Purpose. To evaluate ocular blood flow velocity indices in untreated primary open-angle glaucoma (POAG) and normal pressure glaucoma (NPG).

Methods. Twenty-five untreated patients with NPG, 23 untreated patients with POAG, and 26 age-matched normal control subjects underwent color Doppler imaging for the measurement of blood flow velocity in the central retinal and ophthalmic arteries. Neither the patients nor the control subjects were using systemic beta-blockers or calcium channel blockers. After log transformation of non-normal data, group differences were compared with a one-way analysis of variance followed by unpaired t-tests with the Bonferroni correction. Statistical significance was set at \( P < 0.05 \).

Results. The central retinal artery end diastolic velocity was significantly lower in patients with POAG than in normal subjects. The ophthalmic artery peak systolic velocity (PSV) was significantly greater in patients with POAG than in those with NPG and normal subjects. The resistance index (RI) of both the ophthalmic and central retinal arteries was significantly greater in patients with POAG than in normal subjects, and the central retinal artery RI was significantly greater in those with NPG than in normal subjects. Systemic pulse pressure and systolic blood pressure were significantly greater in patients with POAG compared with normal subjects. Multiple regression analysis showed a significant relation between ophthalmic artery PSV and intraocular pressure (but not with any of the cardiovascular parameters) in the POAG group. Chi-square analysis found significantly more systemic vascular disease in patients with NPG and POAG compared with that of normal subjects.

Conclusions. There was an increased resistance to blood flow in the central retinal artery of untreated patients with NPG and POAG and also in the ophthalmic artery of patients with POAG. The ophthalmic artery peak systolic velocity was elevated in untreated patients with POAG. Altered ocular circulation (with different patterns of presentation) appears to be common to patients with NPG and patients with POAG. Invest Ophthalmol Vis Sci. 1997;38:690-696.

The pathogenesis of glaucoma is still uncertain\(^1\)\(^-\)\(^4\) and recently, there has been a revival of interest in a vascular cause, particularly in patients with normal pressure glaucoma (NPG).\(^5\)\(^-\)\(^8\) Many techniques have been devised to study the hemodynamics of the human eye in glaucoma: fundus fluorescein angiography,\(^9\) the blue-field entoptic phenomenon technique to measure macular circulation,\(^10\) laser Doppler velocimetry to assess retinal blood flow,\(^11\) the estimation of the pulsatile component of total ocular blood flow from the variations that occur in intraocular pressure (IOP) with the systemic pulse\(^12\)\(^,\)\(^13\) and transcranial Doppler ultrasound.\(^14\)

Color Doppler imaging (CDI) has been introduced recently to ophthalmology as a noninvasive imaging method.\(^15\)\(^,\)\(^16\) This technique uses simultaneous B-scan and Doppler imaging to locate and identify orbital blood vessels: the central retinal artery and vein, posterior ciliary arteries, ophthalmic artery, superior ophthalmic vein, and vortex veins. Pulsatile blood flow velocity can be measured with CDI, but the resolution of the ultrasound does not allow accurate measurement of vessel diameter of these orbital vessels.
were as follows: All patients had typical glaucomatous
visual field loss (measured by the Humphrey Visual
Field Analyzer threshold program 24-2; the average
mean deviation was —9.5 [6.5] dB) associated with raised
IOP at the time of diagnosis. None of the patients with
POAG were using glaucoma medications. They were
recruited prospectively from the glaucoma new pa-
tient clinic and had CDI measurements carried out
over a 24-hour period before commencement of treat-
ment. Patients with pseudoexfoliation and the pig-
ment dispersion syndrome were excluded. No patients
(neither NPG nor POAG) were using systemic B-block-
ers, Ca²⁺ channel blockers, or systemic steroids.

A detailed medical history was taken from the pa-
tients with glaucoma and those normal control sub-
jects. A summary of those patients with a history of
vascular disease, migraine, and cold hands and feet is
listed in Table 1. The prevalence of migraine was
based on a migraine questionnaire, which was com-
piled from the International Headache Society crite-
ria. A history of cold hands or feet or both (some-
times necessitating wearing socks in bed or gloves in
summer) was obtained by direct questioning of each
patient.

The normal volunteers were recruited from either
either the Womens' Royal Voluntary Service at the hospital,
the hospital staff, or from friends and relatives of the
patients. None of the control subjects had any
significant cardiovascular, respiratory, neurologic, or
ophthalmologic history; they all had normal clinical
ocular examination results (Haag-Streit slit-lamp ex-
amination of the anterior segment, IOP, and optic
disc assessment using indirect ophthalmoscopy with the
90D Volk lens). They were not using regular sys-
temic medications. One control subject was mildly hy-
pertensive but did not require any treatment for this,
whereas another was a diet-controlled mild diabetic.

For the patients with glaucoma, the eye with the
worst field loss was chosen for CDI measurements. For
the normal group, one eye was chosen at random. All
patients and volunteers were white and all three
groups were age matched.

All patients underwent CDI at the Department of
Radiology with an Acuson 128 machine (Mountain
View, CA), with the patient in the erect and supine
positions. Sterile-coupling gel was applied to the
closed eyelids and, using a 7.5-MHz probe, the exami-
nation was carried out with avoidance of undue man-
ual pressure on the globe based on the technique
described by Baxter et al and Williamson et al. The
color Doppler window was localized over the retrobul-
ar area and flow in the ophthalmic and central reti-
nal arteries identified as noted by us before. The
ophthalmic artery was identified approximately 17
mm back from the optic nerve head, where it lies
parallel and lateral to the optic nerve before giving
off its major branches. The central retinal artery was

PATIENTS AND METHODS

Twenty-five untreated patients with NPG, 23 untreated
patients with POAG, and 26 normal volunteers were
recruited for the study. Regional ethical committee
approval was obtained for this study, and the tenets of
the Declaration of Helsinki were followed. Informed
consent was obtained from all patients and volunteers
after detailed explanation of the study.

The inclusion criteria for the patients with NPG
were as follows: All patients had typical glaucomatous
disc damage (assessed by slit-lamp indirect ophthal-
moscopy with the 90D Volk [Mentor, OH] lens) and
visual field loss (measured by the Humphrey Visual
Field Analyzer threshold program 24-2; the average
mean deviation was —9.5 [6.5] dB). Intracranial disease that might mimic the disc or
field changes was excluded by plain skull radiography
and computed tomography scanning. All patients had
IOP <22 mm Hg as confirmed by diurnal inpatient
phasing, open angles on gonioscopy, visual acuity of
20/40 or better, and no previous ocular inflammation or
laser-surgical intervention.

Those patients with NPG who were using topical
glaucoma medications (n = 11) had a washout period
of 1 month before hospital admission for diurnal IOP
phasing and CDI measurements. Fourteen other pa-
tients with NPG were recruited prospectively from the
glaucoma new patient clinic and had inpatient IOP
phasing and CDI carried out before commencement of
any glaucoma medication. Phasing was carried out
using Goldmann applanation tonometry to measure
IOP every 2 hours from 10 AM to 10 PM, and again
at 8 AM on the next morning.

The inclusion criteria for the patients with POAG
were similar to those with NPG but with IOP >25
mm Hg at presentation (range, 26 to 54 mm Hg). No
patient with POAG had diurnal in-patient phasing.

They all had characteristic optic disc changes and vi-
	extual field defects (average [standard deviation] mean
deviation of —15.7 [8.1] dB) associated with raised
IOP at the time of diagnosis. None of the patients with

POAG were using glaucoma medications. They were
recruited prospectively from the glaucoma new pa-
tient clinic and had CDI measurements carried out
over a 24-hour period before commencement of treat-
ment. Patients with pseudoexfoliation and the pig-
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(neither NPG nor POAG) were using systemic B-block-
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mm back from the optic nerve head, where it lies
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off its major branches. The central retinal artery was
### TABLE 1. Characteristics of the Three Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Normals (n = 26)</th>
<th>NPG (n = 25)</th>
<th>POAG (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.7 (6.0)</td>
<td>69.3 (8.9)</td>
<td>69.0 (8.0)</td>
</tr>
<tr>
<td>Arterial blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>132.6 (21.0)</td>
<td>140.4 (28.3)</td>
<td>155.1 (28.6)</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>79.6 (10.7)</td>
<td>78.8 (12.8)</td>
<td>82.0 (14.2)</td>
</tr>
<tr>
<td>Mean (mm Hg)</td>
<td>98.8 (15.0)</td>
<td>99.3 (16.7)</td>
<td>106.3 (17.7)</td>
</tr>
<tr>
<td>Systemic pulse (mm Hg)</td>
<td>54.6 (17.2)</td>
<td>61.6 (20.5)</td>
<td>72.0 (21.4)</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>65.7 (10.6)</td>
<td>68.4 (16.1)</td>
<td>73.3 (13.7)</td>
</tr>
<tr>
<td>Intraocular pressure (mm Hg)</td>
<td>15.8 (3.0)</td>
<td>16.7 (2.9)</td>
<td>31.2 (6.8)</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Migraine/cold extremities</td>
<td>10</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Smokers</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

Values are mean ± SD. NPG = normal pressure glaucoma; POAG = primary open-angle glaucoma.

Angle correction was applied to the pulsed Doppler recordings where possible to minimize errors in the measured velocities. The CDI was performed by an experienced radiologist\textsuperscript{16,17} (GM) who was masked to the identity of the patients and volunteers.

The repeatability of the Doppler readings was assessed by a statistical analysis described by Altman and Bland\textsuperscript{21} for repeat measurements on a series of subjects. Ten normal control subjects had CDI performed on two independent occasions by the same experienced operator (GM), and the data obtained for the left eye were used for analysis. The coefficient of repeatability\textsuperscript{22} was calculated as twice the standard deviation of the differences between the pairs of repeated measurements. The coefficient of repeatability (where 95% of the differences are expected to be less than two standard deviations) for the ophthalmic artery was PSV 3.2 cm/sec, EDV 1.8 cm/sec, and RI 0.06; and for the central retinal artery, PSV 2.1 cm/sec, EDV 0.8 cm/sec, and RI 0.06.

Supine and erect heart rate and blood pressure were determined at a different time of day to the CDI measurements using an automatic sphygmomanometer (Critikon, Dinamap, Takeda, FL). Mean blood pressure was calculated as the diastolic plus one third of the pulse pressure. Sitting IOP was measured using Goldmann applanation tonometry on a Haag–Streit slit-lamp microscope. For the patients with NPG, the peak IOP was chosen during diurnal in-patient phasing for the study and for the patients with POAG, the highest recorded IOP before starting treatment was used for the study.

**Statistical Analysis**

A log transformation was applied to data that was not distributed normally. A one-way analysis of variance was used to analyze significant differences among the three groups. Comparisons between two groups were with a Student’s t-test for unpaired data using the Bonferroni correction.\textsuperscript{23} Statistical significance was set at $P < 0.05$, $P < 0.01$, or $P < 0.001$. The SPSS for Windows (Release 6.0, SPSS, Chicago, IL) statistical package was used for the analysis. Multiple regression analysis was used to examine the relation between blood velocities (in the ophthalmic and central retinal arteries) as the dependent variable, and both IOP and cardiovascular variables as predictor variables in the normal and glaucoma groups. The chi-square test was used to analyze the significance of vascular disease, smoking, migraine, and a positive history of cold hands and feet.

**RESULTS**

**Ocular and Systemic Vascular Parameters**

A one-way analysis of variance showed no difference among the three groups in age ($P = 0.20$), diastolic ($P = 0.66$), and mean ($P = 0.19$) blood pressure, and heart rate ($P = 0.09$) (Table 1). Significant differences were found in systolic blood pressure (SBP, $P = 0.01$), systemic pulse pressure (SPP, $P = 0.007$) and IOP ($P = 0.001$) (Table 1). Student’s t-test for unpaired data with the Bonferroni correction then were used to ana-
Doppler Velocity Indices

There were no significant within-group postural differences noted for the velocity indices in any of the three groups ($P > 0.21$). Therefore, we present the results obtained in the supine position. The one-way analysis of variance among the three groups showed a significant difference in the PSV ($P = 0.004$) and RI ($P = 0.001$) in the ophthalmic artery, and in the EDV ($P = 0.03$) and RI ($P = 0.001$) of the central retinal artery.

The characteristics of the velocity indices in the three groups are summarized in Table 2. A Student’s $t$-test for unpaired data with Bonferroni correction showed the following results: a significantly greater RI ($P < 0.01$) in the central retinal artery in the patients with NPG compared with those normal subjects. There were no significant differences in the ophthalmic artery velocity indices or RI in patients with NPG compared with those of normal subjects.

Compared with the normal group, there was a significantly greater PSV ($P < 0.001$) and RI ($P < 0.001$) in the ophthalmic artery, and also a significant reduction in EDV ($P < 0.05$) and increased RI ($P < 0.01$) of the central retinal artery in patients with POAG. The only significant difference between NPG and POAG was that the ophthalmic artery PSV was significantly greater ($P < 0.01$) in POAG, whereas the ophthalmic artery RI was greater in patients with POAG than in those with NPG but not statistically significant ($P = 0.06$).

Multiple regression analysis showed a significant correlation between ophthalmic artery PSV and IOP ($r = 0.66, P = 0.007$) in the POAG group only (Table 3). There was no relation noted between the other velocity indices (EDV and RI) and cardiovascular variables in any of the three study groups.

**DISCUSSION**

Color Doppler investigations of the ocular circulation in glaucoma have been reported previously. Galassi et al. found a significantly lower ophthalmic

<table>
<thead>
<tr>
<th>TABLE 2. Comparison of Mean (SD) Blood Flow Velocity and Resistance Index</th>
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<tr>
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<td></td>
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<tr>
<td>Ophthalmic artery</td>
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<tr>
<td>Peak systolic velocity</td>
</tr>
<tr>
<td>End diastolic velocity</td>
</tr>
<tr>
<td>Resistance index</td>
</tr>
<tr>
<td>Central retinal artery</td>
</tr>
<tr>
<td>Peak systolic velocity</td>
</tr>
<tr>
<td>End diastolic velocity</td>
</tr>
<tr>
<td>Resistance index</td>
</tr>
</tbody>
</table>

Blood flow velocity is given in cm/second.

POAG = primary open-angle glaucoma; NPG = normal pressure glaucoma.

<table>
<thead>
<tr>
<th>TABLE 3. Multiple Regression Analysis</th>
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<tbody>
<tr>
<td><strong>Predictor Variables</strong></td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Constant</td>
</tr>
<tr>
<td>Systemic pulse pressure (mm Hg)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Intraocular pressure (mg Hg)</td>
</tr>
</tbody>
</table>

$\eta = 23$.

Ophthalmic artery peak systolic velocity is used as the dependent variable in primary open-angle glaucoma.
artery PSV in patients with POAG and a lower EDV and higher RI in the central retinal artery in a small subset of untreated patients with POAG (n = 8) compared with those of normal subjects. Harris et al reported a significantly lower EDV and higher RI in the ophthalmic artery in patients with NPG. Rankin et al recently showed a greater RI in the central retinal and posterior ciliary arteries in patients with NPG and those with POAG. The current study confirms our previous CDI findings of a greater RI in the central retinal artery in untreated patients with NPG. We also have identified that the untreated POAG group has a reduced EDV and raised RI in the central retinal artery compared with those of the normal group, the results of which are similar to those of Galassi et al and Rankin et al.

Pulsed Doppler sonography has shown a reduced blood velocity and an increased RI in the ophthalmic artery in patients with POAG compared with those of normal subjects. Rojanapongpun et al, using transcranial Doppler ultrasound, found a significant reduction of all three Doppler flow velocities (PSV, EDV, and mean velocity) in the ophthalmic artery of patients with POAG and NPG.

In contrast to the previous reports of Doppler measurements in POAG, we found a significantly greater ophthalmic artery PSV in those with POAG compared with those normal subjects. This difference may have arisen because the patients in all the other studies were on treatment, whereas our patients were diagnosed newly and untreated, with a mean IOP of 31.2 mm Hg. The observation that the higher the IOP, the greater the ophthalmic artery PSV in POAG (r = 0.66, P = 0.007) supports this viewpoint. In the only other study of untreated patients with POAG, Lim et al also found a significantly greater PSV in the ophthalmic artery, which fell to near-normal values after trabeculectomy (poster presentation, American Academy of Ophthalmology, Atlanta, 1995; Ophthalmology 1995; 102(S): 134). This, as-yet unpublished study, appears to support our hypothesis.

In the long term, a more pulsatile and dynamic ophthalmic artery circulation (due to the elevated PSV) would increase shear stress and vascular endothelial damage, release local vasoactive mediators, and tend to promote thrombosis.

None of the patients in our study were using systemic beta-blockers or calcium channel blockers (compounds that have vasoactive properties). Netland et al recently have shown how a topical calcium channel blocker may affect CDI measurements by reducing the vascular RI in the central retinal artery. It is unclear from reading the other Doppler studies on glaucoma whether the patients were using any vasoactive medications.

Both Rankin et al and Trible et al have discussed at length the interpretation of CDI findings, especially the relation between velocity, volume blood flow, and the site of resistance to flow in both the systemic and ocular circulation. It appears that a reduced EDV is a sensitive indicator of increased downstream resistance to flow and will lead to a raised RI. Harris et al have postulated that a partially reversible vasospasm may account for the elevated resistance to flow in patients with NPG. We previously have suggested that atherosclerotic changes in the retinal circulation may contribute to the increased RI in patients with NPG. Using chi-square analysis, a significantly greater amount of systemic vascular disease was found in patients with NPG compared with patients with POAG, and both glaucoma groups had significantly more vascular disease than did the normal group.

Thus, systemic arterial disease also may play a role in the RI of the central retinal artery in POAG, but possibly not to the same extent as in NPG. It is more likely that the high level of ocular pressure within the eye in untreated patients with POAG causes a direct impedance to blood flow in the retinal circulation, leading to increased resistance to flow as shown by the elevated RI (Table 2).

Although blood flow in the central retinal artery is but a small proportion of the total ocular circulation, the increased resistance to flow in the central retinal artery of the POAG group might be expected to cause a similar pattern of blood flow change in the ophthalmic artery, namely a reduced EDV and possibly also a reduced PSV. However, this was not the case, in that the EDV was normal and the PSV significantly elevated in the ophthalmic artery in POAG. An increase in vasomotor tone of the ophthalmic artery causing constriction could lead to an increased PSV, without changing the EDV. Conversely, if the diameter of the ophthalmic artery remained unaltered at the site of measurement, a raised PSV could then be the result of increased blood flow, perhaps in an attempt to maintain the perfusion pressure at the optic nerve head. Because it is not possible to measure blood vessel diameter with CDI accurately, volume blood flow cannot be calculated with this technique. It has been suggested that the measurement of mean flow velocity (which we have not calculated) could be used as indirect evidence of volume blood flow.

We found a higher SBP and SPP in the POAG group compared to both the normal and NPG groups (not reaching significant levels between POAG and NPG) (Table 1). The patients with POAG were recruited prospectively and consecutively once they fulfilled the inclusion and exclusion criteria. Because the differences in SPP and SBP were significant between patients with POAG and the normal subjects, it was not possible to control for them. Several studies have ob-
served a significant correlation between IOP and SBP in POAG, and between IOP and both SBP and heart rate in population studies. Despite having higher blood pressures, only three of the 23 patients with POAG had high enough blood pressures to warrant medical treatment by their primary care physician. Why blood pressure, particularly the systolic component, is significantly greater in our patients with POAG than those with NPG or normal subjects is not known. It possibly could be an attempt to maintain the optic nerve perfusion pressure in the presence of a chronically elevated IOP.

The abnormalities in blood flow velocity found in this study may well be primary (i.e., causative) in terms of the pathogenesis of glaucoma damage or might occur secondary to the loss of retinal neural tissue. It is unlikely, however, that the increased ophthalmic artery PSV in POAG is because of loss of neural elements. We did not measure the velocity indices of the short posterior ciliary arteries. Our radiologist found that localization of these vessels considerably was more variable than were the ophthalmic and central retinal arteries. In addition, the reproducibility of CDI measurements of the posterior ciliary vessels is not as good as that of the two vessels we measured.

To summarize, a disturbance in the ocular circulation (with different patterns of presentation and possibly with different causes) occurs in NPG and POAG. The increased RI seen in the central retinal artery perhaps is caused by longstanding vascular compromise in NPG and raised IOP in POAG. In the ophthalmic artery, the increase in flow velocity may be related to the raised IOP (Table 3), because the elevated PSV is present in patients with POAG only. A study is under way in our department to look at the effect of glaucoma treatment on blood flow velocities in these patients with POAG and those with NPG. This may help to elucidate further the role of IOP and vascular risk factors in the causation of high and normal pressure open-angle glaucoma.

Key Words

blood flow velocity, central retinal artery, color Doppler imaging, glaucoma, ophthalmic artery

References


