Ocular Hemodynamics and Glaucoma Prognosis

A Color Doppler Imaging Study

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Objective: To evaluate the effect of optic nerve circulation, using color Doppler imaging (CDI), on the progression of visual field damage in primary open-angle glaucoma.

Methods: The relationship between the results of retrobulbar CDI, performed shortly after the diagnosis of primary open-angle glaucoma, and the progression of visual field loss for 7 years was evaluated in 44 glaucoma patients. Color Doppler imaging variables in patients with a stable and deteriorating clinical course were compared, and the pattern of increasing risk for different CDI values was analyzed using an additive logistic model. Based on this nonparametric analysis, we arrived at a discriminant CDI value identifying glaucoma patients with a poor prognosis. On the basis of the discriminant value, patients were divided into 2 groups, and the odds ratio of visual field loss for each group was then estimated.

Results: Patients with a stable visual field had a higher diastolic velocity and a lower resistivity index in the ophthalmic artery ($P < .001$ for both) compared with those with a deteriorating visual field during the study. The odds of visual field deterioration in patients with an ophthalmic artery resistivity index of 0.78 or higher was about 6 times that of patients with an ophthalmic artery resistivity index lower than 0.78.

Conclusion: Color Doppler imaging variables of the ophthalmic artery correlate with the risk of visual field deterioration in patients with primary open-angle glaucoma.

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IN GLAUCOMA patients, several risk factors associated with progression of visual field loss have been suggested. The most frequently reported are initial intraocular pressure (IOP) level,1,6 initial visual field defect,1,3,9 sex,1,7 race,6 a high peripapillary atrophy–disc ratio,4,9,12 a high cup-disc ratio,4,7 disc hemorrhages,5,12 myopia,13 and some vascular factors, such as low blood pressure,5,7,14 nocturnal hypotension,15 blood rheology abnormalities,16 and diabetes mellitus. Growing evidence from clinical studies17-19 that circulatory abnormalities can be involved in the pathogenesis of glaucomatous optic nerve disease indicates that vascular factors likely play a role.

New technologies for ocular blood flow evaluation have been introduced to clinical ophthalmology, and color Doppler imaging (CDI) has been particularly useful because of its low invasiveness and the reliability of its results. Color Doppler imaging has been widely used in glaucoma to study pathogenic aspects of the disease and the vascular effects of its treatment. In primary open-angle glaucoma (POAG), several abnormalities of blood flow in the ophthalmic artery (OA), short posterior ciliary arteries (SPCAs), and central retinal artery (CRA) were reported.20-26 In patients who underwent surgery to lower IOP, a significant increase in the end-diastolic velocity and a decrease in the resistance index were observed in the SPCAs and the CRA;27,28 however, the effect of some antiglaucomatous drugs is controversial and may have affected these results. In another study,29 an increased vascular resistance in the OA was reported in normal-pressure glaucoma patients compared with a control group. Differences were also observed in a study30 of subgroups of normal-pressure glaucoma patients: those with senile sclerotic normal-pressure glaucoma had a lower diastolic velocity of the SPCAs compared with control groups and myopic normal-pressure glaucoma subjects.

In the present study, we used CDI to evaluate the effect of ocular blood flow abnormalities on the progression of visual field damage in POAG, considering the possible prognostic value of this tech-
nique in patients with glaucoma. We reviewed the hemodynamic variables obtained in a group of POAG patients during 7 years after the ocular blood flow measurement.

**METHODS**

We studied 44 patients with a clinical diagnosis of POAG who had been examined using CDI shortly after the diagnosis, before beginning antiglaucomatous therapy with topical β-blockers. The group consisted of 24 women and 20 men (mean age, 66 years [range, 53-75 years]). They had mean IOPs higher than 23 mm Hg on diurnal testing and had glaucomatous optic disc abnormalities or visual field losses.

The vertical cup-disc ratio (mean±SD, 0.67±0.06) was assessed using images of the posterior pole of the eyeball. Visual field sensitivity was evaluated with a Humphrey 30-2 full-threshold program (Humphrey Instruments, Dublin, Calif). At baseline, all study patients had a stage 2 or stage 3 glaucomatous defect, according to the classification of Aulhorn, modified by Greve et al. Except for POAG and lens opacities of various degrees, they had no other significant eye disease. Axial length, assessed with a Sonomed Ecobiometer (Sonomed Technology Inc, Lake Success, NY), was between 24.0 and 25.5 mm. When both eyes of the same subject met the inclusion criteria for the study, the eye to be considered was determined at random.

None of the patients included in the study had a clinical history of systemic disease that could interfere with our research; they were free of cancer, diabetes mellitus, and hormonal and metabolic disorders. They had no infectious, cardiovascular, respiratory, hematopoietic, or kidney diseases; demonstrated no carotid artery occlusive abnormalities that reduced the blood flow by more than 30%; and had not taken systemic medications for at least 6 months. Patients with diabetes mellitus or systemic arterial hypertension were excluded from the study. Postmenopausal women were not taking hormone therapy.

Before participation in the study, subjects gave full informed consent to the procedures, which were reviewed and approved by the Florence University institutional review board. All experimental procedures conformed to the tenets of the Declaration of Helsinki. Baseline hemodynamic measurements were performed in all subjects before treatment with any antiglaucomatous drug.

After a standard ophthalmological examination, we checked the IOP by means of Goldmann applanation tonometry and measured the arterial blood pressure using the sphygmomanometer; the heart rate was monitored by electrocardiogram. Among all subjects, the systolic blood pressure was between 120 and 150 mm Hg and the diastolic blood pressure was between 65 and 85 mm Hg; the heart rate was between 60 and 80 beats/min.

In the same session, the eyes were examined by CDI to measure OA, SPCAs, and CRA blood flow. The OA was imaged as it coursed just lateral to the hyporeflective stripe representing the optic nerve, before it changed its course to cross the nerve, and the CRA was imaged in the shadow of the optic nerve, a few millimeters posterior to its entering the globe. Finally, the SPCAs were imaged as colored pixels adjacent to the optic nerve, just behind the posterior pole of the eyeball. Nonrecordable measures (zero velocity values) were excluded from the statistical analysis. We measured the systolic and diastolic velocity in each vessel and calculated the Pourcelot resistivity index.

All CDI examinations were performed with the same QUAD 1 unit (Quantum Medical Systems Inc, Issaquah, Wash), supplied with a 7.5-MHz linear-phased array transducer. All CDI investigations were performed between 1990 and 1993. Immediately after CDI, all patients began treatment with topical β-blockers, but in later years some of them used other drugs (miotics or adrenergic agonists) or underwent argon laser treatment. Fifteen patients were operated on for severe visual field deterioration or uncontrolled IOP. The patients were regularly examined for 7 years, with results reviewed relative to the clinical history of each patient.

Progression of visual field loss was defined as an irreversible increase recorded in at least 3 consecutive perimetric examinations, according to the classification of Aulhorn, modified by Greve et al. For each visual field, 2 of us (F.G. and A.S.), masked to the patient’s name or the other examiner’s findings, determined the stage of the perimetric defect. In case of disagreement between the 2 examiners, the visual field was reconsidered by both, and the final staging was determined through consensus. The examiners were also masked to the patient’s clinical history and CDI results. Visual field deterioration was the only criterion used to classify the patients into the 2 groups. The various treatments received during the follow-up (medications, laser, and surgery) were not considered in the data analysis.

The Kruskal-Wallis test was used to compare distributions of velocities and resistivity indexes in patients with a stable and deteriorating visual field. We chose a nonparametric test because of the small sample size and because the data plot suggested that blood flow velocities were not normally distributed, as reported by other investigators. We then analyzed the data relevant to the OA diastolic velocity and the OA resistivity index. We focused on the OA because it is the main source of the optic nerve blood supply and provides more reproducible hemodynamic data than the SPCAs.

The relationship between a patient’s status (stable vs unstable) and the diastolic velocity or the resistivity index for the OA was studied by means of a regression model. To inspect the pattern of worsening risk for different diastolic velocity or resistivity index values, an additive logistic model was used: \( \logit(\text{worsening probability}) = \frac{\text{diastolic velocity or resistivity index}}{s} \), where \( \text{logit}(p) = \log\left(\frac{p}{1-p}\right) \) and \( s \) is a smoothing spline function of the diastolic velocity or resistivity index with 3 df.

Generally, the smoothing spline is a tool for summarizing the trend of a response measurement as a function of a predictor variable. It produces a nonparametric estimate of the relationship between the variables and a curve that describes the estimated relationship. The df govern the amount of smoothing, ie, the flexibility of the estimated curve. In this study, the smoothing spline was used to investigate the trend of worsening probability relative to the diastolic velocity or resistivity index values.

Three df correspond to a modest flexibility, albeit the data set was small. The curve obtained from the additive logistic model was used to determine a discriminant value that might be used in the clinical identification of glaucoma patients with a poor prognosis.

We defined a cutoff value for the OA resistivity index, over which the risk of visual field deterioration was considered relevant. We then divided our patients into 2 groups, with resistivity index values above or below the cutoff value, and calculated the odds ratio. The statistical analysis was performed using Splus 4.5 (MathSoft Inc, Cambridge, Mass) software.

**RESULTS**

We identified 26 stable patients and 18 patients whose visual field significantly deteriorated during the 7-year study. Fifteen patients required surgery during the follow-up, but their results were similar to those of the patients with progressive visual field loss. In fact, 13 of the patients were operated on because of deterioration of the visual field defect, with 2 patients operated on for uncontrolled IOP.
Summary statistics of blood flow velocities and the resistivity index for the OA, CRA, and SPCAs are reported in Table 1. Box and whisker plots in Figure 1 represent the distribution of these variables in the OA according to patient status. The distribution of the OA systolic blood flow velocity was similar in patients with a stable and deteriorating clinical course (Figure 1A). In contrast, the median OA diastolic velocity for stable patients was higher than the value for worsening patients (Figure 1B). The Kruskal-Wallis statistic was 11.49 ($P < .001$), indicating a statistically significant difference between the 2 groups. Consequently, the distribution of the resistivity index values resulted in a differentiation between groups of patients with a stable and deteriorating clinical course (Figure 1C), with a significantly lower index in stable subjects (Kruskal-Wallis statistic, 12.23; $P < .001$). No significant differences between patients with stable and deteriorating visual fields were found for the SPCAs (Figure 2) and CRA (Figure 3). However, this result could be a consequence of the small sample size; numerous values were missing for these vessels.

The relationship between patient status and the OA resistivity index and diastolic velocity was studied by regression analysis. Figure 4 shows the nonparametric estimate of the relationship between the odds of worsening vs not worsening and the values of the Pourcelot resistivity index obtained from the logistic additive model. Even interpreted cautiously (because of the small sample size), it shows an increasing risk that reaches the maximum slope for index values around the median (0.78), indicating that this is a discriminant value at which to differentiate glaucoma patients with poor prognoses. The smoothing spline function describing the relationship between deteriorating probability and the OA diastolic blood flow velocity shows a decreasing pattern, as expected (Figure 5).

Finally, we divided our patients into 2 groups, those with an OA resistivity index of 0.78 or higher and a resistivity index lower than 0.78 (Table 2), and we estimated that the odds ratio (95% confidence interval) of patient worsening was 6.61 (1.67-26.1) ($P = .007$). Therefore, the odds of the visual field deteriorating vs not deteriorating in patients with an OA resistivity index of 0.78 or higher is about 6 times that in patients with an OA resistivity index lower than 0.78.

### Table 1. Summary Statistics of Blood Flow Velocities and Pourcelot Resistivity Index (RI) for the Ophthalmic Artery, Short Posterior Ciliary Arteries (SPCAs), and Central Retinal Artery

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Ophthalmic Artery</th>
<th>SPCAs</th>
<th>Central Retinal Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>RI</td>
</tr>
<tr>
<td>Minimum</td>
<td>23.00</td>
<td>3.00</td>
<td>0.56</td>
</tr>
<tr>
<td>First quartile</td>
<td>32.87</td>
<td>6.40</td>
<td>0.73</td>
</tr>
<tr>
<td>Median</td>
<td>36.00</td>
<td>8.00</td>
<td>0.78</td>
</tr>
<tr>
<td>Third quartile</td>
<td>37.85</td>
<td>10.00</td>
<td>0.82</td>
</tr>
<tr>
<td>Maximum</td>
<td>46.20</td>
<td>17.10</td>
<td>0.90</td>
</tr>
<tr>
<td>Mean</td>
<td>35.67</td>
<td>8.27</td>
<td>0.76</td>
</tr>
<tr>
<td>SE</td>
<td>5.13</td>
<td>3.00</td>
<td>0.08</td>
</tr>
<tr>
<td>NA, No.</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: NA, missing values out of 44 eyes.

Figure 1. Box and whisker plots for the ophthalmic artery variables: systolic (A) and diastolic (B) blood flow velocities and Pourcelot resistivity index (C), according to patient status.

Based on CDI values in a group of glaucoma patients at the beginning of a 7-year study, those who eventually had more progressive visual field loss had OA diastolic velocities that were significantly lower and OA resistivity indexes that were significantly higher, compared with stable patients. Furthermore, the odds of visual field de-

### Comment

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terioration was greater in patients with an OA resistivity index of 0.78 or higher.

We focused on the OA resistivity index for several reasons: it is independent of the angle of measurement, it includes systolic and diastolic velocity values, and, in our series, it was the hemodynamic variable associated with a more significant difference between patients with deteriorating and stable visual fields. The OA resistivity index is a highly reproducible measure (coefficient of reliability, 6%), especially compared with the resistivity index of the SPCAs (coefficient of reliability, 32%);

Alon Harris, PhD, unpublished data, 1995). The higher variability of hemodynamic variables among SPCAs is caused by the small size of these vessels and by their irregular and tortuous course before entering the eyeball.

Our data are in agreement with those of Drance and Rojanapongpun, who found lower OA blood flow velocities on transcranial Doppler ultrasonography in glaucoma patients with progressive visual field loss, compared with those with a stable clinical course. These results suggest a prognostic value of CDI of the orbital vessels in patients with glaucoma, particularly the OA blood flow variables.

Figure 2. Box and whisker plots for the short posterior ciliary arteries variables: systolic (A) and diastolic (B) blood flow velocities and Pourcelot resistivity index (C), according to patient status.

Figure 3. Box and whisker plots for the central retinal artery variables: systolic (A) and diastolic (B) blood flow velocities and Pourcelot resistivity index (C), according to patient status.

Figure 4. Additive logistic model for the relationship between the ophthalmic artery Pourcelot resistivity index and the probability of a patient with a deteriorating clinical course.

Figure 5. Additive logistic model for the relationship between the ophthalmic artery diastolic blood flow velocity and the probability of a patient with a deteriorating clinical course.
Numerous factors other than ocular hemodynamics may have affected the clinical course of the patients. Various therapeutic interventions (medications, laser, and surgical procedures) that had differed among patients during the follow-up, and some individual factors (genetics, life habits, and treatment compliance), might have modulated patients’ response to therapy and might affect the repeatability of our results. Despite these limitations, a homogeneous group of patients was selected at the outset by CDI, a technique proven to be useful in ocular blood flow assessment and in depicting the clinical picture of patients with glaucoma.

Our findings are consistent with the large body of evidence supporting the effect of vascular factors in the pathogenesis of glaucomatous optic neuropathy and the key position of the OA in the orbital vascular anatomy and in the optic nerve blood supply. This vessel has been effectively imaged using CDI since the outset of our work with this technique. Further studies confirmed that measurements of the hemodynamic variables of this vessel are reproducible and reliable. Moreover, the OA is the main source of blood supply to the optic nerve, and possible abnormalities of its blood flow may represent a significant vascular risk factor for the development of glaucomatous optic neuropathy.

The prognostic aid of CDI in patients with glaucoma supports the use of this technique to select the most appropriate monitoring and therapeutic strategies. The results obtained in our series should be validated in an independent population.

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Table 2. Status and Ophthalmic Artery Resistivity Index (RI) Values

<table>
<thead>
<tr>
<th>Status</th>
<th>RI &lt; 0.70</th>
<th>RI &gt; 0.70</th>
<th>Total No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable</td>
<td>17</td>
<td>9</td>
<td>26</td>
</tr>
<tr>
<td>Unstable</td>
<td>4</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>23</td>
<td>44</td>
</tr>
</tbody>
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REFERENCES