Primary Open-Angle Glaucoma vs Normal-Tension Glaucoma

The Vascular Perspective

Stephanie Mroczkowska, PhD; Alexandra Benavente-Perez, PhD; Anil Negi, MD; Velota Sung, FRCS(Ed); Sunni R. Patel, PhD; Doina Gherghel, PhD

Objective: To compare and contrast the presence of ocular and systemic vascular function in patients with newly diagnosed and previously untreated primary open-angle glaucoma (POAG) vs those with normal-tension glaucoma (NTG) and comparable early-stage, functional loss.

Methods: The systemic vascular function of 19 patients with POAG, 19 patients with NTG, and 20 healthy individuals serving as controls was assessed using 24-hour ambulatory blood pressure monitoring, peripheral pulse wave analysis, and carotid intima-media thickness. Retinal vascular reactivity to flicker light was assessed using dynamic retinal vessel analysis (Imedos, GmbH).

Results: Compared with controls, patients with POAG and those with NTG exhibited similarly increased nocturnal systemic blood pressure variability ($P = .01$), peripheral arterial stiffness ($P = .02$), and a similarly increased fluctuation in arterial and venous baseline diameter ($P = .008$ and $P = .009$, respectively) compared with controls.

Conclusions: Patients with POAG or NTG exhibit similar alterations in ocular and systemic circulation in the early stages of their disease process. This finding highlights the importance of considering vascular risk factors in both conditions and raises questions about the current separation of the two conditions into distinct clinical entities.


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For many years, it has been common practice to separate primary open-angle glaucoma (POAG) into two distinct clinical entities on the basis of intraocular pressure (IOP), with glaucomatous optic neuropathy (GON) in the presence of IOP higher than 21 mm Hg being described as high-tension POAG and all other cases being referred to as either low-tension glaucoma or normal-tension glaucoma (NTG). During recent years, however, additional risk factors, such as ocular and systemic circulation abnormalities, have been linked to the cause and progression of both POAG and NTG, and IOP reduction has been shown to have a positive effect on disease progression in both conditions. Consequently, recent research has recommended the abolishment of the terms POAG and NTG, proposing instead that POAG be considered a disease continuum extending from a predominantly IOP-dependent entity at one end (pure POAG) to a predominantly IOP-independent entity at the other end (pure NTG). Despite this, several important differences have been identified between POAG and NTG, both structurally and functionally, and a clinical separation between the two forms is currently the usual practice. It is likely that the onset and progression of both forms of glaucoma are dictated by a degree of interaction between IOP and vascular factors, which may vary on an individual basis. Therefore, the aim of this study was to evaluate vascular function at the ocular and systemic levels in patients with POAG or NTG and similar degrees of early functional loss in an attempt to help understand and clarify the divisions, if any, between these two forms of glaucoma.

Methods

Patients with successive early-stage, previously untreated POAG or NTG were re-
ingredients from 2 local National Health Service Trusts in England. Only those identified as having glaucomatous cupping of the optic disc on funduscopic assessment, normal open anterior chamber angles by gonioscopy, and visual field defects consistent with the diagnosis of early glaucoma using the Humphrey visual field analyzer (SITA 24-2 [Swedish Interactive Thresholding Algorithm]; Carl Zeiss Meditec) were included. Classification as NTG was based on IOP measurements consistently above 21 mm Hg on diurnal testing with applanation tonometry. Classification as NTG was based on an IOP measurement consistently above 21 mm Hg or less on diurnal testing with applanation tonometry. Patients with a central corneal thickness outside the normal limits (mean [SD], 540 [30] μm),17 closed iridocorneal angles, evidence of secondary glaucoma, pseudoxefosis, history of intraocular surgery, cataract, or any form of retinal or neuro-ophthalmologic disease that could result in visual field defects were excluded from the study.

Healthy individuals recruited for the control group were excluded if any signs consistent with GON, ocular hypertension, or retinal disease were found. Additional systemic exclusion criteria for all participants were consistent with that published elsewhere.35 Well-controlled systemic hypertension was neither an inclusion nor exclusion criterion for either category of patients or controls.

Approval for the study was received from the relevant local ethics committees. Informed consent was obtained from all participants on enrollment. All procedures were designed and conducted in accordance with the tenets of the Declaration of Helsinki.

INVESTIGATIONS

All measurements were performed between 8 AM and 11 AM after a 12-hour overnight fast, which included no alcohol or caffeine.

Systolic blood pressure (SBP) and diastolic BP (DBP) were measured at baseline using an automatic BP monitor (model UA-767, A&D Co Ltd). Baseline IOP was measured using Goldmann applanation tonometry. Weight and height were recorded and the body mass index was determined (calculated as weight in kilograms divided by height in meters squared) (Table 1).

### Ambulatory BP Monitoring

Ambulatory BP data were recorded for all participants during a 24-hour period (Cardiotens-01; Meditech Ltd).30-33 Mean diurnal and nocturnal SBP and DBP were recorded for each participant. Mean BP was then calculated and the mean nocturnal dip in BP was expressed as a percentage of the average daytime reading (Table 2). Finally, the short-term variability in SBP was determined for the diurnal and nocturnal periods through calculation of the average coefficient of variation for each group (Table 3).

### Pulse-Wave Analysis

Arterial stiffness was assessed by pulse-wave analysis, using a validated device (SphygmoCor; AtCor Medical), according to a published protocol.34 Augmentation index was used as a measure of arterial stiffness.35

### Intima-media Thickness Measurement

Intima-media thickness (IMT) was obtained through analysis of ultrasound images taken from the common carotid artery at the neck, using an ultrasound system (Acuson Sequoia; Siemens), according to a published protocol.36

### Dynamic Retinal Vessel Analysis

Retinal vessel reactivity was measured with the dynamic retinal vessel analyzer (Imedos GmbH), using a published protocol.37,38 All measurements were performed in a quiet, temperature-controlled (22°C) room after full dilation of 1 pupil (tropicamide, 1%; Chauvin Pharmaceuticals Ltd). In patients with glaucoma, all measurements were conducted in the eye with the greatest degree of glaucomatous damage. In controls, all measurements were conducted on 1 unselected eye. The Figure depicts the dilation and constriction variables used for analysis. The dynamic nature of the retinal vascular response profile was additionally explored through extracting the raw response data and applying a statistical polynomial regression algorithm (MATLAB; MathWorks), as detailed elsewhere.39

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**Table 1. Summary of Systemic Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>POAG</th>
<th>NTG</th>
<th>Control</th>
<th><em>P</em> Value (ANOVA)</th>
<th>Significant Difference by Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>19</td>
<td>19</td>
<td>20</td>
<td>.28</td>
<td></td>
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<tr>
<td>Sex</td>
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<td>Female</td>
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<td>11</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>65.26 (8.52)</td>
<td>60.16 (12.13)</td>
<td>60.65 (4.20)</td>
<td>.17</td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>136.32 (15.42)</td>
<td>130.06 (15.37)</td>
<td>127.11 (14.47)</td>
<td>.17</td>
<td></td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>79.11 (9.80)</td>
<td>78.39 (11.14)</td>
<td>77.00 (8.84)</td>
<td>.80</td>
<td></td>
</tr>
<tr>
<td>BMIb</td>
<td>27.71 (5.00)</td>
<td>27.92 (4.20)</td>
<td>26.86 (3.79)</td>
<td>.76</td>
<td></td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>23.94 (2.00)</td>
<td>17.40 (1.80)</td>
<td>15.05 (2.48)</td>
<td>&lt;.001c</td>
<td>POAG &gt; NTG and control; NTG = control</td>
</tr>
<tr>
<td>OPPd</td>
<td>41.87 (8.96)</td>
<td>47.29 (8.82)</td>
<td>55.94 (13.98)</td>
<td>&lt;.001c</td>
<td>POAG and NTG &lt; control; POAG = NTG</td>
</tr>
<tr>
<td>Mean deviation</td>
<td>-1.58 (0.54)</td>
<td>-2.18 (3.22)</td>
<td>.55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; DBP, diastolic blood pressure; ellipses, no significant difference; IOP, intraocular pressure; NTG, normal-tension glaucoma; OPP, ocular perfusion pressure; POAG, primary open-angle glaucoma; SBP, systolic blood pressure.

Data are given as mean (SD) unless otherwise indicated.

1. Calculated as weight in kilograms divided by height in meters squared.
2. *P* < .05 was considered a significant difference.
3. Calculated as OPP = 1⁄3 DBP + 1⁄3 SBP – IOP.

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**Table 2. Ambulatory BP by Group**

<table>
<thead>
<tr>
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<th>NTG</th>
<th>Control</th>
<th>Significant Difference by Group</th>
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</tbody>
</table>
STATISTICAL ANALYSIS

All data are reported as mean (SD). The Kolmogorov-Smirnov test was used to determine the distribution of the data. Multivariate analysis was performed to determine the influence of age, body mass index, BP, and circulating markers on the measured variables. Differences between groups were subsequently assessed using 1-way analysis of variance (ANOVA) or analysis of covariance (ANCOVA), as appropriate, followed by Tukey post hoc analysis. In cases in which the normality of the data could not be confirmed, log transformations were made. Significance was set at \( P < .05 \), except for cases in which a lower value (\( P < .01 \)) was used to correct for multiple comparisons. All analyses were performed using commercial software (Statistica, version 6.0; StatSoft).

RESULTS

Nineteen patients with early-stage POAG, 19 patients with early-stage NTG, and 20 healthy, age-matched individuals serving as controls were included in this study. There were no significant differences in age, BP, or body mass index between the groups (\( P > .05 \)). The number of participants with well-controlled hypertension was also similar between groups (POAG, \( n = 4 \); NTG, \( n = 5 \); controls, \( n = 6 \); \( \chi^2 \) test, \( P > .05 \)). Furthermore, there were no significant differences between the degree of visual field loss at the time of diagnosis between POAG and NTG patients (mean deviation; \( P > .05 \)). The IOP was, however, significantly greater in POAG patients compared with NTG patients and controls, as expected (\( P < .001 \)) (Table 1). In addition, ocular perfusion pressure (OPP) was significantly lower in the POAG and NTG patients compared with the controls (\( P < .001 \)) (Table 1).

SYSTEMIC VASCULAR VARIABLES

Ambulatory BP Monitoring

No significant differences in SBP, DBP, or mean BP were identified between groups across the diurnal, nocturnal, or 24-hour measurement period or in the percentage nocturnal dip in BP (all \( P > .05 \)) (Table 2). Furthermore, no significant differences were found in the number of nondippers (\(<10\%\)), physiologic dippers (10%-20%), and overdippers (>20%) between groups in this study. A similarly increased nocturnal variability in SBP was, however, identified in POAG and NTG compared with controls (\( P = .01 \)) (Table 3).

Pulse-Wave Analysis

After correction for DBP, which was identified as an influence factor on multivariate analysis, pulse-wave analysis augmentation index was significantly greater in the
POAG and NTG patients compared with the controls (POAG, 27.88 [8.20]; NTG, 26.06 [11.25]; control, 16.00 [10.66]; ANCOVA, \( P = .02 \)).

**IMT Measurement**

The IMT was similarly increased after correcting for age and body mass index in NTG and POAG patients compared with controls (POAG, 0.063 [0.014]; NTG, 0.064 [0.015]; controls, 0.042 [0.028]; ANCOVA, \( P = .04 \)).

**DYNAMIC RETINAL VESSEL ANALYSIS**

**Arterial Response**

No significant differences were found in maximum retinal arterial dilation, baseline corrected flicker response, or percentage constriction below baseline between all 3 study groups (all \( P > .01 \)) (Table 4). The arterial baseline diameter fluctuation (BDF), however, was significantly greater in POAG and NTG patients compared with controls (ANOVA, \( P = .008 \)) (Table 4), and a significantly steeper arterial constriction slope was demonstrated in both glaucoma groups compared with the control group on evaluation of the dynamic nature of the arterial response (ANOVA, \( P = .007 \)) (Table 4).

**Venous Response**

No significant differences were found in the percentage change in retinal venous diameter from baseline to maximum, baseline-corrected flicker response, percentage change in diameter from baseline to maximum, dilation, or constriction slopes between all 3 study groups (all \( P > .01 \)) (Table 5). The venous BDF, however, was significantly greater in POAG and NTG patients compared with controls (ANOVA, \( P = .009 \)) (Table 5).

**COMMENT**

This study reveals a similarly increased variability in nocturnal SBP, systemic arterial stiffness, and IMT in early-stage POAG and NTG, which was not replicated in age-matched controls. In addition, a comparably reduced OPP, a significantly steeper retinal arterial constriction slope after cessation of flicker, and an increased fluctuation in arterial and venous baseline diameter were identified in both glaucoma groups but not in the control group.

Evaluation of ambulatory BP in patients with glaucoma can provide insight into the presence of associated modifiable vascular risk factors and ischemic risk. In the current study and consistent with previous research, no significant differences in the average diurnal and nocturnal BP variables or the nocturnal dipping status were found between the POAG, NTG, and control groups following 24-hour BP assessment. There is, however, a lack of consistency in results reported by various groups regarding the relationship between systemic BP and glaucoma, with other studies finding associations between abnormal systemic BP and the presence of GON, particularly with regard to hypotension and nocturnal BP dipping. The inclusion/exclusion criteria for these studies are variable, making direct comparison difficult, and it is possible that the strict selection of patients in our study could have contributed to the findings herein. Interestingly, an increased variability in nocturnal SBP, as well as a reduced OPP at the time of testing,
was identified in both glaucoma groups, compared with the control group in this study. Increased variability in BP is widely recognized in cardiovascular and hypertension research as a signal of increased risk for end-organ damage and, during recent years, its occurrence has been increasingly considered with regard to other vascular diseases, including glaucoma. The mechanism by which such increased variability, during the nocturnal period in particular, may relate to the development of GON is unclear. It could be hypothesized that, because of the close relationship between BP and OPP, an increased variability in BP may subsequently lead to increased variability in OPP, which may have a particular effect nocturnally when OPP is already physiologically reduced and the optic nerve head is more vulnerable. To validate this hypothesis, calculation of 24-hour OPP would be ideal; however, in this study and in line with current clinical practice in England, this information is not available since 24-hour IOP was not measured. At the time of assessment, however, OPP was significantly reduced in POAG and NTG patients compared with controls, suggesting that perfusion-related vascular alterations are likely to be playing a part in the pathogenesis of both conditions. However, the relative contribution of IOP to this reduced OPP is likely to vary between our glaucoma groups. Because of this, consideration of the 24-hour IOP and its fluctuations, which themselves have been linked to GON development, would also be beneficial.

In conjunction with increased nocturnal SBP variability, a comparably increased systemic arterial stiffness and carotid artery IMT was identified in the POAG and NTG patients compared with the controls. Arterial stiffness is considered an independent predictor of cardiovascular disease and increased IMT has been suggested as an indirect measure of general atherosclerosis and cardiovascular risk. The presence of cardiovascular disease and structural vascular wall changes has been variably linked to the presence of GON during recent years, with some studies identifying strong associations in POAG and NTG patients individually and others revealing no such associations. The variability in results between these previous studies could in part be accounted for by differences in the inclusion/exclusion of patients with already diagnosed systemic vascular disease, especially because arterial stiffness is a measure of vascular function. Because most patients with glaucoma seen in day-to-day practice experience several vascular pathologies, a careful selection of only patients free from such diseases could bias results toward very rare
occurrences. Consequently, in the current study, we included POAG and NTG patients with well-controlled hypertension, along with a similar number of individuals with such status in the control group. All groups were additionally matched on age and functional loss. In light of this and on the basis of our findings here, systemic vascular wall changes could be hypothesized to, in some way, contribute to or signal a higher risk for the development of GON in the early stages of the disease, regardless of the level of IOP.

With regard to retinal microvascular function, both groups of patients with early-stage glaucoma demonstrated a comparably steeper retinal arterial constriction slope after the cessation of flicker, as well as an increased arterial and venous BDF in comparison with controls. Slope is an important factor that allows an evaluation of the dynamic nature of the vascular constriction profile. A previous study reported a steeper arterial constriction response after flicker light stimulation in NTG patients, and altered retinal arterial constriction has been noted in the presence of vascular disorders such as primary vascular dysregulation syndrome and elevated endothelin-1 levels,

both of which have also been widely linked to the presence of GON. With this in mind, it is not unreasonable to hypothesize that the steeper retinal arterial constriction slope identified in the current study could signal the presence of retinal vascular dysfunction in both POAG and NTG. It is interesting that a steeper arterial constriction slope was identified in both groups of glaucoma patients compared with controls, especially as some of the conditions to which this finding has been theoretically linked (namely, primary vascular dysregulation and elevated endothelin-1 levels) have been more frequently related to NTG. As such, it could be hypothesized that conditions similar to those more commonly exhibited in our NTG patients are also evident in the early stages of POAG. However, to determine whether this is the case, supplementary information—for example, on the presence of primary vascular dysregulation symptoms, such as cold hands and feet, exploration of nail fold capillary perfusion, and determination of endothelin-1 levels in both groups of patients—would be required.

In addition to the steeper retinal arterial constriction slope, comparably increased fluctuations in baseline arterial and venous diameter before the onset of flicker were also identified in both glaucoma groups compared with the control group. Baseline diameter fluctuation is a factor that, although recognized, is not commonly reported in the literature. Its consideration was first recommended by Nagel et al as a way of taking into account the effect of spontaneous variations in vessel diameter, which occur under normal resting conditions, on the response of the vasculature to flicker light. Tentative links have been made in previous studies between the occurrence of increased arterial diameter fluctuations and the presence of vascular disturbance in smokers and individuals with vasospasm, as well as between increased retinal venous diameters and the presence of retinal ischemia and hypoxia. On this basis, it could be hypothesized that the increased BDF identified here in the POAG and NTG groups is a further indicator that common alterations in retinal vascular function may exist in these individuals, perhaps related to an increased variation in vascular tone or rigidity or the presence of ischemic and hypoxic changes.

The aim of this study was to explore the presence of vascular dysfunction at the ocular and systemic levels in POAG and NTG patients with similar early functional loss in an attempt to help understand and clarify the similarities and differences that exist between these two forms of glaucoma. To our knowledge, this is the first time that direct comparisons such as these have been made between these two types of glaucoma across so many ocular and systemic variables simultaneously, making it difficult to directly compare our findings with those of previous studies. Nevertheless, we have identified evidence of altered retinal vascular reactivity, altered OPP, altered nocturnal BP variability, and signs of systemic vascular abnormalities in POAG and NTG patients, which are comparable to and not replicated by controls. Such findings suggest that a considerable overlap may exist in the development of POAG and NTG, especially in the early stages of the disease. The finding of so many comparable variables between our glaucoma groups is perhaps somewhat surprising, especially because, on the basis of previous research, it was hypothesized that the evidence of vascular dysfunction would be more pronounced in NTG patients. The relative influence of IOP on the results obtained in this study is difficult to determine, and the possibility that the mechanisms by which these multiple vascular variables become similarly altered could still vary between glaucoma groups cannot be ruled out. Regardless of this, it appears from our findings that the consideration of glaucoma as a disease continuum rather than 2 separate clinical entities, especially when considering vascular risk, may well be a useful and valid concept.

In conclusion, this study demonstrates multiple comparable alterations in both ocular and systemic vascular function between POAG and NTG patients with similar levels of early functional loss. The findings highlight the importance of considering vascular risk in the development and treatment of both conditions, as well as the need to perhaps become less rigid in our separation of the 2 conditions into distinct clinical entities when considering the therapy for these patients.

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Author Contributions: Dr Gherghel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Financial Disclosure: None reported.


