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Systemic Circulatory Parameters: Comparison Between Patients with Normal Tension Glaucoma and Normal Subjects Using Ambulatory Monitoring

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Purpose: To compare circadian changes of systemic circulation in patients with normal tension glaucoma (NTG) and normal subjects.

Methods: Forty-three patients with NTG and 226 normal subjects were enrolled in this study. Circulatory parameters, including blood pressure (BP) and pulse rate (PR), were measured in all subjects for 49 hours using an ambulatory monitoring system. In addition to a comparison between NTG patients and normal controls, the same parameters were compared between NTG patients who had progressive field defects and NTG patients who had stable field defects.

Results: The BP in NTG patients was significantly higher than in normal subjects. The nocturnal dip of BP in NTG patients was similar to the dip in normal subjects. However, the BP dip in NTG patients showing progressive visual field defects was significantly smaller than in patients with NTG showing stable visual field defects. Blood pressure fluctuation in sleep in the "progressive" patients was significantly greater than in the "stable" patients. Patients with NTG whose random BP was in a normal range showed a higher BP than normal subjects. The dip in PR in NTG patients was significantly lower than in normal subjects.

Conclusions: An insufficient physiological nocturnal BP dip or a greater nocturnal fluctuation in BP may disturb the microcirculation of, and/or may directly damage, the optic nerve, resulting in increasing field loss in NTG. **Jpn J Ophthalmol 2001;45:388–396** © 2001 Japanese Ophthalmological Society

Key Words: Ambulatory blood pressure monitoring, blood pressure, nocturnal dip, normal tension glaucoma, pulse rate.

Introduction

It is well known that an intraocular pressure (IOP) is the most important risk factor for the onset and deterioration of glaucoma. However, since von Graefe reported patients with glaucomatous optic nerve atrophy without IOP elevation,[1] it has been hypothesized that in addition to IOP, other risk factors would affect the onset and/or deterioration of glaucoma, especially in patients with normal tension glaucoma (NTG).

There are several reports describing a relation between systemic circulation and glaucoma. However, the results are not consistent. Leighton et al reported that blood pressure (BP) in patients with NTG was lower than in patients with primary open angle glaucoma (POAG).[2] Kaiser et al reported that patients with progressive POAG and NTG showed lower BP than controls.[3,4] In contrast, Levene reported no relation between BP and glaucoma.[5]

An ambulatory BP monitoring system was recently developed which records BP frequently and precisely along with amplitude of diurnal variation

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and short-term variability.[6,7] This system revealed the relation between systemic circulation and several disorders, such as cerebral damage,[8,9] renal microvascular damage,[8–11] and ocular diseases.[12–15] However, the relation between the circadian change in systemic circulation and glaucoma was not consistent in these previous reports. Graham et al reported that glaucoma patients with progressive visual field defects had a larger nocturnal arterial pressure reduction compared with glaucoma patients with stable visual fields.[13] Detry et al reported that POAG patients with progressive field loss showed a smaller BP dip compared with stable glaucoma patients.[14] Collignon et al reported that an abnormal absence of or increase of nocturnal dip in systolic BP was correlated with disease progression.[15]

Although it is hypothesized that risk factors other than IOP that affect glaucomatous optic nerve damage may be more deeply involved in patients with NTG than with other types of glaucoma, only a few previous reports investigated NTG patients. In the current study, therefore, we utilized an ambulatory BP monitoring system to compare the systemic circulation between patients with NTG and a large number of control subjects.

Materials and Methods

Fifty-three patients with NTG were followed up for more than 2 years (Table 1). They satisfied all of the following criteria: IOP never exceeded 21 mm Hg at any observation, including 24-hour continuous measurement; glaucomatous optic disk cupping and a visual field defect corresponding to optic disk cupping; no abnormal signs in their intracranial space and optic tract confirmed by computed tomography and/or magnetic resonance imaging; no history of severe blood loss or other events possibly causing optic nerve atrophy; no other severe ocular disease resulting in visual acuity loss or visual field defect; no systemic disease, especially no circulatory disease, such as hypertension.

Table 1. Enrolled Subjects

		No. of Subjects	Mean Age*
NTG†	Total	53	59.4 (28–85)
	Male	27	58.4 (32–85)
	Female	26	60.3 (28–78)
Normal	Total	226	48.4 (30–81)
	Male	144	45.9 (30–81)
	Female	82	52.1 (30–79)

*All values are years. Values in parentheses are ranges.
†NTG: normal tension glaucoma.

The normal control group was composed of 226 healthy subjects who had never had any severe disease, including glaucoma; their daily BP was in the normal range, never above 140 mm Hg systolic and 90 mm Hg diastolic. Although we did not perform an ophthalmic examination on each subject, no healthy subject had taken any antiglaucoma treatment. All subjects were well informed and agreed to this study.

Each patient was provided with an ambulatory monitoring system (A & D; Toshima-ku, Tokyo). These systems were made available at the outpatient clinic between 1 pm and 2 pm by one of the authors, who instructed patients participating in the study in their use; BP and pulse rate (PR) were monitored every 30 minutes for 49 hours automatically. All subjects recorded their daily activity during this period for later analysis. All medications including eyedrops were withdrawn from 1 day before the measurements to the end of the monitoring period. Data recorded in the apparatus were employed for a computer-operated analysis.

Patients with NTG were divided into two groups, a progressive group and a stable group. Patients in the progressive group had been followed up for more than 2 years, and had had more than six reliable static visual field tests using the Humphrey Statpac® program 30-2 (Allergan Humphrey System, San Leandro, CA, USA). "Progression" of field defects satisfied the following criteria: a significant deterioration in any eye with a P value $< .05$ in mean deviation or corrected pattern standard deviation was confirmed by the multiple visual field analysis program provided by Humphrey System, or a Spearman correlation coefficient by rank. Patients in the stable group had been followed up for more than 4 years and reliable static visual field tests were done more than six times; in both eyes, the global index of their visual field tests did not show significant deterioration, and their optic disks showed no significant change, as confirmed by two well-trained independent ophthalmologists. Visual field tests showing less than 20% fixation loss, 33% false positive, and 33% false negative, were defined as reliable. Visual acuity of all patients did not show a change of more than two lines throughout follow-up.

Parameters investigated in the current study are listed in Table 2. According to the activity log recorded by each subject, values were divided into waking and sleeping. The IOP in NTG patients was calculated according to their circadian values.

All patients were allocated to two groups by degree of nocturnal decrease in BP, either less than 10% or more than 10%, and are referred to as nondipper or dipper, respectively.

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Table 2. Investigated Parameters Regarding General Circulation

Parameters*
Blood pressure (BP)
Systolic BP
Diastolic BP
Mean BP
Waking BP
Sleeping BP
All-day BP
Hyperbaric index of systolic and diastolic BP
Hypobaric index of systolic and diastolic BP
Nocturnal dip
Pulse rate (PR)
Waking PR
Sleeping PR
All day PR
Hyperbaric index
Hypobaric index
Nocturnal dip

*Mean BP: diastolic BP + 1/3 (systolic BP − diastolic BP); dip: [waking time BP(PR) − sleeping time BP(PR)]/waking time BP(PR).

According to Harlerg et al,[16] excess beyond the normal range was evaluated by total area more than 90% confidence limits and expressed as hyperbaric index or hypobaric index, higher or lower than 90% confidence limits, respectively (Figure 1). These parameters quantify the degree of hypertension or hypotension in BP, and tachycardia or bradycardia in PR. Because no large population-based study to define a normal range for an ambulatory BP monitoring study is available, the 226 normal subjects in the current study were employed to define it in each generation.

The standard deviation of BP measured every 30 minutes was used as an indicator of BP fluctuation.

Because distribution between normal subjects and patients with NTG were not the same, in order to compare these two groups, a test for homogeneity of variance was employed, first using the Bartlett test, and then an analysis of covariance (ANCOVA) was applied. Unpaired Student *t*-test was used for comparison of titers among NTG patients to determine sex difference, hyperbaric index, and hypobaric index. The Spearman correlation coefficient by rank for correlation analysis and the Fisher exact test for analysis of prevalence of nondipper and subject characteristics were employed. *P* values less than .05 were considered statistically significant.

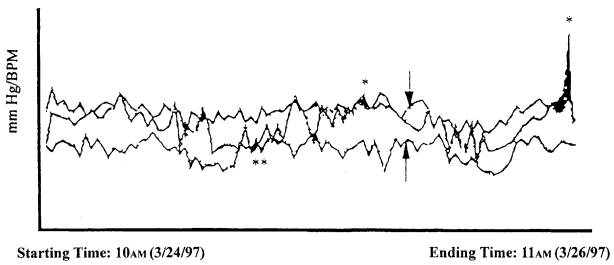

Figure 1. Schematic image of hyperbaric index and hypobaric index. Arrows indicate 90% confidence area. Unit of Y axis is mm Hg for blood pressure and beats per minute (BPM) for pulse rate. All areas in black which lie beyond 90% confidence areas were summed and expressed as *hyperbaric index or **hypobaric index.

Table 3. Characteristics of Patients with Normal Tension Glaucoma

	No. of Patients	(%)
Family history	5	(9.4)
Antiglaucoma eyedrops	1	(1.9)
Refraction		
Enmetropia*	18	(34.0)
Myopia†	25	(47.2)
High myopia‡	4	(7.5)
Hypertropia§	6	(11.3)
Splinter hemorrhage	7	(13.2)
BRVO¶	2	(3.8)

*≥±1 diopter (D).
†<−8D and >−1D.
‡>−8D.
§<1D.
¶branch retinal vein occlusion.

Results

Characteristics of Patients with NTG

Table 3 shows the characteristics of enrolled patients with NTG. One patient used isopropyl unoprostone eyedrops twice a day.

Comparison Between All Patients with NTG and Normal Subjects

The BP and PR in patients with NTG and in normal subjects, as previously reported, were lower during the night. The comparison between patients with NTG and normal subjects is shown in Table 4. Be-

Table 4. Comparison of Dips (Mean ± SD) Between Normal Subjects and Patients with Normal Tension Glaucoma

	Blood Pressure Dip		
Subjects	Systolic	Diastolic	Pulse Rate Dip
Normal (n=226)	10.66 ± 6.73	13.23 ± 8.73	19.93 ± 8.21*
NTG† (n=53)	10.78 ± 7.59	11.92 ± 6.71	15.56 ± 7.66

*$P < .001$, Bartlett test showed homogeneity of variance between two groups. Then, analysis of covariance was employed to compare them.
†NTG: normal tension glaucoma.

Table 5. Circulatory Parameters (Mean ± SD) of Patients with Normal Tension Glaucoma (NTG)*

	NTG (n=53)			
Parameters	Waking BP	Sleeping BP	Hyperbaric index	Hypobaric index
Systolic BP	130.45 ± 16.72	116.32 ± 17.94	3.64 ± 5.30	0.44 ± 0.70‡
Mean BP†	112.14 ± 14.50	98.35 ± 15.47	5.91 ± 6.60	0.09 ± 0.27‡
Diastolic BP	77.74 ± 8.11	68.32 ± 7.76	1.12 ± 1.36	0.25 ± 0.41‡
Pulse rate	70.39 ± 8.67	59.34 ± 8.89	0.56 ± 1.21	0.96 ± 1.54

*BP: blood pressure (mm Hg).
†Mean BP: diastolic BP + 1/3 (systolic BP − diastolic BP), hyperbaric index and hypobaric index: mm Hg/hour per day (BP), and beats per minute/hour per day (pulse rate).
‡$P < .001$ compared with hyperbaric index, paired Student *t*-test.

cause the homogeneity of variance of the BP and PR in both groups was confirmed by the Bartlett test, the ANCOVA was applied for comparison. The systolic BP dip and diastolic BP dip in both groups showed no significant difference, although patients with NTG showed lower values than normal subjects. However, the PR dip in patients with NTG was significantly less than in normal subjects.

Table 5 shows the hyperbaric index and hypobaric index of systolic, diastolic, and mean BP and PR of patients with NTG. The hyperbaric index of BP was significantly higher than their hypobaric index. The mean BP showed the greatest difference between the hyperbaric and hypobaric indices among all BPs, followed by systolic BP and diastolic BP.

No significant difference between the hyperbaric index and hypobaric index in the PR of patients with NTG was observed, but the hypobaric index was slightly higher than the hyperbaric index (Table 5).

Comparison Between BP Dip and PR Dip in NTG Patients

A significantly positive relation between BP dip and PR dip, especially in systolic BP dip ($P = .001$) and mean BP dip ($P = .005$) was observed (Figures 2a,b). The diastolic BP dip showed a positive correlation with PR dip, but it was not statistically significant. However, some cases did not show a nocturnal dip in either BP or PR.

IOP and BP in NTG Patients

Intraocular pressure showed a significant positive correlation with diastolic BP both during waking ($P = .009$) and sleeping ($P = .02$) (Figures 3a,b), but this correlation was not observed with systolic BP or mean BP.

Aging in Patients with NTG

Waking and sleeping systolic BP (Figures 4a,b), and waking mean BP (data not shown), showed a significant increase with age. Other BP parameters showed a positive correlation without statistical significance. The PR showed no change with age.

The BP dip showed a decrease with age, although this decline was confirmed statistically only in diastolic BP. The PR dip reduced significantly with age. Intraocular pressure decreased significantly with age ($P = .003$) (Figure 5).

Sex Difference

In the current study, 27 men and 26 women with NTG were studied; their mean age, refraction, number using antiglaucoma eyedrops, and prevalence of

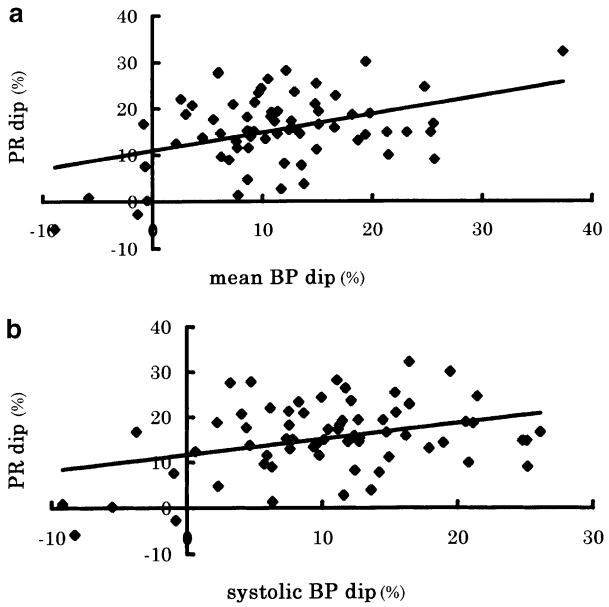

Figure 2. Relation between pulse rate (PR) dip and blood pressure (BP) dip in normal tension glaucoma patients. PR dip showed positive correlation with mean BP [(**a**) y = 0.3847x + 10.936, $P = .005$] and systolic BP [(**b**) y = 0.3535x + 11.627, $P = .001$] that was statistically significant. Statistical analysis was performed by Spearman rank correlation test.

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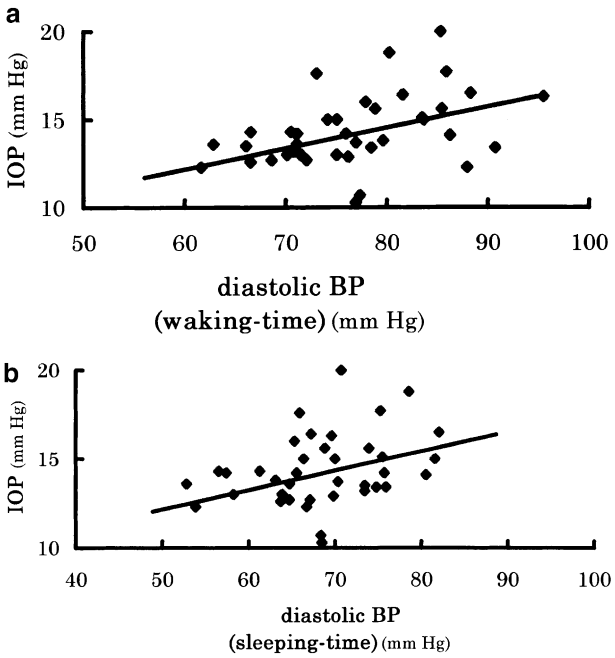

Figure 3. Relation between intraocular pressure (IOP) and blood pressure (BP) in normal tension glaucoma patients. Diastolic BP both in waking [(**a**) y = 0.118x + 5.0982, P = .009] and in sleeping times [(**b**) y = 0.1091x + 66928, P = . 02] showed significant positive relation with IOP by Spearman rank correlation test.

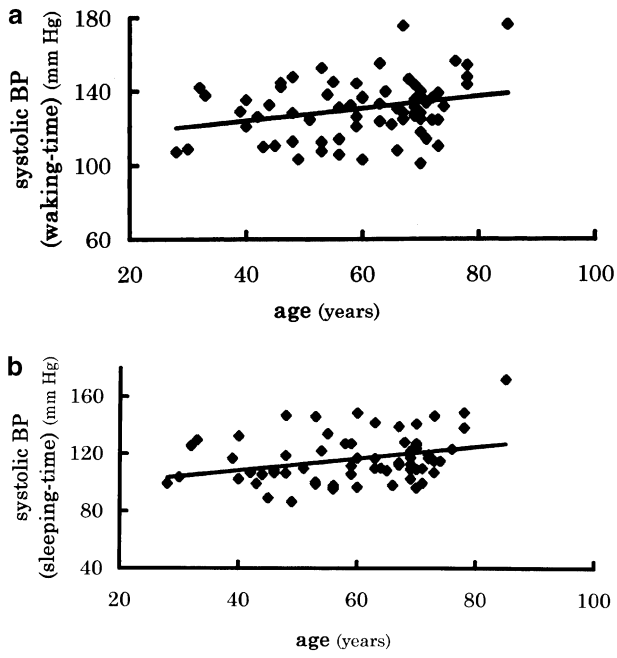

Figure 4. Aging effect on blood pressure (BP) and pulse rate (PR) in normal tension glaucoma patients. Only systolic BP showed positive relation with age in both waking [(**a**) y = 0.3332x + 110.74, P = .03] and sleeping times [(**b**) y = 0.4161x + 91.713, P = .001] and was statistically significant. Other parameters in BP showed tendency toward positive relation except diastolic BP (not shown).

splinter hemorrhage were not statistically different. The comparison between male and female patients with NTG is shown in Table 6. All BP values of the men are higher than those of the women during waking and sleeping. Moreover, the hyperbaric index of all BP parameters was significantly higher in men than in women, as were the PR parameters. The BP dip was smaller in women than in men. However, the fluctuation of BP during sleeping was smaller in men than in women. Minimum BP, PR dip, and other parameters showed no significant difference.

Difference Between "Progressive" Patients and "Stable" Patients

Sixteen patients were classified as "progressive" and 11 as "stable" by the criteria used in the current study. Background characteristics of each group are shown in Table 7. Although the mean age was slightly higher in the stable group than in the progressive group, there was no statistically significant difference between the two groups. Other characteristics showed no significant difference. Use of antiglaucoma eyedrops and occurrence of splinter hemorrhage were more prevalent in the progressive group than in the stable group, but the differences were not significant.

In Table 8, values for the major parameters in the current study are shown. Intraocular pressures in both groups were similar.

In the progressive group systolic and diastolic values and mean BP dips were smaller than in the stable group, although only the difference in the mean BP dip was statistically significant (P = .03).

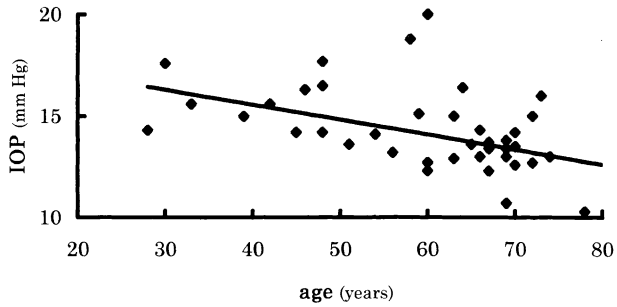

Figure 5. Intraocular pressure (IOP) and age in normal tension glaucoma patients. There was a statistically significant reduction of IOP in patients with normal tension glaucoma as they aged, as shown by Spearman rank correlation test. y = −0.0738x + 18.509, P = .005.

Table 6. Comparison Between Men and Women Subjects

Parameters*	Men†	Women†	*P* Value‡
Systolic BP (waking time) (mm Hg)	134.77 ± 17.06	125.97 ± 15.44	0.05
Diastolic BP (sleeping time) (mm Hg)	81.40 ± 7.24	73.93 ± 7.25	0.0004
Mean BP (waking time) (mm Hg)	116.64 ± 13.76	107.48 ± 13.28	0.02
Diastolic BP (sleeping time) (mm Hg)	70.58 ± 7.47	65.98 ± 7.49	0.03
Systolic BP dip (%)	12.79 ± 7.44	8.169 ± 7.31	0.04
Mean BP dip (%)	13.01 ± 6.85	10.28 ± 8.20	0.19
Diastolic BP dip (%)	13.09 ± 7.53	10.72 ± 5.65	0.2
Maximum BP (mm Hg)	184.11 ± 24.30	172.54 ± 20.15	0.06
Hyperbaric index (mean BP) (mm Hg/hour per day)	7.80 ± 8.17	4.03 ± 3.84	0.03
Hyperbaric index (PR) (BPM/hour per day)	0.93 ± 1.62	0.18 ± 0.22	0.03
BP fluctuation (sleeping time) (mm Hg)	8.07 ± 1.96	9.58 ± 2.37	0.06

*BP: blood pressure, PR: pulse rate, BPM: beat per minute, BP fluctuation: standard deviation of BP values, mean BP: diastolic BP + 1/3 (systolic BP − diastolic BP).
†Values are mean ± SD.
‡*P* values were calculated by nonpaired Student *t*-test.

Waking BP values in both groups were similar, but sleeping BP values and hyperbaric index were higher in the progressive group than in the stable group, although the difference was not statistically significant.

Blood pressure fluctuation during sleeping was significantly greater in the progressive patients than in the stable group, but both during waking hours and all day long, the difference did not reach statistical significance.

Pulse rate was higher in the stable group than in the progressive group at all times, but a significant difference was observed only in the hyperbaric index of PR in the progressive group. Pulse rate dip was slightly smaller in the progressive group than in the stable group.

Discussion

A single random BP measurement may not represent the true value of circulatory parameters. For example, some patients show a very high BP when with doctors, the so-called "white coat hypertension."[17] The ambulatory BP monitoring system, measuring BP and PR repeatedly, even throughout the night, gives more reliable and accurate data than the random measurement, and this system has a good intra-individual correlation and reproducibility.[18,19] Since Tarchanoff reported BP dips in dogs in 1894 and Hill reported the same in humans in 1898, many studies of the circadian change in BP have been performed. A nocturnal decrease in BP may be a factor in causing damage to several organs: silent cerebral microinfarction, even its lethal outcome,[8] or renal failure.[10,11] More recently, Kario et al reported that an extreme decrease of more than 20% was a high risk factor for cerebral infarction.[9]

Table 7. Characteristics of Progressive and Stable Groups*

	Progressive Group	Stable Group
Total subjects	16	11
Age (mean ± SD years)	63.56 ± 8.76	64.26 ± 11.44
Male	7	5
Female	9	6
Antiglaucoma medication	1	0
Splinter hemorrhage	5	1

*No statistically significant difference was observed in any subject by Fisher exact test.

Reports on the relation between BP dip and glaucoma are inconsistent. Graham et al reported that patients with glaucoma tend to have a larger BP dip than normal subjects, and this was emphasized in deteriorating cases.[20,13] Detry et al reported that progressive glaucoma cases showed a smaller nocturnal reduction in BP.[14] In the current study, BP dips in patients with NTG showed no significant difference from those in normal subjects, and progressive NTG subjects showed a smaller dip than stable NTG subjects. There are several ways to explain these differences among the reports. First, the distribution of types of glaucoma in the progressive and stable groups was not the same in the reports. Second, criteria for progression and stability of the visual field are different. Third, the age distribution of patients in the stable group and in the progressive group were not the same. An age-dependent decrease in the BP dip has been reported,[20] and we confirmed it in the current study. Finally, in some previous studies, glaucoma patients were hospitalized during the measurement period, which must have affected their daily BP profile.

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Table 8. Comparison of Progressive and Stable Groups

Parameters*	Progressive†	Stable†	*P* Value‡
Mean BP dip (%)	10.03 ± 4.70	16.65 ± 10.39	.03
Hyperbaric index (PR) (BPM/hour per day)	0.17 ± 0.17	1.01 ± 1.53	.03
BP fluctuation (night) (mm Hg)	9.55 ± 2.57	7.53 ± 1.13	.03
Systolic BP dip (%)	9.26 ± 7.29	14.68 ± 8.20	.07
Diastolic BP dip (%)	10.25 ± 3.79	13.03 ± 9.05	.27
Systolic BP (waking time) (mm Hg)	128.55 ± 17.40	126.75 ± 8.81	.75
Diastolic BP (waking time) (mm Hg)	76.69 ± 9.78	76.08 ± 8.33	.87
Mean BP (waking time) (mm Hg)	109.39 ± 15.81	109.39 ± 8.53	.99
Systolic BP (sleeping time) (mm Hg)	115.9 ± 15.77	107.84 ± 9.66	.14
Diastolic BP (sleeping time) (mm Hg)	68.68 ± 7.55	65.84 ± 6.95	.35
Mean BP (sleeping time) (mm Hg)	98.22 ± 13.88	91.22 ± 12.93	.35
Maximum BP (mm Hg)	174.75 ± 22.56	177.82 ± 22.28	.73
Minimum BP (mm Hg)	51.93 ± 10.98	51.36 ± 10.20	.89
Hyperbaric index (mean BP) (mm Hg/hour per day)	2.12 ± 8.27	3.28 ± 2.84	.48
PR dip (%)	15.63 ± 7.45	16.91 ± 8.25	.63
Mean IOP (mm Hg)	13.94 ± 2.07	14.00 ± 1.15	.92

*BP: blood pressure, PR: pulse rate, BPM: beats per minute, mean BP: diastolic BP + 1/3 (systolic BP − diastolic BP), BP fluctuation: standard deviation of BP values, mean IOP: calculated from IOP values measured for 24 hours (circadian rhythm).

†Values are mean ± SD.

‡*P* values were calculated by nonpaired Student *t*-test.

To determine accurately the relation between circulatory parameters and NTG, we employed several modifications in the current study. Normal values of BP using this ambulatory BP monitoring system are not yet well established. Accordingly, a sufficient number of normal control subjects were recruited to address the disorders of circulation in the current study. Following the advice of Gosse et al, every subject kept a diary to collect data accurately for analysis of values during both waking and sleeping.[21] In addition to BP, PR values were investigated, because PR and BP are very deeply involved in the cardiac output and are vital to a discussion of circulatory function. The data was recorded in all subjects for 49 hours to analyze chronobiology precisely, because it has been pointed out that during the first 24 hours of measurement, artificial effects on results are recognized, but the circadian rhythm settles down in the 25th hour.[6,22] Patients recorded their daily activity during the investigation without hospital admission to obtain their daily values, because admission would probably reduce BP because of less activity.

The hyperbaric index and hypobaric index as employed in the current study are much more sensitive and reliable in detecting abnormal values in BP and PR than a simple comparison of mean values and other parameters.[16] These indices can detect transient changes of BP and PR quantitatively.[23] The areas extending both beyond and below the normal range are calculated automatically, and patients having hypertension or hypotension show a relative increase of hyperbaric index against hypobaric index, or vice versa. Although all participants did not have apparent hypertension confirmed by random BP measurement, a significant increase of the hyperbaric index in systolic, mean, and diastolic BP in patients with NTG was revealed, which means these patients could have latent hypertension.

In the current study, a statistically significant correlation was observed between IOP and diastolic BP, because diastolic BP plays a major role in static venous pressure that determines episcleral venous pressure.

Major regulation of the vasomotion system is in the brain, which regulates BP and PR via the autonomic nervous system (ANS). We previously reported that a disturbance of the circadian rhythm of the ANS might exist in NTG patients.[24] It may be hypothesized that micro damage in some part of the cerebrum involved in regulating the ANS may result in reduction of the dip. Recently, it is reported that glaucoma is often present in patients experiencing lacunal infarction.[25] Interestingly, lacunal infarction has a negative correlation with BP dip,[8] which is consistent with our hypothesis.

It is unclear how changes in the dip result in damage to the optic nerve. Disturbance of pericytes was observed in other organs in which reduction of the dip could be reportedly involved. Therefore, insufficient dip may damage autoregulation by injuring pericytes in the optic head and could be one of the risk factors in glaucoma, especially in NTG.

An extreme BP dip, especially in diastolic BP, may result in an insufficient blood supply to the optic head. However, in the current study only 1 subject was an extreme dipper in the progressive group, a prevalence rate that compares with normal subjects. Therefore, it may be invalid to suggest that an extreme dip is a major risk factor in NTG, at least based on the current study.

In the current study, men showed a higher BP, a higher PR, and a greater dip, but a smaller BP fluctuation compared with women, which is more or less consistent with previous reports.[20,26] Because female hormones, such as estradiol and progesterone, are involved in BP regulation,[27] hormonal effects may possibly explain these sex differences. It is reported that the sympathetic ANS increases the magnitude of BP fluctuation and reduces the nocturnal dip.[28,29] Therefore, a greater BP fluctuation during sleeping and a smaller dip in women patients may indicate that the activity of the ANS in women is greater than in men. The fact that the PR dip in patients with NTG was significantly smaller than in normal subjects may also indicate a disturbance of autoregulation in patients with NTG, because the PR dip is also controlled by the ANS.

In the current study, the progressive group showed a bigger BP fluctuation at night, possibly corresponding to the activity of the sympathetic ANS.[28,29] Disturbance of the ANS is another possible explanation of an increase in BP fluctuation,[30] which has a positive correlation with organ damage.[31] Indeed, we previously reported that a disturbance of the circadian rhythm of the ANS might exist in NTG patients.[24] Bigger fluctuations cause much more damage to some organs, although the precise mechanism is unknown.

The BP dip indicates the activity of the sympathetic nervous system[28,29] in addition to the condition of the ANS, which shows that progressive NTG patients may have a malfunction in their ANS, or that their sympathetic nervous system was stimulated much more than that of stable NTG patients even in sleeping hours.

The design of the current study is cross-sectional, not longitudinal. Thus, it is questionable whether these data represent the circulatory status throughout the period from the onset of glaucoma to the present. According to the population-based glaucoma study by Shiose et al,[32] the prevalence of NTG is approximately 2% in Japan. Therefore, there would be several undetected NTG patients in the normal population in the current study, because we did not perform an ophthalmic examination of each subject.[32] The precise mechanism of an insufficient nocturnal BP causing optic nerve damage and the relation of focal circulation in the optic nerve head with systemic vessels are unclear. Improved instruments and techniques are required to clarify these points. Furthermore, there should be longitudinal and prospective studies to clarify the involvement of systemic circulation in glaucoma. This, in turn, may suggest another approach for treating glaucoma patients more effectively.

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