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 arteryplanationometry, 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 ± 15/77 ± 8 versus 127 ± 16/76 ± 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/cm²/m², 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. 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.

INTRODUCTION

Glaucoma is the second leading cause of blindness worldwide 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. Nonetheless, vascular 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. Moreover, dysregulation often manifests itself systemically as the ‘‘primary vascular dysregulation syndrome.’’ NTG patients often suffer from this syndrome or its hallmarks (eg, cold extremities, migraine, 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 or only at night. Many studies, however, did not find an association between NTG and low blood pressure or show over-dipping. Focusing on more integrative measures of vascular health did not solve these discrepancies. Augustation index (AIx) (a measure of wave reflections) in NTG patients was found increased by Mroczkowska et al, but unaltered by Graham et al. Pulse wave...
vascular abnormalities in it was hypothesized that NTG is associated with systemic factors as well, such as total peripheral resistance, which 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, whose condition might share a common etiology (the brachial) artery was found decreased in patients with migraine, whose condition might share a common etiology. Similarly, total peripheral resistance may be an interesting parameter to examine in NTG, as it can be altered in case of systemic microvascular abnormalities.

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 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. 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 (PWVs) 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; WallTrack 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 \([\pi\times(D/2 - IMT)^2]\) from arterial cross-sectional area \([\pi\times(D/2)^2]\). 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 = \((\Delta A/PP) = \pi \times (D_s^2 - D_l^2)/(4 \times PP)\), and DC = \((\Delta A/\Delta A_0)/PP = (D_s^2 - D_l^2)/(\Delta A_0 \times PP)\), where \(\Delta A\) is the systolic–diastolic change in arterial cross section, \(D_s\) is the arterial diameter at end systole, \(D_l\) is the arterial diameter at end diastole, \(A_0\) 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.

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Aortic stiffness was measured along the carotid–femoral path, using applanation tonometry (SphygmoCor). Carotid-totemoral 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 = PP, and DC = \((\Delta A/\Delta A_0)/PP = (D_s^2 - D_l^2)/(\Delta A_0 \times PP)\), where \(\Delta A\) is the systolic–diastolic change in arterial cross section, \(D_s\) is the arterial diameter at end systole, \(D_l\) is the arterial diameter at end diastole, \(A_0\) 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.

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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 \(\chi^2\) 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 (i.e., 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.

| 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/m² | 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       |

\(\text{BMI} =\) body mass index, \(\text{HDL} =\) high-density lipoprotein, \(\text{IOP} =\) intraocular pressure, \(\text{LDL} =\) low-density lipoprotein, \(\text{NTG} =\) normal-tension glaucoma, \(\text{SD} =\) 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, Nicolella et al\(^{33}\) 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, but this effect may disappear with aging.

Table 4 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.

### Strengths and Limitations

The strength of this study is that the influence of founders 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 chemical (eg, cholesterol, fasting glucose, and others) and physical (eg, height, weight, and others) variables between founders 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 cardio-vascular function in NTG patients.

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