

Diurnal blood pressure parameters in normal tension glaucoma, primary open angle glaucoma, and healthy subjects

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ABSTRACT

Objective: The pathophysiology of glaucoma is still undisclosed. Cardiovascular hemodynamic changes are hypothesized to contribute to glaucoma. This study aimed to determine the differences in the diurnal blood pressure (BP) of patients with normal tension glaucoma (NTG), primary open angle glaucoma (POAG), and controls without glaucoma.

Methods: A total of 129 patients were included in this study. The day–night average systolic and diastolic BPs, the day–night average pulse pressures (PPs), the day–night average heart rates, and the percentage of BP decline at night were obtained from the Holter devices and compared. Study design: Prospective, randomized, case-control study.

Results: This study included 43 NTG patients (Group 1), 44 POAG patients (Group 2), and 42 healthy subjects without glaucoma (Group 3). The age ($p=0.138$) and sex ($p=0.216$) distributions between the groups were similar. The average day–night PP values of Group 1 were 49.17 ± 9.90 and 46.07 ± 10.84 mm Hg, respectively, while their total average PP was 48.48 ± 9.60 , their total average systolic BP was 120.02 ± 12.65 , and their night average systolic BP was 111.93 ± 15.87 mm Hg. In Group 2, the average day and night PP values were 54.83 ± 10.35 and 51.73 ± 9.10 mm Hg, respectively, their total average PP was 54.00 ± 9.87 , their total average systolic BP was 126.75 ± 11.50 , and their night average systolic BP was 119.21 ± 12.38 mm Hg. These differences were statistically significant and the corresponding p values were 0.040, 0.040, 0.037, 0.033, and 0.038.

Conclusion: NTG patients have low diurnal BP parameters, which may reduce their optic nerve perfusion and may be responsible for their glaucomatous visual field damage. (*Anatol J Cardiol* 2017; 18: 62-7)

Keywords: normal tension glaucoma, primary open angle glaucoma, optic nerve perfusion, blood pressure

Introduction

Glaucoma is a heterogeneous eye diseases family characterized by chronic-progressive glaucomatous optic neuropathy leading to retinal ganglion cell loss, optic nerve atrophy, and irreversible visual field loss. The pathophysiology of glaucoma is still undisclosed. It is likely multifactorial and considered to be affected by vascular factors, in addition to elevated intraocular pressure (IOP). Among the primary types of glaucoma with an open anterior chamber angle, primary open angle glaucoma (POAG) and normal tension glaucoma (NTG) are the most common. POAG is characterized by high IOP, whereas IOP is not elevated in NTG, unlike in all other glaucoma types. Today, IOP is the only modifiable risk factor that can be treated by medical and/or surgical techniques.

Cardiovascular hemodynamic characteristics are thought to be very important parameters in the pathogenesis and progression of glaucoma. Vascular risk factors have been studied not only during the progression (1) of glaucoma, but also during the pathogenesis (2,3) of glaucomatous damage. Few studies have investigated the systemic circulatory changes in glaucoma patients.

Both vascular and mechanical factors are hypothesized to contribute to damage. According to the mechanical theory, direct compression of the axonal fibers results in disruption of the axoplasmic flow and death of the retinal ganglion cells on the lamina cribrosa plane. The ischemic theory focuses on the decreased optic nerve perfusion leading to intraneural ischemia. Decreased perfusion may result from the resistant of IOP on the blood supply to the nerve or from decreased blood flow to the intrinsic capillary of the optic nerve.

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By arranging the tone of optic nerve vessels, appropriate blood supply could be maintained. However, impairment of vascular auto-regulation or alterations in the systemic blood flow parameters may decrease optic nerve perfusion and lead to nerve damage independently of IOP.

Ambulatory blood pressure monitoring (ABPM) is a simple and noninvasive method of measuring both blood pressure (BP) and pulse pressure (PP) during daily activities and sleep, eliminating the "white coat" effect. PP, defined as the difference between the systolic and the diastolic pressures, is suggested to be correlated with end-organ perfusion. Nocturnal hypertension is associated with end-organ damage and is a much better indicator than daytime BP readings (4). Nevertheless, nocturnal hypotension is also associated with decreased end-organ perfusion. While sleeping, the IOP is increased due to lying in the supine position. If a patient has both nocturnal hypotension and high IOP, the ocular perfusion decreases and this may result in anterior ischemic optic neuropathy and increase the risk of glaucoma progression. Glaucomatous damage decreases with low IOP and associated high systolic BP levels (5).

We hypothesize that 24-hour blood pressure variations may have an important role in the pathogenesis of glaucoma and that it may vary between subgroups of the disease. This study aimed at comparing and assessing the cardiovascular hemodynamic characteristics of the primary causes of the two most common types of open angle glaucoma and those of healthy subjects. The relationship between glaucoma and the BP parameters has been subject of many studies; however, to the best of our knowledge, there are no previous reports comparing PP levels during the day and at night (dipper and non-dipper, respectively) using 24-hour ABPM in patients with POAG, NTG, and healthy controls.

Methods

A total of 129 consecutively chosen participants were included in the study. Patients with POAG and NTG were recruited from the Adnan Menderes University, Department of Ophthalmology, Glaucoma Unit between April 2012 and April 2013, while control subjects were recruited from the outpatient clinic of the same department. Patients with hypertension were excluded from the study. Office blood pressure measurements were performed with the auscultatory method using calibrated aneroid manometers for both arms, and hypertension was excluded after at least three measurements. ABPM for 24 hours was performed automatically with the Mobil-O-Graph NG (IEM, Stolberg, Germany) device; 20–31 cm or 28–36 cm cuff sizes were used according to the subjects' arm circumferences measured at the biceps level. Diurnal BP measurements were automatically obtained every 30 minutes between 7:00 a.m. to 10:59 p.m. (daytime) and from 11:00 p.m. to 6:59 a.m. (nighttime). Recordings were defined as acceptable if there were at least 6 readings for nighttime and 30 readings daytime. Patients were categorized into two groups, dipper and non-dipper, after measurement of the night/day ratios. This

study was designed as a prospective, randomized, case-control study, was approved by the Ethics Committee of the Adnan Menderes University, and was carried out according to the rules of the Helsinki Declaration.

Inclusion criteria for all participants were age of ≥ 18 years with the following diagnostic criteria mentioned below. Glaucoma patients with the best-corrected visual acuity (BCVA) of ≥ 0.8 Snellen were included in the study. All glaucoma patients were followed for at least one year in our glaucoma unit and they underwent detailed ophthalmologic examinations at least three times a year. POAG diagnosis was based on typical glaucomatous optic disk changes (i.e., progressive excavation or "cupping" of the optic nerve due to focal or diffuse thinning of the optic nerve rim, cup-to-disk ratio >0.6 or cup-to-disk ratio asymmetry >0.2 between the eyes, and/or optic disk hemorrhages), glaucomatous visual field defects with a normal appearing open irido-corneal angle and an untreated IOP ≥ 21 mm Hg of the baseline diurnal IOP during office hours. Patients were diagnosed with NTG if they had an untreated IOP <21 mm Hg together with characteristic glaucomatous findings (6,7).

Participants were excluded from the study if they had a family history of glaucoma or ocular hypertension, refractive error >0.50 diopters, or if they were on any systemic or topical medication, had any retinal pathology, corneal scars, central corneal thickness outside the normal limits, closed irido-corneal angles, history of angle closure glaucoma crisis or findings of narrow angle, evidence of secondary glaucoma, pseudoexfoliation, high myopia, history of previous ocular surgery or trauma, history of ocular or systemic diseases including diabetes mellitus, obesity, or any form of retinal, neuro-ophthalmologic, or systemic diseases that could result in optic neuropathy, or visual field defects (6,7). Patients with obstructive sleep apnea and with requirement of cuff size over 36 or below 20 cm were excluded. Smokers and alcoholics were also excluded from the study.

All participants underwent detailed ophthalmologic examinations, including slit-lamp biomicroscopy, diurnal IOP measurements with Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland), gonioscopy, pachymetry, optic disk assessment with a 78-diopter lens under dilated pupils, retinal nerve fiber analysis, and automated visual field test using 24-2 SITA (Swedish Interactive Threshold Algorithm, HFA II 750; Carl Zeiss Meditec, Dublin, California, USA).

Control subjects were healthy individuals with BCVA of 1.0 Snellen, normal optic disks (cup-to-disk ratio <0.3 with no localized defects in neuroretinal rim or margin, no splinter hemorrhage around the disk), open angles at gonioscopy, IOP <21 mm Hg on two different days, CCT greater than 500 μm in both eyes, and no visual field defect.

It is possible to determine the extent to which BP decreases during the night when compared to daytime values. As recommended by the American Heart Association (AHA), the dipper profile was defined as the percent decrease in nocturnal BP as follows: $\text{Dip} = [1 - (\text{nSBP}/\text{dSBP})] \times 100\%$, where nSBP is mean

Table 1. The demographic data of the patients

	NTG group	POAG group	Control group	P
Gender (n)	43	44	42	0.216
Female	15 (35%)	23 (52%)	16 (38%)	
Male	28 (65%)	21 (48%)	26 (62%)	
Age, years (95% CI)	66±11 (63–70)	69±10 (66–72)	65±7 (63–67)	0.138
CI - confidence interval for mean; NTG - normal-tension glaucoma; POAG - primary open-angle glaucoma				

nocturnal systolic blood pressure and dSBP is mean daytime systolic blood pressure. Nocturnal changes in BP are classified according to AHA as follows: if the percent decrease of nocturnal BP is less than 10% of the daytime levels, this patient is a “non-dipper,” but if the nocturnal BP decreases between 10%–20%, the patient is considered a “dipper.” If the nocturnal BP drop is more than 20%, the patient is defined as an “extreme dipper.” The day–night average systolic and diastolic BPs, day–night average PPs, day–night average heart rates, and BP decline at night were obtained from ABPM and were compared between the groups.

Statistical analysis

Statistical analyzes were performed using SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) version 21. The Kolmogorov–Smirnov test was used to assess the normality of numeric variables. For all of the numeric variables that were normally distributed, comparison between the three groups was performed using a one-way analysis of variance; the descriptive statistics are presented as mean±standard deviation. To analyze the categorical data, a chi-squared test was used; descriptive statistics are presented as frequency (%). Receiver Operating Characteristic (ROC) curve was used to determine the cut-off points, sensitivity, specificity, and area under the curve (AUC) for the cardiovascular parameters. A p-value <0.05 was considered significant.

Results

A total of 129 patients were included in this study. There were 43 NTG patients (Group 1), 44 POAG patients (Group 2), and 42 healthy subjects without glaucoma (Group 3). Groups were simi-

lar according to sex (p=0.216) and age distributions (p=0.138). The demographic data for each of these groups is presented in Table 1.

The mean PP during daytime (daytime mPP), nighttime mPP, 24-hour mPP (day- and nighttime), the mean SBP during nighttime (nighttime mSBP), and 24-hour mSBP (day- and nighttime) values were significantly lower in NTG patients when compared to those of POAG patients and control subjects (p<0.05). However, these values were higher in POAG patients (Table 2); the differences between the NTG and POAG groups were statistically significant according to the post-hoc multiple comparison test. The values for the control subjects fell between those of the POAG and NTG patients. The differences between the NTG and the POAG patients were statistically significant (Table 3). However, there were no statistical differences in any of the values between the POAG and the control groups. According to the highest AUC value, 0.671, it is possible to distinguish POAG patients from NTG patients through nighttime mPP value of >45.7 mm Hg with the sensitivity of 76.19 and specificity of 61.90. There were no statistical differences between any of the groups for the other cardiovascular parameters (i.e., mean systolic and diastolic BPs during day time, mean diastolic BP at nighttime, diastolic BP during day- and nighttime, and mean heart beats).

The distribution of the patients in the groups according to dipper, extreme dipper, and non-dipper features is presented in Table 4. There was no statistical significance between the NTG (n=6) and POAG (n=1) groups by means of extreme dippers (p>0.05). The circadian systolic and diastolic BP fluctuations for all of the groups are presented in Figures 1 and 2.

Discussion

This study revealed that the BP fluctuations between night and day vary according to the type of glaucoma. We found that NTG patients had low systolic BP levels during 24-hour and nighttime. NTG patients also had low PP values (24-hour, day- and nighttime). These differences might play an important role in the pathogenesis of NTG.

Glaucoma patients are known to have an autoregulatory disorder of the blood flow mechanism in the optic nerve head (8). Some studies have reported a relationship between nocturnal hypotension and glaucoma (9,10), although others have shown that there is no correlation between them (11,12). The Egna–Neumarkt

Table 2. Cardiovascular parameters are different between the groups

	NTG group	POAG group	Control group	P
Daytime ^b mPP ^a	49.17±9.90*	54.83±10.35	53.61±11.47	0.038
Nighttime ^b mPP	46.07±10.84*	51.73±9.10	49.81±10.64	0.047
mPP in day- and nighttime ^b	48.48±9.60*	54.00±9.87	52.74±11.09	0.037
Nighttime ^b mSBP	111.93±15.87*	119.21±12.38	117.85±11.61	0.034
mSBP in day- and nighttime ^b	120.02±12.65*	126.75±11.50	125.34±12.69	0.032

^aCalculated as mPP= mean systolic BP - mean diastolic BP; ^bmm Hg; mPP - mean pulse pressure; mSBP - mean systolic blood pressure; NTG - normal-tension glaucoma; POAG - primary open-angle glaucoma; *The differences between NTG and POAG groups were statistically significant according to post-hoc analysis

Table 3. ROC analysis and P values of the cardiovascular parameters shown as pair wise comparisons

NTG vs. CONTROLS	Cut-off	Sensitivity	Specificity	AUC	P
Daytime ^b mPP ^a	≤49.6	64.29	65.85	0.618	0.062
Nighttime ^b mPP	≤45.7	61.90	62.50	0.607	0.089
mPP in day- and nighttime ^b	≤52.69	73.81	48.78	0.611	0.076
Nighttime^bmSBP	≤111	54.76	75.00	0.647	0.017 *
mSBP in day- and nighttime^b	≤128	80.95	43.90	0.629	0.036 *
POAG vs. CONTROLS					
Daytime ^b mPP ^a	>44.2	90.70	31.71	0.527	0.679
Nighttime ^b mPP	>49.6	57.14	65.00	0.574	0.251
mPP in day- and nighttime ^b	>44.4	88.37	31.71	0.536	0.575
Nighttime ^b mSBP	>122	40.48	75.00	0.529	0.658
mSBP in day- and nighttime ^b	>122	63.64	46.34	0.527	0.676
POAG vs. NTG					
Daytime^bmPP^a	>49.2	74.42	61.90	0.667	0.005 *
Nighttime^bmPP	>45.7	76.19	61.90	0.671	0.004 *
mPP in day- and nighttime^b	>49.6	69.77	64.29	0.665	0.006 *
Nighttime^bmSBP	>111	71.43	54.76	0.661	0.007 *
mSBP in day- and nighttime^b	>119	72.73	54.76	0.663	0.006 *

AUC - area under the ROC curve; mPP - mean pulse pressure; mSBP - mean systolic blood pressure; NTG - normal-tension glaucoma; POAG - primary open-angle glaucoma. Daytime: 07:00-22:59; Nighttime-23:00-06:59. P<0.05 was considered a significant difference. *Statistically significant; ^aCalculated as mPP=mean systolic BP - mean diastolic BP; ^bP value

Table 4. Distribution of the patients according to dipper features

	Extreme dipper	Dipper	Non-dipper	Total
NTG group	6 (13.95%)	13 (30.23%)	24 (55.81%)	43
POAG group	1 (2.27%)	16 (36.36%)	27 (61.36%)	44
Control group	0 (0.0%)	16 (38.09%)	26 (61.9%)	42

NTG - normal-tension glaucoma; POAG - primary open-angle glaucoma

(13), Rotterdam (14), and Blue Mountain Eye (15) studies have shown that high BP levels are associated with POAG. However, the Barbados Eye Study (16) and the Proyecto Ver Early (17) studies reported that low BP worsens the progression of open angle glaucoma. Previous studies have shown that patients with NTG and POAG have low BP levels at night (9,18). Leske et al. (5) reported that low BP levels may increase the progression of POAG and NTG. However, in our study, only NTG patients had low BP levels while POAG patients had higher BP levels than did the controls.

The systolic and diastolic BP levels, as well as the perfusion pressure, have been shown to be related with POAG (13,17). In addition, the decrease in the mean diurnal ocular perfusion pressure is associated with POAG (19). Topouzis et al. (20) showed that low diastolic BP due to anti-hypertensive treatment increased the cup/disk ratio and resulted in glaucomatous visual field damage in non-glaucomatous hypertensive patients. However, in our study, the diastolic BP levels were slightly lower among NTG patients as compared to those of POAG patients. This difference did not reach statistical significance. This may be due to the relatively small number of our study. Topouzis et

al. (20) reported that low ocular perfusion is related to low diastolic BP. We agree with them about low ocular perfusion in NTG. However, our findings indicate that low systolic BP might play an important role in the ocular perfusion and NTG pathogenesis as well. The effects of systolic and diastolic BP over ocular perfusion pressure can be clearly seen among the formula; ocular perfusion pressure = $0.666 \times [(0.333 \times (\text{systolic BP} - \text{diastolic BP}) + \text{diastolic BP}) - \text{IOP}$ (21).

NTG was shown to be associated with reduced nocturnal BP (22). Low catecholamine levels are thought to reduce optic disk perfusion by decreasing the sympathetic system activation (22). When we compared the patients with POAG and NTG and the normal subjects, the lowest nocturnal BP levels were found in the NTG Group. The 24-hour ocular perfusion pressure fluctuation is thought to be a risk factor for NTG (23). In our study, although the number of extreme dippers was higher in the NTG group as compared to the control and POAG groups, this difference did not reach statistical significance.

Sung et al. (21) reported that 24-hour mean ocular perfusion pressure fluctuation was the most consistent prognostic factor for the progression of glaucoma in NTG patients. In accordance with previous results, our study showed that PP may play an important role in the pathogenesis of NTG. Our ROC analysis showed that a cut-off value of nighttime mPP <45 mm Hg may allow to differentiate NTG from POAG with a sensitivity of 76.19 and specificity 61.90 (AUC=0.671, p=0.0044). Moreover, daytime and 24-hour mPP levels of NTG and POAG patients were also found significantly different.

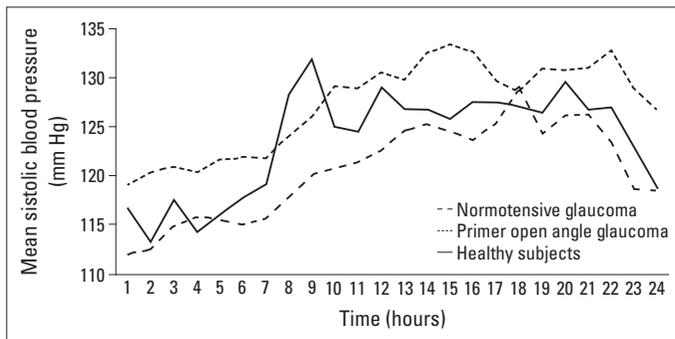


Figure 1. Circadian systolic blood pressure fluctuations in all groups. The difference between the POAG and NTG groups is evident after midnight. In the control group, peaks are observed in the early morning. However, these peaks are vestigial in both glaucomatous groups

When the BP charts (Fig. 1 and 2) were analyzed in more detail, the systolic and diastolic BP tracings found in healthy patients (especially in the early morning) appeared blunt in glaucomatous patients. These findings suggest that blunted sympathetic activity in the early morning hours may play a role in the pathophysiology of glaucoma. The inability to control BP changes in patients with glaucoma is responsible for glaucomatous damage of the optic nerve head, which supports our opinion (8). In addition, low diastolic perfusion pressure may induce glaucomatous damage (13, 14).

Study limitations

The main limitation of our study is the small number of patients. Further studies are needed to analyze the patients in terms of different levels of nocturnal BP drops in detail.

Conclusion

Results of this study suggest that the physiopathologies of the two subgroups of glaucoma (NTG and POAG) may vary; unlike POAG, low systolic BP and PP levels may play important roles in NTG pathogenesis. Systolic BP levels (24-hour and nocturnal) and mPP values (24-hour, day- and night time) were the lowest in NTG group (even lower than the healthy controls). It also suggests that it would be better not to decrease the BPs, especially during the night, in NTG patients as this may further minimize perfusion of the optic nerve under normal values. Further studies, not only on IOP but also on other cardiovascular parameters, will allow us to better understand the role of other factors on glaucomatous damage.

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Competing interests: There are no competing interests (for all authors).

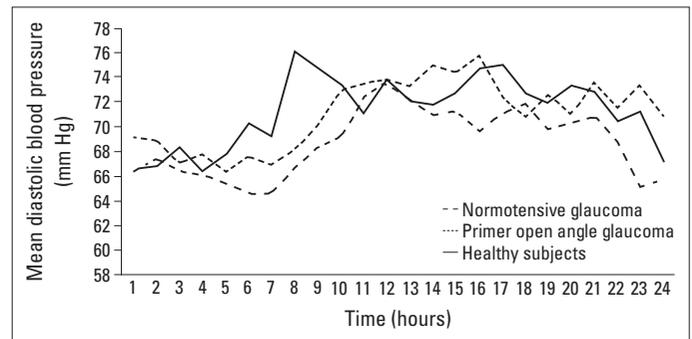


Figure 2. Circadian diastolic blood pressure fluctuations in all groups. There is no difference in terms of mean diastolic blood pressure between the groups over 24-hour, day- and nighttime. Peaks observed in healthy subjects are vestigial in both glaucomatous groups during 24-hour trend

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