difference among groups in SBP fluctuation. Mean MOPP, diurnal MOPP, and nocturnal MOPP were not significantly different among groups. Among these parameters, even if there was not a significant difference between the groups, overdippers had a higher diurnal MOPP (48.5 ± 7.7 mm Hg for overdippers, 45.6 ± 5.2 mm Hg for nondippers, and 47.5 ± 6.2 mm Hg for dippers) and a lower nocturnal MOPP (46.3 ± 6.6 mm Hg for overdippers, 49.0 ± 6.2 mm Hg for nondippers, and 48.6 ± 6.6 mm Hg for dippers) than did other groups. CMF in each group was 15.1 ± 4.9 mm Hg for nondippers, 15.6 ± 5.0 mm Hg for dippers, and 18.3 ± 5.8 mm Hg for overdippers. There was a significant difference in CMF among groups ($P = 0.007$). Overdippers had a significantly larger CMF than did the other groups on the post hoc comparison test (Fig. 2). HFA indices (MD, CPSD) at the initial diagnosis of NTG did not differ among the groups ($P > 0.05$).

Results of univariate and multivariate modeling are presented in Table 2. In univariate modeling, of four IOP parameters, only IOP fluctuation was a significant predictor of CMF ($P = 0.026$, linear regression). Of four BP parameters, mean SBP ($P = 0.003$) and both SBP ($P < 0.001$) and DBP ($P < 0.001$) fluctuations were significant predictors of CMF. When all variables were considered simultaneously by multivariate modeling, peak in-hospital IOP was a significant predictor of CMF ($P = 0.004$), with an increase of 1 mm Hg in peak in-hospital IOP equating to increases of 0.27 mm Hg in the CMF. SBP fluctuation was a significant predictor of CMF ($P < 0.001$), with an increase of 10 mm Hg in SBP fluctuation equating to an increase of 1.0 mm Hg in CMF. DBP fluctuation was a significant predictor of CMF ($P < 0.001$), with an increase of 10 mm Hg in DBP fluctuation equating to increases of 5.4 mm Hg in CMF.

CMF correlated significantly with MD ($R^2 = 0.056$, $P = 0.008$) and CPSD ($R^2 = 0.038$, $P = 0.046$) on HFA indices at initial presentation on linear regression (Fig. 3).

DISCUSSION

To our knowledge, this is the first report to address the association between nocturnal BP reduction and CMF. Of 132 patients with NTG, 55 (41.7%) were classified in the overdipper group. The prevalence of overdippers in the normal population has not been accurately established, since the definition

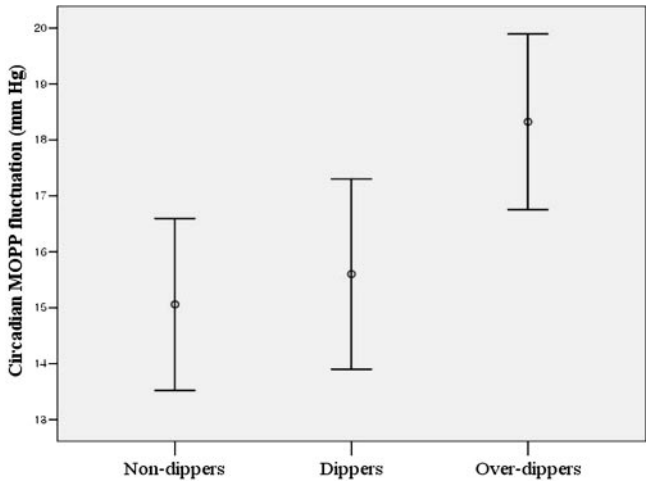

FIGURE 2. CMF in three groups of subjects. Overdippers had a significantly larger CMF than did the other groups on post hoc comparison test (Dunnett's test; $P = 0.007$ between nondippers and overdippers, $P = 0.035$ between dippers and overdippers). Error bars, 95% confidence interval.

TABLE 2. Probabilities for Tests of Significance of Variables in Predicting Circadian Fluctuation of MOPP: Univariate and Multivariate Models

	Circadian MOPP Fluctuation	
	Univariate Modeling	**Multivariate Modeling**
IOP parameters		
Mean Office IOP	0.478	—
Mean in-hospital IOP	0.475	—
Peak in-hospital IOP	0.095	0.004*
IOP fluctuation	0.026*	—
BP parameters		
Mean SBP	0.003*	—
Mean DBP	0.160	—
SBP fluctuation	<0.001*	<0.001*
DBP fluctuation	<0.001*	<0.001*

* $P < 0.05$; ellipses, not applicable

of nocturnal BP reduction varies in the literature, and few studies have been performed on normal subjects. It has been reported that blunted BP and heart rate modulation are frequently observed in NTG subjects.[31] Yazici et al.[32] found that excessive and repetitive nocturnal BP decreases occur more frequently in some patients with NTG, compared with those with high-tension glaucoma (HTG) or ocular hypertension. In this point of view, our finding of 55 (41.7%) overdippers in 132 patients could be regarded as higher than in the normal population. This relatively high proportion of overdippers in our series of patients with untreated NTG may reflect a vascular etiology of the disease.

It has been suggested that the range of IOP fluctuation is larger in patients with untreated glaucoma, and that large diurnal variation in IOP is an independent risk factor for the development of glaucoma.[20,33–36] In contrast, Bengtsson et al.[25] demonstrated that IOP fluctuation was not an independent risk factor for the incidence of glaucomatous visual field loss in subjects with ocular hypertension. Detry et al.[37] showed that 24-hour IOP profiles were closely comparable between two groups: one with stable visual fields and the other progressive visual field defects. These conflicting studies on whether IOP fluctuation is a risk factor for development of glaucoma caused us to consider CMF as a novel risk factor. In the present study, there was no difference in IOP fluctuation between the groups. We cannot directly compare our results with the previous data, because our work has a different study design based on the subgroup comparison within patients with NTG. Mean office/in-hospital IOP and peak in-hospital IOP did not also differ among the groups. Diurnal ranges of IOP variation in previous studies have been reported between 4.0 and 5.5 mm Hg in patients with untreated NTG,[38,39] which was similar to that reported in normal subjects.[40,41] Circadian ranges of IOP fluctuation in our study nearly fell within this range, with an average of 5.1 ± 2.5, 5.6 ± 2.5, and 5.4 ± 1.7 mm Hg for nondippers, dippers, and overdippers, respectively, with no significant differences among the groups. This implies that IOP fluctuation was not affected by the magnitude of nocturnal BP reduction, despite the evidence that IOP increases significantly with increasing systolic and diastolic BPs.[42,43]

Liu et al.[22] reported that the peak of ocular perfusion pressure was noted in the nocturnal period for normal adults in a clinical sleep laboratory. Our results revealed that there were differences between the diurnal and nocturnal MOPP level in nondippers and overdippers ($P < 0.001$, paired *t*-test), whereas there was no difference in dippers. Diurnal MOPP was higher in overdippers, whereas nocturnal MOPP was higher in nondippers. From these, we can deduce that there might be different pattern of CMF in patients with untreated NTG, when

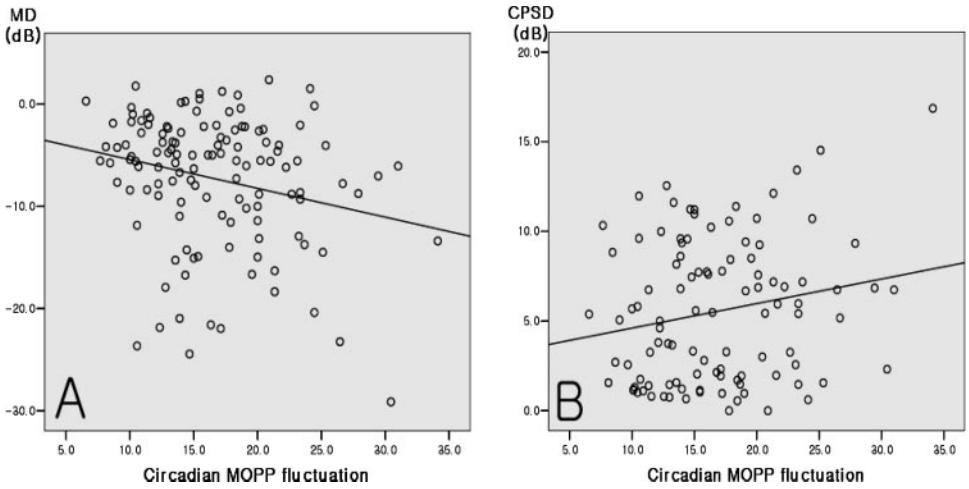

FIGURE 3. Scatter plots of circadian MOPP fluctuation versus MD and CPSD on Humphrey Field Analyzer (HFA; Carl Zeiss Meditec, Inc.) full-threshold 24-2 strategy. (**A**) CMF versus MD ($R^2 = 0.056$; $P = 0.008$) (**B**) CMF versus CPSD ($R^2 = 0.038$; $P = 0.046$).

they were classified by the degree of nocturnal BP reduction. As BP takes an important portion in theoretical MOPP calculation, we should take into account that classification of subjects by the degree of nocturnal BP reduction is very important in determining CMF.

Recently, emerging evidences have pointed to a role of ischemia in the pathogenesis of glaucoma. It has been suggested that in glaucoma patients the perfusion parameters of the lamina cribrosa and neuroretinal rim are significantly correlated with visual field defects as measured with a scanning laser Doppler flowmeter.[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 the IOP level. These previous reports raise the question of what causes the ischemia of the optic nerve head in the development of glaucoma. Reduced ocular perfusion pressure may play a role in ischemia of ocular structure. Based on the findings by Harris et al.,[26] as described earlier, we could carefully hypothesize that circadian fluctuation of ocular perfusion pressure may be a contributing factor in the pathogenesis of glaucomatous optic neuropathy. In detail, our hypothesis is that relatively excessive reduction of ocular perfusion pressure in overdippers may lead to short-term ischemia of ocular tissue, followed by reperfusion damage. Daily repetitive ischemic insults to ocular structures may be an underlying mechanism of glaucomatous optic neuropathy in patients with large CMF.

Previous studies constantly find that lower diastolic perfusion pressure (DBP – IOP) is a risk factor in glaucoma.[1,43,47,48] To demonstrate fluctuation of general ocular perfusion in our study, we thought that MOPP would be a more appropriate parameter as it integrates IOP, SBP, and DBP together and can therefore represent ocular perfusion status more appropriately than either systolic or diastolic perfusion pressure. As indicated in the formula, IOP and BP parameters affect theoretical MOPP value at each point of measurement. There are, however, little evidences on how these separate parameters contribute to the "circadian MOPP fluctuation," which has been found to have a positive association with glaucoma severity in our study. With these in mind, we investigated the circadian fluctuation patterns of MOPP.

Sehi et al.[27] reported that a significant difference was observed in the MOPP pattern between POAG and normal controls. Riccadonna et al.[31] showed that they did not confirm a different pattern of circadian BP fluctuation in NTG subjects compared with HTG and control groups. However, subgroup analysis based on nocturnal BP reduction was not performed in these studies. Our study design was not based on the comparison between the case and control groups, but based on the comparison of subgroups in patients with NTG. In our study, we classified patients with NTG into three groups based on different nocturnal BP reduction level and found that CMF was larger in overdippers of patients with NTG. Positive correlations between CMF and MD and CPSD on HFA indices support our hypothesis that CMF may be a contributing factor for the development of glaucomatous optic neuropathy in patients with NTG. As it is widely known that nocturnal BP reduction can cause various end-organ damage,[13,17,18] glaucomatous optic neuropathy in NTG may have been caused by large CMF in similar mechanism. In addition, we might also explain the widely recognized poor prognosis of overdippers based on our hypothesis.[15,49,50]

In this study, the patients on anti-hypertensive or other hemodynamically active medications were not excluded from enrollment. Most patients with previously diagnosed hypertension had been treated with antihypertensive medication. We know that taking antihypertensives could be a biasing factor to evaluate BP status. This study, however, was mainly designed to reveal the differences among patients with NTG with different nocturnal BP reduction level, rather than to describe natural BP aspects of patients with NTG. In addition, we have shown that there was no difference in prevalence of hypertension among groups in Table 1. Whether antihypertensive treatment has beneficial effect on CMF by flattening circadian BP fluctuation or not could be another subject for future research.

There were several limitations of our study. First, we did not observe the progression of glaucomatous damage in the patients. Rather, our data reflect the findings at the initial examination only. Second, even though we selectively chose patients with reliable visual field indices, there would be some variability in the results, since some patients may have had some difficulty in performing visual field examination for the first time. Third, 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 may also play a role, which can affect the real blood flow. Fourth, there may have been some selection bias in our patient population because patients referred to a tertiary hospital may have more advanced glaucomatous damage. Fifth, we are also aware that measuring BP and IOP in 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. However, as all patients in each group had measurements in the same condition, we believe that our results reasonably reflect true differences between groups. Further studies are needed to investigate longitudinal progression of the glaucomatous damage with different levels of CMF. Risk factors that make overdippers susceptible to the development of glaucoma should also be investigated.

In conclusion, a high percentage of patients with NTG had marked nocturnal BP reduction. Marked circadian MOPP fluctuation was associated with peak in-hospital fluctuation of IOP, SBP, and DBP from 24-hour data on IOP and BP. CMF was a significant predictor of advanced glaucomatous damage, as measured by HFA indices at the initial diagnosis of NTG. Our results suggest that larger CMF may have an important role in the pathogenesis of glaucomatous optic neuropathy in patients with NTG.

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