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Vascular Dysregulation in Normal-Tension Glaucoma Is Not Affected by Structure and Function of the Microcirculation or Macrocirculation at Rest

A Case–Control Study

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Abstract: In normal-tension glaucoma (NTG), optic nerve damage occurs despite a normal intraocular pressure. Studies implicating systemic blood pressure or, more recently, arterial stiffness in the pathophysiology of NTG have produced conflicting results. Our aim was to investigate whether NTG is associated with alterations in the macrocirculation or microcirculation, cardiac function, and peripheral and central hemodynamics.

Thirty patients with NTG (mean age 65 years, range 46–79) and 33 healthy subjects (mean age 67 years, range 42–79) matched for age and sex were included in the study. Exclusion criteria (for both cases and controls) were history of cardiovascular disease, diabetes mellitus, severe hypertension, and hypercholesterolemia. Aortic stiffness was measured using carotid–femoral pulse wave velocity (PWV), central hemodynamics using carotid artery applanation tonometry, and diameter, stiffness, and intima-media thickness (IMT) of the carotid and femoral artery using echo-tracking. Total peripheral resistance index (TPRI) was derived from mean arterial pressure and cardiac index, measured using ultrasound.

There were no statistically significant differences in arterial structure nor function between NTG patients and age and sex-matched controls. NTG versus controls, respectively: brachial blood pressure $126 \pm 15/77 \pm 8$ versus $127 \pm 16/76 \pm 7$ mm Hg, $P = 0.81$; carotid–femoral PWV 9.8 ± 2.1 versus 10.1 ± 1.9 m/s, $P = 0.60$; TPRI 1833 ± 609 versus 1779 ± 602 dyne.s/cm^5/m^2, $P = 0.79$; and carotid IMT 0.65 ± 0.14 versus 0.68 ± 0.13 mm, $P = 0.39$.

This study could not show an association of NTG with altered IMT, arterial stiffness, total peripheral resistance, cardiac output, and peripheral or central hemodynamics at rest. Although the majority of these NTG patients do exhibit symptoms of vascular dysregulation, in the present study this was not translated into alterations in the microcirculation or macrocirculation at rest.

(*Medicine* 94(2):e425)

Abbreviations: AIx = augmentation index, AUC = area under the curve, CC = cross-sectional compliance, CI = cardiac index, CVD = cardiovascular disease, DBP = diastolic blood pressure, DC = distensibility coefficient, HR = heart rate, IMT = intima-media thickness, IOP = intraocular pressure, MAP = mean arterial pressure, NTG = normal-tension glaucoma, PP = pulse pressure, PWF = pressure waveform, PWV = pulse wave velocity, RM = reflection magnitude, SBP = systolic blood pressure, SVI = stroke volume index, TPRI = total peripheral resistance index, WCSA = wall cross-sectional area.

INTRODUCTION

Glaucoma is the second leading cause of blindness worldwide[1] and is characterized by typical damage to the optic nerve head, termed ''glaucomatous optic neuropathy.'' According to the vascular theory, this damage results from either low or fluctuating ocular blood flow, causing ischemia and reperfusion injury at the optic nerve head, respectively.[2] Although ocular blood flow is often reduced because of elevated intraocular pressure (IOP), the existence of normal-tension glaucoma (NTG, with IOP < 21 mm Hg) suggests that other factors are also involved. Indeed, dysregulation of vascular resistance is now considered a key pathogenic factor, particularly in NTG.[3] Moreover, dysregulation often manifests itself systemically as the ''primary vascular dysregulation syndrome.'' NTG patients often suffer from this syndrome[4] or its hallmarks (eg, cold extremities,[5–8] migraine,[9,10] reduced sensation of thirst, and others). However, the exact role of systemic dysregulation in the pathophysiology of NTG remains to be identified.

Historically, NTG has been linked with low arterial blood pressure, either diurnally[11,12] or only at night.[13,14] Many studies, however, did not find an association between NTG and low blood pressure[15–24] or show overdipping.[17,25–27] Focusing on more integrative measures of vascular health did not solve these discrepancies. Augmentation index (AIx) (a measure of wave reflections) in NTG patients was found increased by Mroczkowska et al,[21] but unaltered by Graham et al.[23] Pulse wave

Editor: Ignatios Ikonomidis.
Received: November 7, 2014; revised: December 3, 2014; accepted: December 6, 2014.
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This study has received grants from the Funds for Research in Ophthalmology (FRO) and the Belgian Glaucoma Society (Research Award 2008).
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000425

velocity (a measure of arterial stiffness) in NTG was found increased in one study[28] whereas not different from controls in other studies.[18,29] Since an association between increased stiffness of the carotid artery[30] and aorta[31] and retinal arteriolar narrowing has been shown, it is very likely that these factors may also play a role in the pathophysiology of NTG. Therefore, it was hypothesized that NTG is associated with systemic vascular abnormalities in ≥1 arterial beds.

However, at present, not all hemodynamic variables, such as muscular artery properties and total peripheral resistance, have been investigated in NTG. However, compliance of a muscular (the brachial) artery was found decreased in patients with migraine,[32] whose condition might share a common etiology with NTG.[33] Similarly, total peripheral resistance may be an interesting parameter to examine in NTG, as it can be altered in case of systemic microvascular abnormalities.[34]

Therefore, the aim of this study was to gain more insight into the function of the systemic microcirculation and macrocirculation in NTG, by comparing NTG patients with healthy age and sex-matched controls. To this aim, noninvasive measurements of arterial structure and function were performed: diameter, intima-media thickness (IMT), and stiffness of elastic (carotid) and more muscular (femoral) arteries; aortic stiffness (carotid-to-femoral pulse wave velocity [PWV]); total peripheral resistance; and peripheral and central hemodynamics.

METHODS

Study Design

A cross-sectional case–control study was carried out at the Heymans Institute of Pharmacology of the Ghent University, Ghent, Belgium. The study consisted of a screening visit (between June 2012 and April 2013) and a study visit (no later than 3 months after study visit). At screening, a fasted blood sample was drawn (to determine total cholesterol, low-density lipoproteins, high-density lipoproteins, creatinine, glucose, and triglycerides), brachial blood pressure was measured, and a questionnaire was completed (medical history, lifestyle habits, medication use, and signs of vascular dysregulation; Table 1). The study visit included all hemodynamic measurements. Subjects who were on vasoactive drugs were asked to stop treatment 3 days before study visit. NTG subjects were asked not to use eye drops on the day of the examinations (or only after the examinations were over). The study was approved by the Ethics Committee of Ghent University and conducted according to the ICH Good Clinical Practice and in compliance with the Declaration of Helsinki. All participants gave written informed consent.

Participants

Thirty-two patients diagnosed with NTG were recruited from the Department of Ophthalmology of the University hospital. NTG was defined as neuroretinal rim loss assessed by stereo disc assessment and photography, with a typical visual field defect, despite normal IOP <21 mm Hg. Thirty-three healthy control subjects were recruited from the local community and matched with cases for age and sex. Exclusion criteria were history of cardiovascular disease (CVD), modest or severe arterial hypertension (ie, systolic blood pressure [SBP] >160 and/or diastolic blood pressure [DBP] >100 mm Hg), diabetes mellitus, severe hypercholesterolemia (defined as total cholesterol >290 mg/dL), and pregnancy or lactation.

Control and NTG subjects underwent the following examinations: visual acuity assessment, slit-lamp examination, Goldmann applanation tonometry, fundoscopy, Haag-Streit Octopus 311 perimeter, spectral domain optical coherence tomography (Heidelberg): nerve fiber layer thickness, and central corneal thickness measurement.

Hemodynamic Measurements

Hemodynamic measurements were done in supine position and under standardized conditions.[35] Supine brachial SBP and DBP and heart rate (HR) were recorded with a validated semi-automated oscillometric device (OMRON M6; OMRON Healthcare, Hoofddorp, The Netherlands). Mean arterial pressure (MAP) was calculated by taking the area under the curve of scaled brachial artery pressure waveforms (PWFs) obtained by applanation tonometry (Sphygmocor; AtCor Medical, Sydney, Australia).

Carotid and femoral artery diameter (D), distension, and wall thickness (IMT) were measured on the right common carotid artery and the right common femoral artery, at diastole, 2 cm proximal to the bifurcation, with a 10-MHz pulsed ultrasound echotracking system (Wall Track system; AU5, Esaote Pie Medical, Maastricht, The Netherlands). Wall cross-sectional

TABLE 1. Results of the Study Questionnaire

Variable	NTG (n = 30)	Control (n = 33)	*P* Value
Comorbidities			
Respiratory disease, n (%)	3 (10)	2 (6)	0.56
Hypothyroidism, n (%)	2 (7)	2 (6)	0.92
Hyperthyroidism, n (%)	1 (3)	1 (3)	0.95
Rheumatoid arthritis, n (%)	1 (3)	3 (9)	0.35
Sleep apnea, n (%)	3 (10)	1 (3)	0.26
Fibromyalgia, n (%)	2 (7)	0 (0)	0.13
Allergy, n (%)	9 (30)	6 (18)	0.27
Symptoms of vascular dysregulation			
History of hypotension, n (%)	4 (13)	2 (6)	0.33
History of migraine, n (%)	10 (33)	6 (18)	0.17
Cold extremities, n (%)	22 (73)	9 (27)	<0.001
Reduced thirst sensation, n (%)	5 (17)	5 (15)	0.87

NTG = normal-tension glaucoma.

area (WCSA) was calculated by subtracting luminal area [$\pi*(D/2 - IMT)^2$] from arterial cross-sectional area [$\pi*(D/2)^2$]. Reproducibility, expressed as the coefficient of variation between 2 measurement series, was 2.4% for femoral IMT, 2.0% for femoral diameter, 1.4% for carotid IMT, and 1.9% for carotid diameter.

Femoral and carotid arterial cross-sectional compliance (CC, a measure of the buffering capacity) and distensibility coefficient (DC, the inverse of the stiffness) were calculated as $CC = \Delta A/PP = \pi \times (D_s^2 - D_d^2)/(4 \times PP)$, and $DC = (\Delta A/A_d)/PP = (D_s^2 - D_d^2)/(D_d^2 \times PP)$, where ΔA is the systolic–diastolic change in arterial cross section, D_s is the arterial diameter at end systole, D_d is the arterial diameter at end diastole, A_d is the arterial cross section at end diastole, and PP is the local pulse pressure.[36] Local PP was obtained by recording local PWFs with applanation tonometry (Sphygmocor), calibrated using brachial artery DBP and MAP.[37] Pulse-pressure amplification was calculated as brachial/carotid PP. Reproducibility of femoral and carotid DC was 9.0% and 8.5%, respectively.

Aortic stiffness was measured along the carotid–femoral path, using applanation tonometry (Sphygmocor). Carotid-to-femoral PWV was calculated using the 80% rule.[38] Reproducibility of PWV was 4.3%.

Wave reflections were assessed by the AIx, which was calculated from the carotid PWFs as P2/P1, in which P2 indicates the amplitude of the late systolic peak and P1 indicates the amplitude of the early systolic peak.[39] As a more accurate estimation of the amount of wave reflection, reflection magnitude (RM) was calculated using an average physiologic flow waveform as described by Kips et al.[40]

Cardiac function was measured using echocardiography (AU5; Esaote, Genoa, Italy). Stroke volume index (SVI) was calculated from aortic cross-sectional area multiplied by the flow velocity integral, divided by body surface area.[41] Cardiac index (CI) was calculated as SVI∗HR. Total peripheral resistance index (TPRI) was calculated as MAP/CI. Reproducibility of cardiac output was 4.4%.

Statistical Analysis

Continuous variables were compared between the groups by an independent samples *t* test when normally distributed, or by Mann–Whitney U test when nonnormally distributed. Categorical variables were compared between groups by Pearson χ^2 test. Values of $P < 0.05$ were considered significant. Data are reported as mean ± standard deviation or frequencies (percentages). Cases and controls were matched by keeping age and sex distributions as close as possible (ie, statistically not significantly different from each other; $P > 0.05$). All analyses were done using PASW18 (SPSS Inc, Chicago, IL).

RESULTS

Of all screened NTG subjects (n = 32), 2 participants were excluded because of type II diabetes mellitus and history of CVD, respectively. No cases of optic disc hemorrhages have been observed. Baseline characteristics of subjects are summarized in Table 2. There were no significant differences between NTG and control subjects for age, sex, body mass index, lifestyle habits, or any of the biochemical variables. When asked, all subjects taking vasoactive medication (NTG 17% versus controls 18%, $P = 0.87$) stopped treatment 3 days prior to the study visit. Survey data (Table 1) revealed that significantly more NTG patients suffered from cold hand and/or feet (73% versus 27%, $P < 0.001$). This effect was maintained after excluding patients with migraine in the control group ($P < 0.001$). There were also trends toward an increased prevalence of migraine ($P = 0.17$), fibromyalgia ($P = 0.13$), and sleep apnea ($P = 0.26$) in the NTG group.

TABLE 2. Baseline Characteristics of the Study Population

Variable	NTG (n = 30)	Control (n = 33)	*P* Value
Age, y	65 ± 8	67 ± 8	0.46
Male, n (%)	7 (23)	8 (24)	0.93
BMI, kg/m^2	25.8 ± 3.5	26.3 ± 3.6	0.57
IOP			
Left eye, mm Hg	12 ± 2	13 ± 3	0.37
Right eye, mm Hg	12 ± 3	13 ± 2	0.41
Biochemical parameters			
Total cholesterol, mg/dL	201 ± 34	215 ± 30	0.08
HDL cholesterol, mg/dL	69 ± 16	75 ± 21	0.18
LDL cholesterol, mg/dL	111 ± 28	120 ± 32	0.25
Triglycerides, mg/dL	94 ± 31	98 ± 40	0.72
Creatinin, mg/dL	0.82 ± 0.13	0.85 ± 0.19	0.61
Glucose, mg/dL	94 ± 12	92 ± 10	0.51
Lifestyle variables			
Active smoking, n (%)	0 (0)	1 (3)	0.34
Regular alcohol use, n (%)	8 (27)	9 (27)	0.96
Medication use			
Lipid-lowering drugs, n (%)	8 (27)	7 (21)	0.61
Antihypertensive drugs, n (%)	12 (40)	14 (42)	0.85
Of which vasoactive*, n (%)	5 (17)	6 (18)	0.87

BMI = body mass index, HDL = high-density lipoprotein, IOP = intraocular pressure, LDL = low-density lipoprotein, NTG = normal-tension glaucoma, SD = standard deviation. Data are mean ± SD or frequency (percentage).

* All vasoactive drugs were stopped 3 days prior to the study visit.

None of the cardiovascular parameters were different between NTG and control subjects (Table 3). Femoral IMT was borderline significant ($P = 0.05$), and lower in the NTG subjects. However, when this parameter (IMT) was corrected for differences in arterial diameter (WCSA), this near statistical significance disappeared ($P = 0.21$).

DISCUSSION

A comprehensive assessment of the macrocirculation and microcirculation at rest did not reveal any difference between NTG patients and age and sex-matched healthy controls. This finding confirms those of others who observed no difference in blood pressure and/or waveform parameters, and PWV.[18,23] In addition, we showed that muscular artery stiffness, RM, and total peripheral resistance, which to our knowledge constitute a blind spot in NTG research, were also not different from the controls. However, questionnaire reports do suggest that vascular dysregulation is present in the majority of NTG patients, and not restricted to the eye. To summarize, despite arguments for a systemic involvement, no systemic differences in cardiovascular structure and function were found at rest.

There are several possible explanations for this paradox.

- Vascular dysregulation represents a defective response to a certain stressor, whereas all cardiovascular parameters were measured at rest. As symptoms of vascular dysregulation occur only episodically (eg, at night, after cold exposure, and others), provocative tests may be needed to unmask alterations in cardiovascular function. Indeed, Su et al[42] observed no differences in brachial artery blood flow at baseline, but an impaired response following ischemia in NTG patients. Similarly, Nicolela et al[8] found no difference in plasma endothelin-1 levels at baseline, but a significantly higher endothelin-1 concentration in glaucoma patients after cold exposure.
- Although it is evident to consider improper cardiovascular function as a direct cause of inadequate ocular blood flow, the pathophysiology of NTG may involve defects in other organ systems as well. Glaucoma is a multifactorial disease, having an immunological, endocrine, and neurological component, which may make it difficult to isolate a single (cardiovascular) profile.[43–47]
- This is a cross-sectional study. Therefore, we cannot exclude the possibility that cardiovascular alterations were present long before diagnosis, but were in the meantime influenced by other factors, such as lifestyle changes, medication, course of disease, and others. To illustrate, glaucoma patients often recall having low blood pressure in youth,[48] but this effect may disappear with aging.

Table 4[5–8,18,21,23,49–55] gives an overview of literature data and associations with NTG tested in the present study. From this Table, it is clear that the vast majority of studies find associations between NTG and signs of vascular dysregulation, but not consistently with vascular alterations at rest, while no literature data exists on muscular artery stiffness, total peripheral resistance, and RM.

TABLE 3. Hemodynamic Measurements

Variable	NTG (n = 30)	Control (n = 33)	*P* Value
Hemodynamics			
Peripheral			
SBP, mm Hg	126 ± 15	127 ± 16	0.81
DBP, mm Hg	77 ± 8	76 ± 7	0.60
PP, mm Hg	49 ± 9	51 ± 11	0.49
MAP, mm Hg	96 ± 10	96 ± 10	0.98
Central			
cSBP, mm Hg	122 ± 16	125 ± 17	0.49
PP amplification	1.11 ± 0.17	1.06 ± 0.14	0.19
RM, %	69 ± 6	71 ± 7	0.41
AIx, %	128 ± 20	130 ± 18	0.55
Cardiac			
HR, beats/min	63 ± 8	65 ± 8	0.32
SVI, mL/m^2	41 ± 9	39 ± 10	0.62
CI, L/min/m^2	2.4 ± 0.6	2.4 ± 0.6	0.99
TPRI, dyne.s/cm^5/m^2	1833 ± 609	1779 ± 602	0.79
Vascular properties			
Femoral artery			
Diameter, mm	8.61 ± 1.45	8.44 ± 1.00	0.59
IMT, mm	0.71 ± 0.18	0.83 ± 0.26	0.05
WCSA, mm^2	17.9 ± 5.4	19.8 ± 6.3	0.21
CC, mm^2/kPa	0.99 ± 0.49	0.97 ± 0.68	0.90
DC, 10^{-3}/kPa	17.6 ± 9.3	18.3 ± 14.1	0.84
Carotid artery			
Diameter, mm	6.92 ± 0.64	7.16 ± 0.85	0.21
IMT, mm	0.65 ± 0.14	0.68 ± 0.13	0.39
WCSA, mm^2	12.8 ± 3.3	13.9 ± 3.7	0.26
CC, mm^2/kPa	0.78 ± 0.26	0.80 ± 0.34	0.78
DC, 10^{-3}/kPa	21.3 ± 8.7	20.5 ± 9.3	0.74
Aorta			
PWV, m/s	9.8 ± 2.1	10.1 ± 1.9	0.60

Data are mean ± SD. AIx = augmentation index, CC = cross-sectional compliance, CI = cardiac index, DBP = diastolic blood pressure, DC = distensibility coefficient, HR = heart rate, IMT = intima-media thickness, MAP = mean arterial pressure, NTG = normal-tension glaucoma, PP = pulse pressure, PWV = pulse wave velocity, RM = reflection magnitude, SBP = systolic blood pressure, SD = standard deviation, SVI = stroke volume index, TPRI = total peripheral resistance index, WCSA = wall cross-sectional area.

Strengths and Limitations

The strength of this study is that the influence of confounders is limited by matching subjects for age and gender, which was successful and resulted in similar levels of biochemical (eg, cholesterol, fasting glucose, and others) and physical (eg, height, weight, and others) variables between the case and the control group. However, this study has some limitations as well. First, this study suffers from its cross-sectional design. Second, because of low prevalence of NTG, the sample size was small. However, to detect a difference in CC of 20%, as was found in patients with migraine,[32] this sample size was deemed adequate (power 80%, $\alpha = 0.05$). Third, vasoactive drugs were stopped 3 days prior to the measurement visit, which may not be sufficient to cancel out all its hemodynamic effects. However, even if there are residual effects, it is not likely that this has affected our conclusions, since use of vasoactive medication was not different between glaucoma and control subjects. Fourth, cases and controls with history of CVD, hypercholesterolemia, or severe hypertension (causing increased levels of arterial stiffness and wave reflections) were excluded, since we aimed to investigate NTG in its purest form. Fifth, the TPRI is a calculated parameter, constituting a rough index of the systemic microcirculation.

TABLE 4. Associations With NTG Tested in Literature and/or in This Study

	Literature		
	Association With NTG	**No Association With NTG**	**This Study**
Primary vascular dysregulation			
Female sex	Refs. [49–52]		++
Cold extremities	Refs. [5–8]		++
History of migraine	Refs. [53,54]	Ref. [55]	+
Reduced thirst sensation	NA	NA	–
Alterations in the macrocirculation			
Carotid intima-media thickening	Ref. [21]		–
Increased augmentation index	Ref. [21]	Ref. [23]	–
Increased reflection magnitude	NA	NA	–
Elastic artery stiffening		Ref. [18]	–
Muscular artery stiffening	NA	NA	–
Increased central pressure		Ref. [23]	–
Alterations in the microcirculation			
Total peripheral resistance	NA	NA	–

References are shown for associations described in literature between NTG and symptoms of PVD, and alterations in macrocirculation or microcirculation ($P < 0.05$). ''NA'' indicates not described in literature. Associations with NTG in the present study are indicated with symbols: ++ significant association with NTG ($P < 0.05$); + trend ($P > 0.05$); – no association. NTG = normal-tension glaucoma, PVD = peripheral vascular disease.

CONCLUSION

To conclude, our data show no alterations of the microcirculation or macrocirculation in NTG at rest, despite a history of clinical symptoms of systemic vascular dysregulation. In particular, vascular dysregulation did not lead to statistically significant alterations in vascular tone as evidenced by no differences in function of the muscular femoral artery, total peripheral resistance, MAP, and measures of wave reflection. Provocative tests may be needed to reveal alterations in cardiovascular function in NTG patients.

REFERENCES

1. Kingman S. Glaucoma is second leading cause of blindness globally. *Bull World Health Organ.* 2004;82:887–888.
2. Mozaffarieh M, Flammer J. New insights in the pathogenesis and treatment of normal tension glaucoma. *Curr Opin Pharmacol.* 2013;13:43–49.
3. Weinreb RN, Harris A. Ocular Blood Flow in Glaucoma: The 6th Consensus Report of the World Glaucoma Association Amsterdam, The Netherlands: Kugler Publications; 2009.
4. Flammer J, Konieczka K, Flammer AJ. The primary vascular dysregulation syndrome: implications for eye diseases. *EPMA J.* 2013;4:14.
5. Gasser P, Flammer J. Blood-cell velocity in the nailfold capillaries of patients with normal-tension and high-tension glaucoma. *Am J Ophthalmol.* 1991;111:585–588.
6. Broadway DC, Drance SM. Glaucoma and vasospasm. *Br J Ophthalmol.* 1998;82:862–870.
7. O'brien C. Vasospasm and glaucoma. *Br J Ophthalmol.* 1998;82:855–856.
8. Nicolela MT, Ferrier SN, Morrison CA, et al. Effects of cold-induced vasospasm in glaucoma: the role of endothelin-1. *Invest Ophthalmol Vis Sci.* 2003;44:2565–2572.
9. Corbett JJ, Phelps CD, Eslinger P, et al. The neurologic evaluation of patients with low-tension glaucoma. *Invest Ophthalmol Vis Sci.* 1985;26:1101–1104.
10. Phelps CD, Corbett JJ. Migraine and low-tension glaucoma. A case-control study. *Invest Ophthalmol Vis Sci.* 1985;26:1105–1108.
11. Demailly P, Cambien F, Plouin PF, et al. Do patients with low tension glaucoma have particular cardiovascular characteristics? *Ophthalmologica.* 1984;188:65–75.
12. Kaiser HJ, Flammer J, Graf T, et al. Systemic blood pressure in glaucoma patients. *Graefes Arch Clin Exp Ophthalmol.* 1993;231:677–680.
13. Graham SL, Drance SM, Wijsman K, et al. Ambulatory blood pressure monitoring in glaucoma: the nocturnal dip. *Ophthalmology.* 1995;102:61–69.
14. Meyer JH, Brandi-Dohrn J, Funk J. Twenty four hour blood pressure monitoring in normal tension glaucoma. *Br J Ophthalmol.* 1996;80:864–867.
15. Leighton DA, Phillips CI. Systemic blood pressure in open-angle glaucoma, low tension glaucoma, and the normal eye. *Br J Ophthalmol.* 1972;56:447.
16. Meyer JH, Brandi-Dohrn J, Funk J. Twenty four hour blood pressure monitoring in normal tension glaucoma. *Br J Ophthalmol.* 1996;80:864–867.
17. Plange N, Kaup M, Daneljan L, et al. 24-h blood pressure monitoring in normal tension glaucoma: night-time blood pressure variability. *J Hum Hypertens.* 2005;20:137–142.
18. Hulsman CAA, Vingerling JR, Hofman A, et al. Blood pressure, arterial stiffness, and open-angle glaucoma: the Rotterdam study. *Arch Ophthalmol.* 2007;125:805–812.
19. Kim Y-K, Oh WH, Park KH, et al. Circadian blood pressure and intraocular pressure patterns in normal tension glaucoma patients with undisturbed sleep. *Korean J Ophthalmol.* 2010;24:23–28.
20. Na K-S, Lee NY, Park S-H, et al. Autonomic dysfunction in normal tension glaucoma: the short-term heart rate variability analysis. *J Glaucoma.* 2010;19:377–381.
21. Mroczkowska S, Ekart A, Sung V, et al. Coexistence of macro- and micro-vascular abnormalities in newly diagnosed normal tension glaucoma patients. *Acta Ophthalmol (Copenh).* 2012;90:e553–e559.

22. Wierzbowska J, Wierzbowski R, Stankiewicz A, et al. Cardiac autonomic dysfunction in patients with normal tension glaucoma: 24-h heart rate and blood pressure variability analysis. *Br J Ophthalmol.* 2012;96:624–628.
23. Graham SLM, Butlin M, Lee M, et al. Central blood pressure arterial waveform analysis, and vascular risk factors in glaucoma. *J Glaucoma.* 2013;22:98–103.
24. Mroczkowska S, Benavente-Perez A, Negi A, et al. Primary open-angle glaucoma vs normal-tension glaucoma: the vascular perspective. *JAMA Ophthalmol.* 2013;131:36–43.
25. Kashiwagi K, Hosaka O, Kashiwagi F, et al. Systemic circulatory parameters comparison between patients with normal tension glaucoma and normal subjects using ambulatory monitoring. *Jpn J Ophthalmol.* 2001;45:388–396.
26. Kim Y-K, Oh WH, Park KH, et al. Circadian blood pressure and intraocular pressure patterns in normal tension glaucoma patients with undisturbed sleep. *Korean J Ophthalmol.* 2010;24:23–28.
27. Wierzbowska J, Wierzbowski R, Stankiewicz A, et al. Cardiac autonomic dysfunction in patients with normal tension glaucoma: 24-h heart rate and blood pressure variability analysis. *Br J Ophthalmol.* 2012;96:624–628.
28. Ikuyo O, Futoshi I, Hiroshi O, et al. Arterial sclerosis grade in normal-tension glaucoma patients. *J Eye.* 2004;21:397–400.
29. Chiba T, Chiba N, Kashiwagi K. Systemic arterial stiffness in glaucoma patients. *J Glaucoma.* 2008;17:15–18.
30. Liao D, Wong TY, Klein R, et al. Relationship between carotid artery stiffness and retinal arteriolar narrowing in healthy middle-aged persons. *Stroke J Cereb Circ.* 2004;35:837–842.
31. Cheung N, Sharrett AR, Klein R, et al. Aortic distensibility and retinal arteriolar narrowing: the multi-ethnic study of atherosclerosis. *Hypertension.* 2007;50:617–622.
32. Vanmolkot FH, Van Bortel LM, de Hoon J. Altered arterial function in migraine of recent onset. *Neurology.* 2007;68:1563–1570.
33. Schacknow PN, Samples JR. The Glaucoma Book: A Practical Evidence-Based Approach to Patient Care New York: Springer; 2010
34. Greene AS, Tonellato PJ, Lui J, et al. Microvascular rarefaction and tissue vascular resistance in hypertension. *Am J Physiol.* 1989;256 (1 Pt 2):H126–H131.
35. Van Bortel LM, Duprez D, Starmans-Kool MJ, et al. Clinical applications of arterial stiffness Task Force III: recommendations for user procedures. *Am J Hypertens.* 2002;15:445–452.
36. Boutouyrie P, Bussy C, Hayoz D, et al. Local pulse pressure and regression of arterial wall hypertrophy during long-term antihypertensive treatment. *Circulation.* 2000;101:2601–2606.
37. Van Bortel LM, Balkestein EJ, van der Heijden-Spek JJ, et al. Non-invasive assessment of local arterial pulse pressure: comparison of applanation tonometry and echo-tracking. *J Hypertens.* 2001;19:1037–1044.
38. Van Bortel LM, Laurent S, Boutouyrie P, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens.* 2012;30:445–448.
39. Chen C-H, Ting C-T, Nussbacher A, et al. Validation of carotid artery tonometry as a means of estimating augmentation index of ascending aortic pressure. *Hypertension.* 1996;27:168–175.
40. Kips JG, Rietzschel ER, De Buyzere ML, et al. Evaluation of noninvasive methods to assess wave reflection and pulse transit time from the pressure waveform alone. *Hypertension.* 2009;53:142–149.
41. Gehan EA, George SL. Estimation of human body surface area from height and weight. *Cancer Chemother Rep.* 1970;54:225–235.
42. Su W-W, Cheng S-T, Hsu T-S, et al. Abnormal flow-mediated vasodilation in normal-tension glaucoma using a noninvasive determination for peripheral endothelial dysfunction. *Invest Ophthalmol Vis Sci.* 2006;47:3390–3394.
43. Pache M, Flammer J. A sick eye in a sick body? Systemic findings in patients with primary open-angle glaucoma. *Surv Ophthalmol.* 2006;51:179–212.
44. Cartwright MJ, Grajewski AL, Friedberg ML, et al. Immune-related disease and normal-tension glaucoma. A case-control study. *Arch Ophthalmol.* 1992;110:500–502.
45. Jämsén K. Thyroid disease, a risk factor for optic neuropathy mimicking normal-tension glaucoma. *Acta Ophthalmol Scand.* 1996;74:456–460.
46. Kesler A, Haber I, Kurtz S. Neurologic evaluations in normal-tension glaucoma workups: are they worth the effort? *Isr Med Assoc J.* 2010;12:287–289.
47. Erb C, Batra A, Lietz A, et al. Psychological characteristics of patients with normal-tension glaucoma. *Graefes Arch Clin Exp Ophthalmol.* 1999;237:753–757.
48. Gherghel D, Orgül S, Gugleta K, et al. Retrobulbar blood flow in glaucoma patients with nocturnal over-dipping in systemic blood pressure. *Am J Ophthalmol.* 2001;132:641–647.
49. Orgul S, Flammer J, Gasser P. Female preponderance in normal-tension glaucoma. *Ann Ophthalmol Glaucoma.* 1995;27:355–359.
50. Levene RZ. Low tension glaucoma: a critical review and new material. *Surv Ophthalmol.* 1980;24:621–664.
51. Drance SM, Sweeney VP, Morgan RW, et al. Studies of factors involved in the production of low tension glaucoma. *Arch Ophthalmol.* 1973;89:457–465.
52. Nicolela MT, Drance SM. Various glaucomatous optic nerve appearances: clinical correlations. *Ophthalmology.* 1996;103:640–649.
53. Phelps CD, Corbett JJ. Migraine and low-tension glaucoma. A case-control study. *Invest Ophthalmol Vis Sci.* 1985;26:1105–1108.
54. Wang JJ, Mitchell P, Smith W. Is there an association between migraine headache and open-angle glaucoma? Findings from the Blue Mountains Eye Study. *Ophthalmology.* 1997;104:1714–1719.
55. Usui T, Iwata K, Shirakashi M, et al. Prevalence of migraine in low-tension glaucoma and primary open-angle glaucoma in Japanese. *Br J Ophthalmol.* 1991;75:224–226.