Association of dipping status of blood pressure, visual field defects, and retinal nerve fiber layer thickness in patients with normotensive glaucoma

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Abstract

The aim of this study was to evaluate the association between dipping status of blood pressure (BP), visual field defects (VFDs), and retinal nerve fiber layer (RNFL) thickness in patients with normotensive glaucoma (NTG). Our University echocardiography, electrocardiogram, 24-hour BP monitor and glaucoma database were reviewed from 2016 to 2018 to identify patients with NTG and hypertension (HTN). These NTG patients were followed for a mean 26.4 ± 13.6 months and were divided into 2 groups according to the absence or presence of VFDs. Among the 110 patients with NTG, 55 (50%) patients had VFDs. There were no differences of baseline characteristics between 2 groups. In univariate analysis, extreme dipper status at night in the 24-hour BP monitoring, HTN, age, diabetes mellitus, and hyperlipidemia were significantly associated with VFDs. In multivariate analysis, extreme dipper status at night in the 24-hour BP monitoring (odds ratio [OR] 4.094; $P = .045$) and HTN (OR 2.368; $P = .048$) were independent risk factors for VFDs at 2-year follow-up. Moreover, the RNFL thickness was thinner in NTG patients with VFDs ($P < .001$). VFDs group had more increased fluctuation of systolic and diastolic BP in 24-hour BP monitoring and that the extreme dipper status at night in the 24-hour BP monitoring and HTN itself were also associated with higher incidence of VFDs and thinning changes of the RNFL in patients with NTG, suggesting that more intensive medical therapy with close clinical follow-up will be required for these patients.

Abbreviations: BP = blood pressure, DBP = diastolic blood pressure, DM= diabetes mellitus, GON = glaucomatous optic neuropathy, HTN = essential hypertension, IOP = intraocular pressure, LV = left ventricle, NLR = neutrophil to lymphocyte ratio, NTG = normotensive glaucoma, OPP = ocular perfusion pressure, OR = odd ratio, POAG = primary open angle glaucoma, RNFL = retinal nerve fiber layer, SAP = standard automated perimetry, SBP = systolic blood pressure, SD = standard deviation, SD-OCT = spectral-domain optical coherent tomography, VFDs = visual field defects.

Keywords: dipping status of blood pressure, normotensive glaucoma, retinal nerve fiber layer, visual field defect

1. Introduction

Glaucoma is a heterogenous eye disease characterized by progressive neuropathy that is leading cause of blindness and visual impairment as well as the leading cause of irreversible blindness worldwide. It usually presented elevated intraocular pressure (IOP). And primary open angle glaucoma (POAG) is the most common type. Normotensive glaucoma (NTG) is defined as glaucomatous optic neuropathy without associated elevated IOP above normal limits. And the pathophysiology of NTG is still unclear.[1,2]

It is believed that general vascular dysfunction and defective cardiovascular neuro-regulation may play a major role in the pathogenesis of NTG.[3] A higher incidence of cardiovascular disorders and ischemic cerebral lesions has been reported in patients with NTG compared to patients with POAG or ocular hypertension.[4]

The association between systemic blood pressure (BP) and progression of glaucoma is complex and involves unclear mechanisms. Hypertension (HTN) can increase IOP and cause progressive vascular sclerosis, leading to end-organ damage.[5] However, other studies have reported that systemic hypotension can also decrease ocular perfusion pressure (OPP), which is defined as the difference between systemic BP and IOP. Low OPP may results in ischemic damage to the optic nerve.[6,7]

Ambulatory BP monitoring is a simple and noninvasive method for measuring both BP and pulse pressure (PP) during daily activities and sleep, eliminating the "white coat" effect. PP, defined as the difference between the systolic and diastolic

pressures, is suggested to be correlated with end–organ perfusion. Nocturnal HTN is associated with end–organ damage and is a much better indicator than daytime BP readings.[3]

However, NTG patients also had low systemic BP at night in 24-hour ambulatory BP monitoring.[3,7] The increased prevalence of systemic conditions such as low arterial BP with nocturnal hypotension, Raynaud's syndrome, migraines, and obstructive sleep apnea, especially in patients with NTG compared with those with POAG is suggestive of defective vascular autoregulation as an underlying factor in the pathogenesis and progression of NTG.[8] Nonetheless, the clinical importance of nocturnal hypotension in NTG patients is unproven, and there are limited data on the association between this nocturnal dipping status and progression of visual field defects (VFDs) in patients with NTG.

The aim of this study was to evaluate the impact of a dipping status of BP on VFD, retinal nerve fiber layer (RNFL) thickness and long-term clinical outcomes in patients with NTG.

2. Methods

2.1. Study design and study population

We retrospectively reviewed the medical records of 250 patients with NTG or pre-perimetric NTG (mean age, 61.0 ± 15.2 years; male, 43.3%) referred to a tertiary hospital (Kosin University Gospel Hospital) for evaluation of visual disturbance from February 2016 to November 2018.

Inclusion criteria included patients with clinically diagnosed NTG, who underwent 24-hour BP monitoring. Exclusion criteria included age >80 years; a history of cardiomyopathy, valvular or congenital heart disease; hepatic or renal disease; history of an acute cardiovascular, or cerebrovascular event within the preceding 3 months; history of any major trauma or surgery within the preceding 3 months; hyperthyroidism; uncontrolled HTN; presence of any malignancy; and diagnosis of any connective tissue disease; or any acute or chronic inflammatory disease. We used the following disease-specific exclusion criteria for glaucoma: previous ophthalmologic surgery, visual disturbance symptoms caused by conditions other than glaucoma.

Finally, 110 consecutive patients with NTG (mean age; 56.6 ± 14.1 years) were enrolled. Fifty five patients had VFDs and 55 patient did not have VFDs.

We compared the 24-hour BP parameters including total average of systolic blood pressure (SBP)/diastolic blood pressure (DBP), day average of SBP/DBP, night average of SBP/DBP and maximum SBP/DBP, and minimum SBP/DBP between groups. Extreme dipper status with 24-hour blood pressure monitoring was defined as greater than 20 mm Hg difference of SBP between day time and night time.

HTN was defined as having a systolic BP > 140 mm Hg and diastolic BP of greater than 90 mm Hg as recorded by repeated BP measurement in accordance to guidelines set by the Korean Society of Hypertension, or if the patient had a previous diagnosis. Diabetes mellitus (DM) was defined as having a fasting plasma glucose level of greater than 126 mg/dl on 2 consecutive assessments or a level of HbA1c greater than 6.5% in accordance to guidelines set by the Korean diabetes association, or if the patient is currently undergoing treatment for DM.

We also compared echocardiographic parameters, measurements of visual fields by standard automated perimetry, and

RNFL thickness measured by spectral-domain optical coherence tomography (SD-OCT).

2.2. Ethical considerations

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and the research protocol was approved by the ethics committee of Kosin University Gospel Hospital (IRB no. 2015-11-011). All patients provided written informed consent.

2.3. Definition of normotensive glaucoma and pre-perimetric NTG

NTG was diagnosed by a glaucoma specialist (LSU) based on the presence of glaucomatous optic neuropathy (GON) and compatible glaucomatous visual field loss; the presence of open angles on gonioscopy; maximal bilateral untreated intraocular pressure of less than 22 mm Hg, as measured by Goldmann applanation tonometry in an outpatient clinic at both 9 AM–12 PM and 2 PM–5 PM time periods; and the absence of secondary cause for glaucoma or other optic neuropathy. Pre-perimetric NTG was defined as satisfying all conditions of NTG except glaucomatous visual field loss. GON was diagnosed to be present in an eye with a vertical cup-to-disc ratio of more than 0.7, an asymmetrical rim-to-disc ratio of less than 0.2, a rim width-to-disc diameter ratio at the superior portion (11–1 o'clock positions) or the inferior portion (5–7 o'clock positions) of less than 0.1, or the presence of retinal nerve fiber layer defects detected in stereoscopic fundus examinations, SD-OCT, or both.[9]

2.4. Visual field test

Using standard automated perimetry (Humphrey Field Analyzer; Carl Zeiss Meditec, Inc. Dublin, CA) with the 24-2 Swedish interactive threshold algorithm, visual field testing was performed on patients. The eyes were considered to have glaucomatous visual field loss if the glaucoma hemifield test (GHT) results were outside normal limits and the pattern standard deviation showed a P value of less than .05 or the pattern deviation probability plots showed a cluster of 3 or more nonedged contiguous points having decreased sensitivity with a probability of less than 5% in the upper or lower hemifield and in 1 of these with a probability of less than 1%, confirmed on 2 consecutive reliable visual field tests. A reliable visual field test was defined as false-positive and false-negative error rates of less than 15% respectively and fixation loss of less than 20%.

2.5. Measurements of retinal nerve fiber thickness

The RNFL thickness measurements were derived using the Heidelberg Engineering Spectralis SD-OCT (Heidelberg Engineering Inc., Heidelberg, Germany). Spectralis OCT provides an automatic real-time function with an eye-tracking system that can increase image quality. A circular scan was manually placed in the center of the optic disc while the eye-tracking system was activated. The peripapillary RNFL thickness of the scans was determined automatically based on the software algorithms. The RNFL was also automatically segmented into 6 (superonasal, nasal, inferonasal, inferotemporal, temporal, and superotemporal segments). Then the computed average RNFL thickness values for the overall RNFL thickness and for each sector were presented

in the Spectralis OCT RNFL printouts. As suggested by the manufacturer, scans with signal strength of <15 dB (range, 0–40 dB) were excluded from the analysis.

2.5.1. Clinical endpoints. The primary end point was to find independent parameters which can predict VFDs in patients with NTG in relation to 24-hour BP monitoring data during follow-up. The secondary endpoint was to evaluate the RFNL thickness, 24-hour BP pattern, ECG and cardiovascular characteristics in relation to dipping status in patients with NTG during follow-up.

2.5.2. 24-hour BP monitoring. All enrolled subjects underwent 24-hour BP monitoring. The 3-channel 24 hours register was obtained by positioning 7 electrodes at the thoracic surface: 2 at both infra-clavicular spaces, 1 at the superior sternal aspect, 1 at the right 4th intercostal space at the mid-axillary axis, 1 at the right precordial region, 1 at the subxiphoid space and the last 1 (neutral electrode) at the right inferior costal area. The electrodes were connected to a Seer Light recorder (General Electric, Milwaukee, WI, USA).

2.5.3. Transthoracic echocardiography. All enrolled subjects underwent 2-dimensional transthoracic echocardiography. All examinations were performed using a commercially available Vivid 9™ (GE Medical System, Vingmed, Horten, Norway) ultrasound system. All recorded echocardiograms were measured and interpreted with clinical information blinded using a computerized off-line analysis station (Echopac 6.3.4; GE Medical System). All measurements were derived from 3 consecutive cardiac cycles and averaged. The left ventricular (LV) dimensions, wall thicknesses and left atrial dimensions were determined in the parasternal long-axis view with the M-mode cursor positioned just beyond the mitral leaflet tips perpendicular to the long axis of the ventricle according to the recommendations of the American Society of Echocardiography.[10] The LV ejection fraction was obtained via the modified biplane Simpson method from the apical 4- and 2-chamber views.

2.6. Statistical analysis

All continuous variables were expressed as either mean ± standard deviation (SD) or median (25th, 75th interquartile range), depending on the distribution. For continuous data, statistical differences were evaluated using Student t test or the Mann–Whitney U test, depending on the data distribution. Categorical variables were presented as frequencies (percent) and were analyzed using the Chi-Squared test. To determine whether any of the variables were independently related to VFDs, a multivariate analysis of variables with a P value <.05 in the univariate analysis was performed using logistic regression analysis. All correlations were calculated using the Spearman's rank correlation test. All statistical analyses were conducted using SPSS statistical software, version 19.0 (SPSS Inc., Chicago, IL, USA), and statistical significance was set at $P < .05$ (two-sided).

3. Results

The baseline demographics, medications and echocardiographic parameters are listed in Table 1. Among the 110 patients with NTG, 55 (50%) patients had VFDs. And there were no differences in baseline characteristics, including:- demographics, history of medication uses, and echocardiographic findings in both groups.

Table 1

Baseline demographics and echocardiographic findings in normotensive glaucoma patients according to visual field defects.

Variables	VFDs group (n = 55)	Non-VFDs group (n = 55)	P value
Age (years)	56.1 ± 14.6	57.4 ± 13.8	.363
Gender (Male, %)	25 (45.5)	23 (41.8)	.848
DM (%)	6 (10.9)	12 (21.8)	.197
HTN (%)	20 (36.4)	26 (47.3)	.334
CAD (%)	7 (12.7)	8 (14.5)	1.000
Stroke (%)	3 (5.5)	4 (7.3)	1.000
Medications			
Aspirin (%)	10 (18.2)	7 (12.7)	.599
Statin (%)	23 (41.8)	22 (40.6)	.960
Beta-blocker (%)	11 (20.0)	14 (25.5)	.650
ACEi or ARB (%)	18 (32.7)	24 (43.6)	.327
CCB (%)	16 (29.1)	20 (36.4)	.542
Diuretics (%)	1 (1)	1 (1)	1.000
Echo parameters			
LVEF (%)	63.6 ± 11.1	64.8 ± 7.8	.603
LVIDs (mm)	29.2 ± 5.5	30.1 ± 4.7	.507
LVIDd (mm)	45.8 ± 5.2	44.7 ± 4.7	.239
IVSD (mm)	11.8 ± 5.3	11.0 ± 2.2	.420
LVPWD (mm)	9.9 ± 1.9	9.8 ± 2.2	.799
LAD (mm)	34.8 ± 7.5	35.3 ± 7.4	.772
E velocity (cm/sec)	0.7 ± 0.1	0.7 ± 0.2	.832
A velocity (cm/sec)	0.7 ± .0.2	0.7 ± 0.2	.529
E/A	0.9 ± 0.4	1.1 ± 0.6	.298
E/E'	10.9 ± 4.5	9.6 ± 4.5	.246

VFDs = visual field defects, DM = diabetes mellitus, HTN = essential hypertension, CAD = coronary artery disease, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = calcium channel blocker, LVEF = left ventricular ejection fraction, LVIDs = left ventricular systolic diameter, LVIDd = left ventricular diastolic diameter, IVSD = interventricular septal thickness, LVPWD = left ventricular posterior wall thickness, LAD = left atrial diameter, E = the peak mitral flow velocity of the early rapid filling wave, A = peak velocity of the late filling wave due to atrial contraction, E' = early diastolic mitral annulus velocity, A' = late diastolic mitral annulus velocity.

The reasons for 24-hour BP monitoring were abnormal BP (99 patients, 90%), dyspnea (8 patients, 7.2%), fatigue (2 patients, 1.8%), and dizziness (1 patient, 1%) (supplementary figure, http://links.lww.com/MD/F327).

In the 24-hour BP monitoring findings, although there were no differences in total average, day time average of SBP and DBP, night time average of SBP and DBP were significantly different between 2 groups (VFDs group vs non-VFDs group; SBP 122.6 ± 23.1 mm Hg vs 133.8 ± 16.4 mm Hg, $P = .018$; DBP 76.9 ± 11.2 mm Hg vs 81.9 ± 9.6 mm Hg, $P = .038$). And dipping percentage of BP (SBP and DBP) at night compared to those of day time BP (SBP and DBP) were higher in patients with VPDs (VFDs group vs. non-VFDs group; SBP −7.9 ± 0.6 mm Hg vs −4.0 ± 0.9 mm Hg, $P = .031$; DBP −10.7 ± 0.1 mm Hg vs −6.6 ± 0.2 mm Hg, $P = .038$) in Table 2.

In regards to visual field parameters, the VFDs group had a significantly lower value for mean deviation compared with non-VFDs group. Retinal nerve fiber layer thickness measured by SD-OCT was significantly thinner in the VFDs group (Table 3).

Extreme dipper status of night BP in 24-hour BP monitoring, HTN, age, diabetes mellitus, and hyperlipidemia were significantly associated with VFDs in univariate analysis at 2-year follow-up.

In multivariate analysis, Extreme dipper status of night BP in 24-hour BP monitoring ($P = .045$) and HTN ($P = .048$) were independent predictors of VFDs in patients with NTG at 2-year follow-up (Table 4).

Table 2

24 hours blood pressure monitoring findings in normotensive glaucoma patients according to visual field defects.

Variables	VFDs group (n = 55)	Non-VFDs group (n = 55)	P value
Total average BP			
SBP total average (mm Hg)	133.0 ± 12.2	138.6 ± 14.1	.065
DBP total average (mm Hg)	84.5 ± 9.7	87.3 ± 9.2	.204
Pulse pressure total (mm Hg)	48.5 ± 9.3	51.3 ± 10.1	.203
Day time average BP			
SBP day average (mm Hg)	135.9 ± 12.2	139.5	.231
DBP day average (mm Hg)	86.9 ± 9.9	87.8 ± 10.4	.704
Pulse pressure day (mm Hg)	49.0 ± 9.7	51.7 ± 10.2	.233
Night time average BP			
SBP night average (mm Hg)	122.6 ± 23.1	133.8 ± 16.4	.018
DBP night average (mm Hg)	76.9 ± 11.2	81.9 ± 9.6	.038
Pulse pressure night (mmHg)	45.7 ± 19.8	51.8 ± 11.9	.106
BP trends during 24hr BP monitoring			
SBP max (mm Hg)	169.9 ± 15.5	172.2 ± 24.3	.620
DBP max (mm Hg)	114.1 ± 17.1	116.9 ± 24.3	.540
SBP min (mm Hg)	101.8 ± 12.8	108.0 ± 14.5	.051
DBP min (mm Hg)	58.4 ± 10.5	63.0 ± 10.1	.055
Dipping percentage (%) of BP at night compared to day time BP			
SBP ↓ percentage (%)	−7.9 ± 0.6	−4.0 ± 0.9	.031
DBP ↓ percentage (%)	−10.7 ± 0.1	−6.6 ± 0.2	.038

VFDs indicates visual field defects, BP = blood pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure.

Table 3

Ophthalmologic findings (Both eyes) in normotensive glaucoma patients according to visual field defects.

Variables	VFDs group (n = 55)	Non- VFDs group (n = 55)	P value
Right eye			
Visual field value (dB), mean ± SD			
Mean deviation	−8.6 ± 7.4	−1.9 ± 2.4	.003*
Pattern Standard Deviation	8.0 ± 19.7	1.5 ± 0.4	.262
Retinal nerve fiber layer thickness (μm), mean ± SD			
Average thickness	83.8 ± 24.7	102.4 ± 32.4	.001*
Superonasal segment	95.1 ± 53.9	111.7 ± 46.0	.116
Nasal segment	64.3 ± 37.8	74.5 ± 43.6	.216
Inferonasal segment	83.1 ± 30.5	106.4 ± 49.8	.004*
Infertemporal segment	101.5 ± 46.6	142.8 ± 35.2	<.001*
Temporal segment	73.5 ± 21.5	85.3 ± 38.1	.046*
Sueprotemporal segment	114.9 ± 37.6	138.2 ± 33.3	.002*
Left eye			
Visual field value (dB), mean ± SD			
Mean deviation	−8.0 ± 7.4	−3.0 ± 6.2	.029*
Pattern Standard Deviation	22.8 ± 83.4	2.5 ± 2.5	.403
Retinal nerve fiber layer thickness (μm), mean ± SD			
Average thickness	81.6 ± 17.7	111.4 ± 36.9	<.001*
Superonasal segment	98.5 ± 29.7	143.6 ± 66.7	<.001*
Nasal segment	59.1 ± 13.9	80.2 ± 44.4	<.001*
Inferonasal segment	89.2 ± 22.9	115.4 ± 52.1	.001*
Infertemporal segment	106.1 ± 42.9	135.5 ± 42.8	.001*
Temporal segment	66.2 ± 14.9	89.3 ± 48.9	.001*
Sueprotemporal segment	109.2 ± 31.7	156.14 ± 70.2	<.001*

* Visual field values were derived from ZEISS Humphrey Field Analyzer. Retinal nerve fiber layer thickness values were derived from Heidelberg Engineering Spectralis OCT. * indicate statistical significance.
VFDs = visual field defects, SD = standard deviation.

Kaplan–Meier analysis for event-free survival from VFDs in patients with NTG according to the dipping status of night BP in 24-hour BP monitoring was significantly lower in patients with extreme dipper status ($P < .001$; Fig. 1) compared with those without extreme dipper status at 2-year follow-up.

4. Discussion

Normotensive glaucoma is one of the subtypes of the glaucoma family which unusually presents without increased intraocular pressure. The pathogenesis of NTG is unclear, but appears to be a consequence of heterogenous etiologies such as nocturnal systemic hypotension and autonomic dysfunction.[1]

The interaction between systemic BP, intraocular pressure and OPP is a complex one that is not well understood in regards to the development and progression of NTG. One of the major factors is that vascular dysfunction and disturbed autoregulation leads to reduced perfusion in the capillary network of the optic nerve.[6] A previous study reported that the association between arterial blood pressure and progression of POAG showed a J curve phenomenon in patients with POAG.[11] Therefore, nocturnal hypotension and HTN may be risk factors for progression in glaucoma.

In our study, we evaluated the 24-hour ambulatory BP pattern in regards to its relation with VFDs in NTG patients. We found that the VFDs group had significantly lower nocturnal systolic and diastolic blood pressure compared to the non-VFDs group. This extreme dipping status may be an independent predictor for progression of VFDs in patients with NTG (OR: 4.09).

Although there are limited studies on the association between nocturnal hypotension and progression of VFDs in NTG patients, our result is similar with previous studies in Early Manifest Glaucoma trial, which suggested that low BP is a risk factor for progression of POAG with low baseline IOP.[12] A previous study also reported that a drop in nocturnal blood pressure is a risk factor for progression of glaucomatous optic neuropathy with a nocturnal dip of more than 10% in systemic

Table 4

Univariate and multivariate Cox analyses for visual field defects in patients with normotensive glaucoma at 2-year follow-up.

Variable. N (%)	Univariate analysis OR (95% CI)	P value	Multivariate analysis OR (95% C.I)	P value
Extreme dipper status of night BP in 24 hours BP monitoring	4.237 (1.112–16.141)	.034	4.094 (1.029–16.282)	.045
Hypertension	2.132 (1.085–4.615)	.045	2.368 (1.007–5.570)	.048
Age	1.005 (1.079–1.132)	.047		
Diabetes Mellitus	2.791 (1.010–8.554)	.043		
Hyperlipidemia	1.789 (1.000–4.288)	.051		

OR indicates odd ratio, CI = confidence interval, BP = blood pressure, Extreme dipper status = >20mmHg lower night blood pressure compared to day blood pressure in 24 hours blood pressure monitoring.
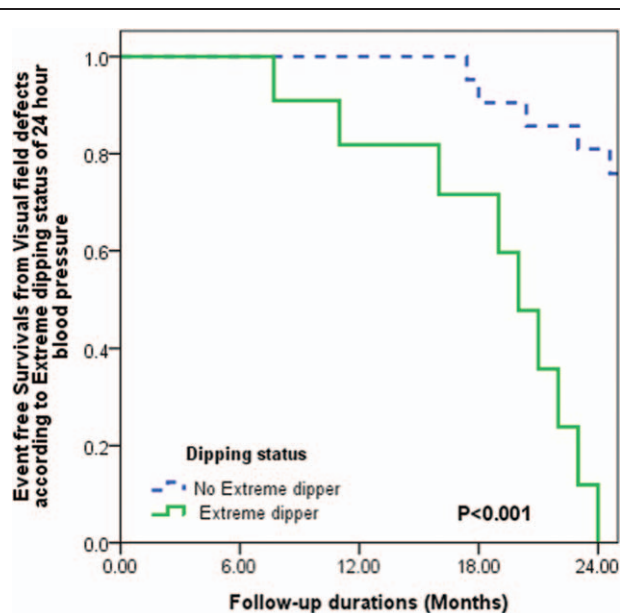
Figure 1. Kaplan–Meier curves for event free survivals from Visual field defect in patients with normotensive glaucoma according to dipping status.

BP being a significant risk factor for progressing VFDs in patients with both NTG and POAG.[6] Progressive NTG has been linked to increased BP variability and nighttime BP fluctuations, which are theorized to play a role in its pathogenesis.[2,13]

In our study, the VFDs group also showed more increased fluctuation of SBP and DBP. This result is consistent with previous studies suggesting that severe BP variability exceeding the limit of normal vascular auto-regulation causes an ocular blood flow deficit, resulting in ischemic optic nerve damage. Therefore, various approaches to managing BP variability as well as adequate BP control appear to be important in glaucoma management. In addition, increased BP variability caused by abnormal autonomic modulation of cardiovascular responses seems to function as a risk factor that can affect the early progression of NTG.[3,14,15]

In hypertensive patients with NTG, it is difficult to treat HTN using antihypertensive medications. However, excessive BP control for cardiovascular risk may lead to decreased OPP and may results in progression of NTG. There are also no clear management guidelines for NTG patients without HTN who had increased fluctuation of systemic blood pressure.

Glaucomatous structural changes are normally accompanied by functional losses, which can result in significant deterioration of vision and, diminished quality of life.[16] It is possible, though, that some patients will undergo structural optic nerve or RNFL changes before the condition can be detected with standard automated perimetry (SAP). The RNFL thickness of the defect area was noted markedly thinner in POAG with low-teen IOP values.[17] In our study, we also evaluated VFDs and optic neuropathy with SAP. The optic nerve fiber thickness was measured by OCT. In the VFDs group, optic nerve fibers were thinner and standard deviation values of the visual field were statistically lower, which is consistent with previous studies.[18,19]

Previous studies have shown some abnormal immune activity against the optic nerve in patients with VFDs. Neutrophil to lymphocyte ratio (NLR) is a novel marker of inflammation.[20,21] Therefore, we also checked NLR in our study. However, there

was no significant difference (VFDs group vs non-VFDs group; 2.3 ± 1.6 vs 2.3 ± 1.1, $P = .986$) in patients with NTG, which was consistent with another NTG study.[22]

Metabolic health status significantly increased the risk of POAG from a nationwide database.[23,24] This emphasizes the importance of glaucoma screening in patients with metabolic syndrome and obesity, including not only those who are metabolically unhealthy obese, but also those who are metabolically unhealthy non-obese. In addition, POAG patients manifested a cardiac autonomic failure associated with a significant depressor response soon after eating. Following carbohydrate ingestion, NTG patients exhibited a cardiac sympathetic hyper-responsiveness and vagal inhibition in the later phase of the postprandial state, irrespective of insulin resistance. In addition, both NTG and POAG showed blunted cardiac autonomic responses to postural challenge. Therefore, the current study provides important experimental evidence that glaucoma is associated with a systemic cardiovascular disorder. It provides a new mechanistic insight that the distinct autonomic dysregulation may underlie, or correlate with, the pathogenesis of the 2 forms of glaucoma. Clinically, it is worth noting that the assessment procedure is simple and noninvasive, and may be useful as a tool for monitoring responses to treatment in individual patients.

However, in our study, there was no difference in demographic characteristics including body mass index and, metabolic status in both groups.

There are some limitations in our study. First, this study was a single-center, retrospective study derived from real-world practice with inherent limitations. Hence the results of our study should be considered as more hypothesis generating, with future prospective studies being warranted to confirm our results. Second, asymptomatic episodes of NTG may not have been recognized because VFDs diagnosis was based on clinical symptoms, standard automated perimetry results, and retinal nerve fiber thickness by optical coherence tomography (OCT) in a 2-year period, which would not account for the insidious long-term nature of NTG. Third, patients with potentially reversible causes were excluded from the study. Therefore, the results of this study cannot be transferred to other patient populations with initial NTG diagnoses. This study presents new insights regarding systemic causes of NTG focusing on the effects of 24-hour blood pressure patterns beyond local intraocular chronic pressure variants.

In conclusion, the VFDs group in NTG patients had more increased fluctuation of systolic and diastolic BP in 24-hour BP monitoring as well as an extreme dipper status at night. HTN itself also was associated with a higher incidence of VFDs and thinning changes of the RNFL in patients with NTG, suggesting that more intensive medical therapy with close clinical follow-up will be required for these patients.

Author contributions

Conceptualization: Hyun Su Kim, Sung Il Im.
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