Relationship Between Ocular Perfusion Pressure and Retrobulbar Blood Flow in Patients With Glaucoma With Progressive Damage

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• PURPOSE: To evaluate the relationship between ocular perfusion pressure and color Doppler measurements in patients with glaucoma.

• MATERIALS AND METHODS: Twenty patients with primary open-angle glaucoma with visual field deterioration in spite of an intraocular pressure lowered below 21 mm Hg, 20 age-matched patients with glaucoma with stable visual fields, and 20 age-matched healthy controls were recruited. After a 20-minute rest in a supine position, intraocular pressure and color Doppler measurements parameters of the ophthalmic artery and the central retinal artery were obtained. Correlations between mean ocular perfusion pressure and color Doppler measurements parameters were determined.

• RESULTS: Patients with glaucoma showed a higher intraocular pressure ($P < .0008$) and a lower mean ocular perfusion pressure ($P < .0045$) compared with healthy subjects. Patients with deteriorating glaucoma showed a lower mean blood pressure ($P = .033$) and a lower end diastolic velocity in the central retinal artery ($P = .0093$) compared with normals. Mean ocular perfusion pressure correlated positively with end diastolic velocity in the ophthalmic artery ($R = 0.66$, $P = .002$) and central retinal artery ($R = 0.74$, $P < .0001$) and negatively with resistivity index in the ophthalmic artery ($R = -0.70$, $P = .001$) and central retinal artery ($R = -0.62$, $P = .003$) in patients with deteriorating glaucoma. Such correlations did not occur in patients with glaucoma with stable visual fields or in normal subjects. The correlations were statistically significantly different between the study groups (parallelism of regression lines in an analysis of covariance model) for end diastolic velocity ($P = .001$) and resistivity index ($P = .0001$) in the ophthalmic artery, as well as for end diastolic velocity ($P = .0009$) and resistivity index ($P = .001$) in the central retinal artery.

• CONCLUSIONS: The present findings suggest that alterations in ocular blood flow regulation may contribute to the progression in glaucomatous damage. (Am J Ophthalmol 2000;130:597–605. © 2000 by Elsevier Science Inc. All rights reserved.)

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GLAUCOMA IS A PROGRESSIVE OPTIC NEUROPATHY involving characteristic structural changes of the optic nerve and characteristic visual field defects.[1] Increased intraocular pressure is the risk factor most often associated with glaucomatous optic neuropathy. However, the existence of patients with normal intraocular pressure developing glaucomatous disk and visual field changes as well as the substantial number of cases with open-angle glaucoma continuing to progress in damage despite therapeutically lowered intraocular pressure has urged the search for risk factors other than increased intraocular pressure.[2] A lack of autoregulation or vascular dysregulation, featuring, among other characteristics, a vasospastic responsiveness to such stimuli as coldness or psychological stress, a propensity that has been shown to be more frequent in patients with glaucoma without increased intraocular pressure,[3] have been advocated as possible contributing factors in the cause of glaucoma.[4–6] The exact nature of vascular dysregulation remains, however, elusive. In a recent study, color Doppler measurements were obtained in the central retinal artery of otherwise healthy vasospastic subjects and in age-matched and sex-matched controls.[7] This study disclosed a higher resistivity index in the central retinal artery of vasospastic individuals with lower ocular perfusion pressure, suggesting a paradoxically constricted peripheral vascular bed when perfusion

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pressure is low. Such a constellation would, potentially, increase the susceptibility of the eye to higher intraocular pressure or lower blood pressure. Hypothetically, because vasospasm has been suggested to be a risk factor in glaucoma, a similar vascular dysregulation may be involved in glaucoma. The purpose of the present study was to evaluate the relationship between ocular perfusion pressure and blood flow velocities in retrobulbar vessels of patients with glaucoma progressing in damage despite an intraocular pressure lowered below 21 mm Hg.

SUBJECTS AND METHODS

WE STUDIED 20 PATIENTS (10 WOMEN AND 10 MEN) WITH progressive primary open-angle glaucoma (mean ± SD age: 65.9 ± 5.1 years). All procedures conformed to the Declaration of Helsinki. Patients with closed iridocorneal angles, evidence of secondary glaucoma, pseudoexfoliation, pigmentary dispersion, a history of intraocular surgery, any form of retinal or neuroophthalmologic disease that could result in visual field defects, or with a history of chronic systemic medication or disease, especially diabetes mellitus, systemic hypertension, or occlusive vascular disorders, were not included in this study. All patients had typical glaucomatous disk and visual field damage and had been addressed by their ophthalmologist because of suspected progression in damage. After approval by the ethical committee, informed consent for the use of their clinical data in a scientific publication was obtained from each patient. The patients with glaucoma underwent a diurnal intraocular pressure curve (6:00 AM, before arising from bed, 8:00 AM, 11:00 AM, 4:00 PM, and 10:00 PM) during 2 days, showing no readings above 21 mm Hg among the selected patients. Retrospective information regarding visual field results was obtained from the clinical charts. Visual field examinations were performed with the program G1[8] on the Octopus Visual Field Analyzer (Interzeag, Schlieren, Switzerland). The criteria for glaucomatous visual field defects were a cluster of three points (except rim points) in at least one hemifield reduced by 5 dB or greater, and including at least one point reduced by 10 dB or greater; a cluster of two points reduced by 10 dB or greater; or three adjacent points on the nasal horizontal meridian that differed by 5 dB or greater from their mirror points on the opposite side of the meridian.

The progression in visual field damage was evaluated retrospectively. All patients had periodic visual field studies during follow-up for at least 2 years (mean ± SD: 5.3 ± 2.2 years). After the first fields were excluded to avoid learning effect, five to 11 examinations per eye (mean ± SD: 7.6 ± 1.8 examinations) were included into the present analysis. Patients with poor visual field reliability (false-positive or false-negative errors exceeding 33%) were not enrolled. Enrolled patients had 3 mm or larger pupil diameters when their fields were plotted. Eyes had to have a visual acuity of 20/30 or better at the beginning and the end of the observation period, with no change throughout the observation period, and no clinical evidence of opacity of the media at the time the patient was included into the study, respectively, no cataract surgery had been performed during the observation period. Minimally, each patient underwent five reliable visual field examinations during the follow-up period, including the examination obtained before color Doppler imaging, which was always obtained at the end of the observation period. The last visual field examination was always obtained the day before color Doppler imaging measurement, and this visual field examination also had to satisfy the criteria outlined above. The definition of visual field progression consisted of a deepening of an existing scotoma, the expansion of an existing scotoma, or a fresh scotoma in a previously normal part of the visual field, at least in the penultimate and the last fields of the selected series per eye. A deepening or an expansion of an existing scotoma was diagnosed if two adjacent points had decreased 10 dB from their original values, and a new scotoma was diagnosed if an alteration meeting the criteria for a visual field defect occurred in a previously normal part of the field.

As a first control group, we selected 20 age-matched patients with glaucoma (six women and 14 men; mean ± SD age: 65.3 ± 9.1 years) satisfying all the criteria outlined above, except for progression in visual field damage. In addition, we recruited 20 age-matched healthy controls (13 women and seven men; mean ± SD age: 70.6 ± 10.1). Healthy control subjects were enrolled from volunteers, collaborators, and relatives and friends of the patients who responded to a notice posted at the Eye Clinic informing of the opportunity to participate in a scientific research project. After informed consent was obtained, each healthy subject was screened for ocular and systemic diseases. A detailed medical and ophthalmic history was recorded, and all of the subjects completed an ophthalmologic examination. Subjects were not included if they had a history of ocular or systemic disease, a family history of glaucoma, a history of eye surgery, a history of frequent cold hands (vasospastic propensity), any chronic systemic or topical medication, a best-corrected visual acuity worse than 20/25, an intraocular pressure higher than 20 mm Hg, or any other pathological finding upon ophthalmologic examination, including slit-lamp biomicroscopy and fundoscopy. Both eyes had to satisfy these criteria.

In patients with glaucoma, no attempt was made to wash out the patients from their topical glaucoma medication before the color Doppler imaging examination. However, patients using topical antiglaucoma medication had to use the same treatment in both eyes throughout the entire follow-up period.

All the subjects and patients with glaucoma underwent blood flow velocity assessment of their ophthalmic and central retinal arteries by means of color Doppler imaging.

All retrobulbar color Doppler imaging examinations were performed by the same experienced sonographer, who was unaware of the subjects' clinical status. Blood-flow velocity was measured by means of a color Doppler imaging device (Siemens Albis AG, Zürich, Switzerland) using a 7.5-MHZ linear phase-array transducer. The transducer was applied gently to the closed eyelid using a coupling gel, and care was taken to avoid applying any pressure to the eye. During the examination, patients were in the supine position, with the upper body tilted upward at about a 30-degree angle. The ophthalmic artery and the central retinal artery were examined following a standard protocol, as described previously.[9,10] The proximal and distal portions of the vessels were imaged as well as possible to determine the Doppler flow angle. The ophthalmic artery was traced nasal to the optic nerve after their crossing, and measurements were performed approximately 10 to 15 mm posterior to the globe. The central retinal artery was depicted within the anterior part of the optic nerve shadow, about 2 to 3 mm behind the surface of the optic disk.

The peak-systolic velocity, defined as the highest velocity of blood flow during the systolic phase of the cardiac cycle, the end-diastolic velocity, defined as the velocity of blood flow at the end of the diastolic phase of the cardiac cycle, and the resistivity index (resistivity index = [peak-systolic velocity − end diastolic velocity]/peak-systolic velocity) were computed in every subject and every patient with glaucoma for the ophthalmic artery and the central retinal artery.

Before color Doppler imaging or intraocular pressure measurements, patients and controls rested for 20 minutes in a supine position. The intraocular pressure was measured by means of a Perkins applanation tonometer after applying one drop of 0.4% benoxinate hydrochloride and staining the tear film with a strip of fluorescein sodium. Color Doppler imaging parameters were obtained subsequently. Throughout the entire experimental procedure, systemic blood pressure and heart rate were recorded at 3-minute intervals by means of an automatic device (Profilomat; Roche, Basel, Switzerland). This device measures blood pressure automatically, on the same principal as the conventional mercury sphygmomanometer, with a cuff and a microphone.

The blood pressure readings for systolic blood pressure and diastolic blood pressure obtained just before color Doppler imaging were used to calculate the mean arterial blood pressure according to the formula: mean arterial blood pressure = 2/3*diastolic blood pressure + 1/3*systolic blood pressure. The mean ocular perfusion pressure was calculated as: mean ocular perfusion pressure = 2/3*mean arterial blood pressure − intraocular pressure.

One eye per subject or patient was selected for statistical analysis. In patients with glaucoma without progression the eye with the more advanced visual field damage was studied, and in the group with the progressive damage the eye with progression or more marked progression was selected. In patients with glaucoma with symmetric disease and in healthy subjects, the study eye was chosen randomly.

Sample size calculation was based on a previous study.[7] For a power of 90% and a 5% probability of an α error, the sample size necessary to obtain similar correlations as in the cited study, 20 individuals needed to be included into each group. Differences in systemic and ocular hemodynamic parameters (systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, mean ocular perfusion pressure, peak-systolic velocity, end diastolic velocity, and resistivity index in ophthalmic artery and central retinal artery), as well as in intraocular pressure were assessed by means of analysis of variance (ANOVA). The difference in number of patients taking topical medication was assessed by means of a two-tailed Fisher exact test.

The correlation between mean ocular perfusion pressure and blood flow velocities in the ophthalmic artery and the central retinal artery were calculated by means of Pearson's linear correlation factor. In order to evaluate differences in these regressions among the three study groups, the interaction by the covariate mean ocular perfusion pressure (parallelism of the regression lines) was computed in a covariance analysis model.[11] *P* values less than .05 were considered statistically significant.

RESULTS

SYSTEMIC BLOOD PRESSURE (SYSTOLIC BLOOD PRESSURE, diastolic blood pressure, mean arterial blood pressure), mean ocular perfusion pressure, intraocular pressure, and hemodynamic parameters measured in the ophthalmic artery and in central retinal artery are listed in Table 1. The ANOVA showed statistically significant differences between the three groups for systolic blood pressure, mean arterial blood pressure, intraocular pressure, mean ocular perfusion pressure, and for end diastolic velocity in the central retinal artery. Post-hoc comparisons (Table 2) revealed that the progressive glaucoma group was different from the nonprogressive glaucoma group only with regard to systolic blood pressure ($P = .032$), but the progressive glaucoma group was different from normal subjects with regard to systolic blood pressure, mean arterial blood pressure, intraocular pressure, mean ocular perfusion pressure, and end diastolic velocity measured in the central retinal artery, with lower values in the progressive glaucoma group, except for intraocular pressure. The nonprogressive glaucoma group was different from normal subjects only with regard to intraocular pressure and mean ocular perfusion pressure.

In the progressive glaucoma group, the mean ocular perfusion pressure correlated, statistically significantly, positively with end diastolic velocity and negatively with resistivity index in the ophthalmic artery as well as in the central retinal artery (Table 3). Such correlations did not

TABLE 1. Hemodynamic Parameters in Study Groups

	Prog. Glauc. (20 patients)	Nonprog. Glauc. (20 patients)	Normal Subjects (20 subjects)	*P* Values
SBP (mm Hg)	123.5 ± 16.2	136.3 ± 15.6	142.7 ± 13.0	.0006
DBP (mm Hg)	75.6 ± 10.9	73.9 ± 8.5	78.8 ± 6.4	.22
MBP (mm Hg)	91.5 ± 11.7	94.7 ± 10.4	100.1 ± 7.7	.032
IOP (mm Hg)	17.0 ± 2.8	17.9 ± 2.6	14.0 ± 1.4	<.0001
MOPP (mm Hg)	44.1 ± 8.4	45.2 ± 7.0	52.8 ± 4.9	.0003
OA-PSV (cm/s)	34.7 ± 6.6	35.8 ± 6.5	37.0 ± 4.5	.48
OA-EDV (cm/s)	7.3 ± 2.2	7.2 ± 2.9	7.9 ± 2.7	.70
OA-RI	0.78 ± 0.07	0.79 ± 0.06	0.78 ± 0.05	.71
CRA-PSV (cm/s)	9.4 ± 1.9	10.0 ± 3.3	11.0 ± 2.0	.11
CRA-EDV (cm/s)	2.1 ± 0.6	2.3 ± 1.1	2.9 ± 0.7	.0064
CRA-RI	0.8 ± 0.05	0.8 ± 0.08	0.7 ± 0.03	.13

CRA = central retinal artery; DBP = diastolic blood pressure; EDV = end diastolic velocity; IOP = intraocular pressure; MBP = mean blood pressure; MOPP = mean ocular perfusion pressure; nonprog. glauc. = nonprogressive glaucoma; OA = ophthalmic artery; Prog. glauc. = progressive glaucoma; PSV = peak systolic velocity; RI = resistivity index; SBP = systolic blood pressure.

TABLE 2. Post Hoc Comparison (Scheffé test) Between Groups (*P* Values)

	Prog. Glauc. Versus Nonprog. Glauc.	Prog. Glauc. Versus Normal Subjects	Nonprog. Glauc. Versus Normal Subjects
SBP (mm Hg)	.032	.00072	.40
MBP (mm Hg)	.61	.033	.25
IOP (mm Hg)	.45	.00079	.00001
MOPP (mm Hg)	.87	.00093	.0045
CRA-EDV (cm/s)	.74	.0093	.064

Abbreviations as in Table 1.

occur in the nonprogressive glaucoma group or in the group of normal subjects (Table 3).

The difference between the three study groups with regard to the correlation between mean ocular perfusion pressure and color Doppler imaging parameters (parallelism of the regression lines in a model of analysis of covariance) was statistically significant for end diastolic velocity (Figure 1; $P = .001$), and resistivity index (Figure 2; $P = .0001$) measured in the ophthalmic artery, as well as for end diastolic velocity (Figure 3; $P = .0009$) and for resistivity index (Figure 4; $P = .001$) measured in the central retinal artery. Between the two glaucoma groups these differences were statistically significant for end diastolic velocity ($P = .001$) and resistivity index ($P = .0002$) measured in the ophthalmic artery, as well as for end diastolic velocity ($P = .0007$) and resistivity index measured in the central retinal artery ($P = .001$). The differences between patients with progressive glaucoma and normal subjects were statistically significant for end diastolic velocity ($P = .002$) and resistivity index ($P = .002$) measured in the ophthalmic artery, as well as for end diastolic velocity ($P = .007$) measured in the central retinal artery, but not for resistivity index measured in the central retinal artery ($P = .30$). The group with nonprogressive glaucoma did not differ from normal subjects in either of the measured parameters (*P* values ranging from .14 to .49).

The number and the percentage of patients receiving topical medication during the test period are outlined in Table 4. A two-tailed Fisher exact test showed a statistically significant difference only in the number of patients treated with topical β blockers ($P = .041$). The influence of topical treatment was evaluated by separating the 40 patients with glaucoma into one group taking topical β blockers (27 patients with 17 patients showing a progressive damage and 10 patients not showing such a progression) and one group not taking topical β blockers (13 patients with three patients showing a progressive damage and 10 patients not showing such a progression). Patients without topical β-blocker treatment showed no correlations between mean ocular perfusion pressure and color Doppler imaging parameters (*P* values ranging from .17 to .73), whereas those with topical β-blocker treatment showed a significant correlation between mean ocular perfusion pressure and resistivity index measured in the ophthalmic artery ($R = -0.41$; $P = .033$) and end diastolic velocity measured in the central retinal artery ($R = 0.39$; $P = .045$). However, the difference between the patients taking topical β blockers and those without such a treatment with regard to the correlation between mean ocular perfusion pressure and color Doppler imaging parameters (parallelism of the regression lines in a model of analysis of covariance) was not statistically significant for resistivity index measured in the ophthalmic artery ($P = .061$) or for end diastolic velocity measured in the central retinal artery ($P = .19$).

DISCUSSION

COLOR DOPPLER MEASUREMENTS WERE OBTAINED IN THE ophthalmic artery and the central retinal artery of 20 patients with primary open-angle glaucoma with visual field deterioration in spite of an intraocular pressure lowered below 21 mm Hg, as well as in 20 age-matched patients with glaucoma with stable visual fields, and 20 age-matched healthy controls. Mean ocular perfusion pressure was statistically significantly lower in patients with glaucoma, compared with age-matched healthy controls, but comparable between the two populations with glaucoma. In patients with glaucoma with progressive visual field damage, linear parametric regression analysis dis-

TABLE 3. Correlation of Ocular Perfusion Pressure and Ocular Hemodynamics

	Prog. Glauc.	Nonprog. Glauc.	Normal Subjects
OA-PSV	R = 0.24; *P* = .318	R = 0.09; *P* = .72	R = 0.23; *P* = .33
OA-EDV	R = 0.66; *P* = .002	R = −0.25; *P* = .28	R = −0.06; *P* = .81
OA-RI	R = −0.70; *P* = .001	R = 0.40; *P* = .08	R = 0.13; *P* = .58
CRA-PSV	R = 0.30; *P* = .195	R = 0.13; *P* = .57	R = 0.34; *P* = .14
CRA-EDV	R = 0.74; *P* < .0001	R = −0.05; *P* = .84	R = 0.28; *P* = .23
CRA-RI	R = −0.62; *P* = .003	R = 0.30; *P* = .19	R = −0.28; *P* = .23

R = Pearson's linear correlation factor; *P* = significance level of statistical analysis; other abbreviations as in Table 1.

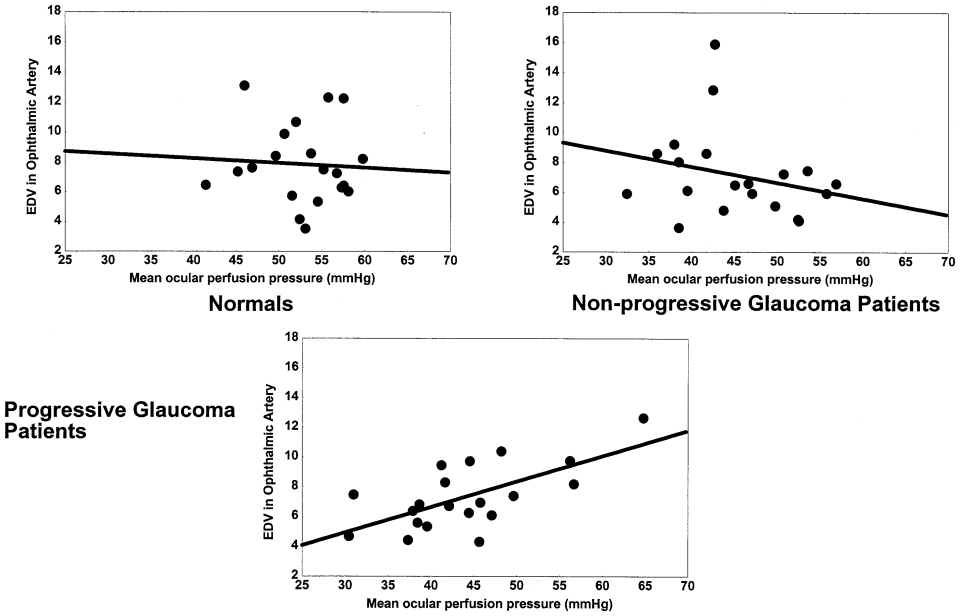

FIGURE 1. Mean ocular perfusion pressure correlated positively with end diastolic velocity in the ophthalmic artery (R = 0.66, *P* = .002) of patients with glaucoma with progressive damage in spite of an intraocular pressure lowered below 21 mm Hg, whereas such a correlation did not occur in the other two age-matched study groups. The correlations were statistically significantly different between the study groups (parallelism of regression lines in an analysis of covariance model: *P* = .001).

closed a low end diastolic blood flow velocity in the ophthalmic artery and the central retinal artery of vascular beds with low perfusion pressure. In addition, in this group of patients, a high resistivity index, a factor related to blood flow resistance in the vascular system downstream to the measurement point, was observed in the ophthalmic artery and the central retinal artery of vascular beds with low perfusion pressure. Similar correlations did not occur in the two control groups. Differences with regard to correlations between mean ocular perfusion pressure and color Doppler imaging parameters were statistically significant for end diastolic velocity and resistivity index in the ophthalmic artery as well as in the central retinal artery between patients with progressive glaucoma and patients with stable visual fields, and, except for resistivity index in the central retinal artery, between patients with progressive glaucoma and healthy controls. No differences were observed between patients with glaucoma with stable visual fields and healthy controls. These observations suggest that in the ocular circulation of patients with glaucoma with deteriorating visual fields despite an intraocular pressure lowered below 21 mm Hg, retrobulbar blood flow is low and ocular resistance to blood flow high when ocular perfusion pressure is low.

Several studies support the idea that circulatory abnormalities represent risk factors for glaucoma.[2] With the use of Doppler ultrasound of the orbit, a noninvasive examination of the retrobulbar circulation is possible. Several studies using orbital color Doppler imaging have revealed altered orbital hemodynamics in patients with glaucoma.[12–20] It remains to establish whether such alterations are present primarily and thus pathogenically active, or

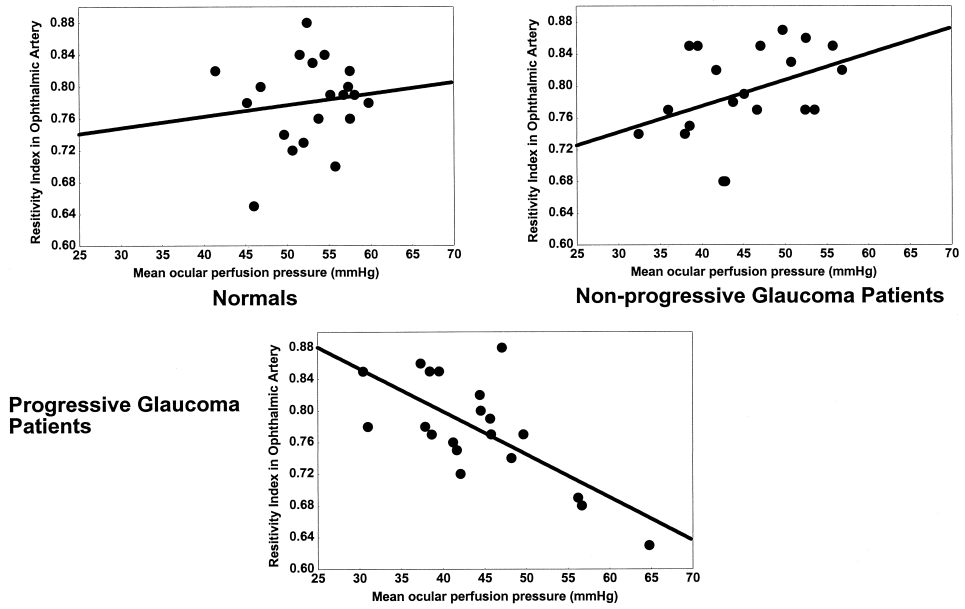

FIGURE 2. Mean ocular perfusion pressure correlated negatively with resistivity index in the ophthalmic artery (R = −0.70, *P* = .001) of patients with glaucoma with progressive damage in spite of an intraocular pressure lowered below 21 mm Hg, whereas such a correlation did not occur in the other two age-matched study groups. The correlations were statistically significantly different between the study groups (parallelism of regression lines in an analysis of covariance model: *P* = .0001).

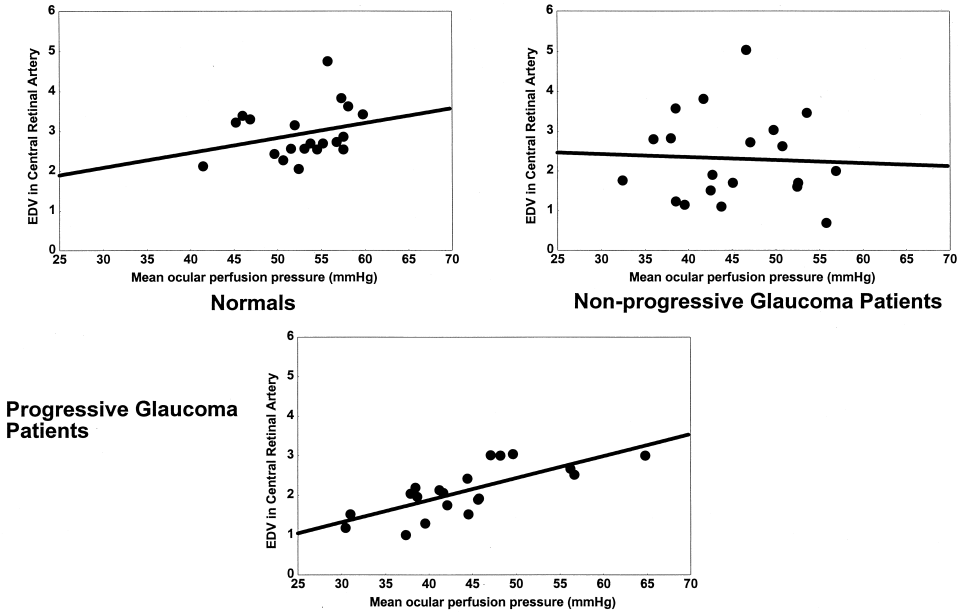

FIGURE 3. Mean ocular perfusion pressure correlated positively with end diastolic velocity in the central retinal artery (R = 0.74, *P* < .0001) of patients with glaucoma with progressive damage in spite of an intraocular pressure lowered below 21 mm Hg, whereas such a correlation did not occur in the other two age-matched study groups. The differences in correlations were statistically significant (parallelism of regression lines in an analysis of covariance model: *P* = .0009).

whether they occur secondarily. Interestingly, retrobulbar hemodynamic alterations seem not to be present in patients with stable visual fields, whereas those with progressive visual field damage, especially patients with normal-tension glaucoma, show altered retrobulbar hemodynamics.[20] Patients with asymmetric glaucomatous damage seem to have lower retrobulbar hemodynamics in the eye with the more advanced damage.[21] In patients with glaucoma with progressive damage, the eye with the more marked progression in damage has more marked alterations in orbital color Doppler imaging measurements, independently of the extent in visual field damage.[22] These

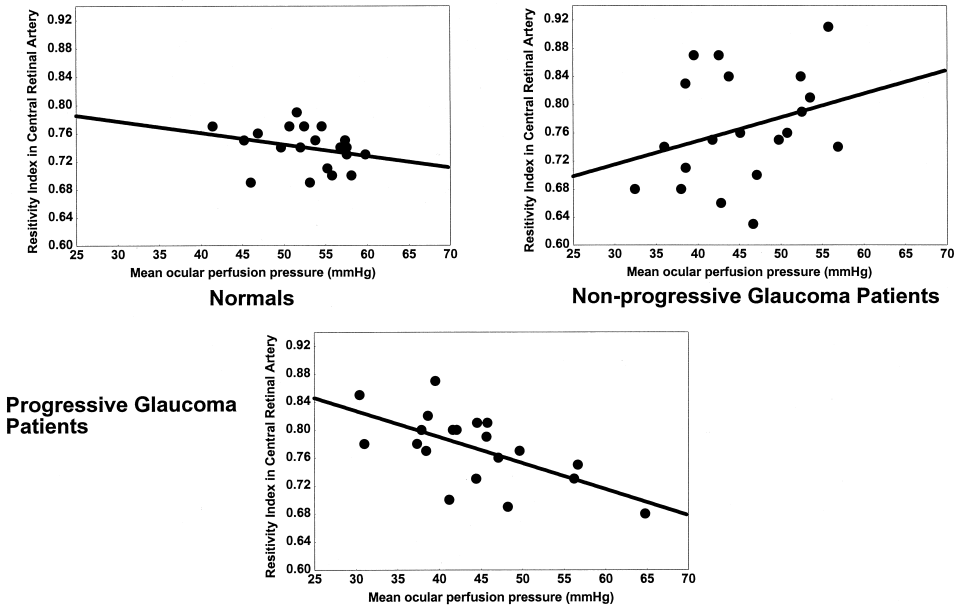

FIGURE 4. Mean ocular perfusion pressure correlated negatively with resistivity index in the central retinal artery (R = −0.62, P = .003) of patients with glaucoma with progressive damage in spite of an intraocular pressure lowered below 21 mm Hg, whereas such a correlation did not occur in the other two age-matched study groups. The correlations were statistically significantly different between the study groups (parallelism of regression lines in an analysis of covariance model: P = .001).

TABLE 4. Number of Patients Receiving Topical Medication

	Prog. Glauc.	Nonprog. Glauc.	*P* Value
Topical β blockers	17	10	.041
Topical carbonic anhydrase inhibitor	6	4	.72
Prostaglandin analogue	3	2	1.0
Pilocarpine	9	6	.51
α Agonists	3	3	1.0

Abbreviations as in Table 1.

observations, as well as the report on a lack of secondarily altered orbital color Doppler imaging measurements in nonischemic atrophy,[23] suggest that retrobulbar hemodynamic alterations might be primarily present in patients with glaucoma.

The reason for the observed correlations is not clear. If the positive correlation between end diastolic velocity and mean ocular perfusion pressure represents some kind of adapting mechanism, the regulating mechanisms in patients with deteriorating glaucoma despite an intraocular pressure lowered below 21 mm Hg must be different from those governing vascular tone in stable patients with glaucoma or healthy subjects, because no similar relationship was observed in the control groups. However, because there was also a higher resistivity index in the ocular circulation of patients with deteriorating glaucoma with lower ocular perfusion pressure, the present study rather suggests a vascular dysregulation in patients with glaucoma with progressive damage despite an intraocular pressure lowered below 21 mm Hg. Resistivity index is a factor related to blood flow resistance in the vascular system downstream to the measurement point.[24–26] In an autoregulated vascular bed such as the retinal circulation, blood flow resistance is expected to decrease with decreasing perfusion pressure. Consequently, only a positive, if any, correlation between resistivity index and mean ocular perfusion pressure was expected. The negative correlation between resistivity index and mean ocular perfusion pressure in patients with deteriorating glaucoma suggests a paradoxically constricted peripheral ocular vascular bed in these patients when there is concomitantly a low perfusion pressure. This observation is in accordance with earlier findings demonstrating a stronger propensity for peripheral vasospasm in patients with larger drops in systemic blood pressure,[27] as well as reports on an increased peripheral responsiveness to endothelin in patients with glaucoma with low systemic blood pressure.[28]

The present findings cannot be explained by differences in perfusion pressure. Perfusion pressure in both groups with glaucoma was statistically comparable. It seems rather to be some kind of vascular dysregulation that differentiates the three study groups, a vascular dysregulation, hypothetically, brought about by a reduction in perfusion pressure, especially if the result of low blood pressure. As an alternative explanation, systemic vascular dysregulation might be manifesting itself through a high resitivity index

as well as a low systemic blood pressure, both resulting from a common cause, but not being related through a cause and effect relationship. The present study does not allow a choice between these two interpretations. Indeed, only baseline conditions were compared and no experimental manipulations of perfusion pressure supposed to cause alterations in color Doppler imaging parameters were performed.

No attempt was made to wash out the patients with glaucoma from their topical glaucoma medication before the color Doppler imaging examination. The advanced nature of the visual field defect in some patients precluded such a washout, especially among those with progressive damage. Furthermore, this study addressed the question whether altered vascular regulation may be involved in the progression of visual field damage of patients with glaucoma but was not designed to differentiate whether this influence, if it existed, was the result of a genuine disorder or was secondary to antiglaucomatous treatment. In this first approach, it seemed senseless to evaluate hemodynamics after discarding drugs that may have been perturbing the same hemodynamics and the survival of the visual field. Patients with deteriorating glaucoma used significantly more often topical β blockers. Because no statistically significant differences were observed between patients with glaucoma taking β blockers and those without such a treatment, it is unlikely that β blockers alone can explain the present results. However, because only three patients among the patients with deteriorating glaucoma did not use β blockers, this issue could not be addressed properly. Consequently, the present study cannot differentiate whether the observed dysregulative features within the ocular circulation of patients with glaucoma with progressive visual field damage despite an intraocular pressure lowered below 21 mm Hg represent genuine characteristics or are secondary to antiglaucomatous treatment.

Surprisingly, only one single color Doppler imaging parameter showed a statistically significant difference between the three study groups (end diastolic velocity in central retinal artery), which is in contradiction with earlier reports. We have not been able to find a sound explanation for such a discrepancy. We observed a few normal subjects with slightly increased systolic blood pressure readings during color Doppler imaging measurement, which we interpreted as being the result of the anxiety during an unusual situation for this study group. However, because similar blood pressure readings have been noted in normal controls in earlier studies,[18] this alone can hardly explain the inconsistency with earlier results.

In Doppler ultrasonography, the interpretation of differences in blood flow velocity and resistivity index is difficult. Color Doppler imaging measures blood velocities, and not blood flow, because it is impossible to determine accurately the diameter of orbital vessels in vivo with this technique. Despite this limitation, good correlation has been demonstrated between blood velocity and blood flow, especially in cerebral vessels.[29,30] Furthermore, evidence points to a close relationship between resistivity index and vascular resistance downstream from the point of color Doppler imaging measurement.[31–33] Nevertheless, the interpretation of retrobulbar blood flow velocity measurements, especially that, in eyes with progression in glaucomatous damage in spite of an intraocular pressure lowered below 21 mm Hg, there is a paradoxically constricted peripheral ocular vascular bed when perfusion pressure is low, remains, although an attractive conjecture, speculative. Indeed, some factors might confound the present findings. The degree of optic nerve damage and visual field loss may play a role in the progression of glaucoma damage. Furthermore, the level and variation of intraocular pressure before treatment is important in determining how effectively this risk factor is controlled in patients with glaucoma. The patients included in the present study were not matched for these factors. However, the two populations of patients with glaucoma had comparable intraocular pressure, mean systemic blood pressure, and mean ocular perfusion pressure levels. Nonetheless, one population showed a progression in damage, suggesting a higher susceptibility to one of these potentially damaging factors. A further limitation of the present study was that visual field progression was assessed retrospectively. In future studies, it will especially be important to assess blood flow regulation and its impact on the incidence of glaucoma and progression in glaucomatous damage in a prospective manner.

Systemic vascular dysregulation has been suggested to occur more often in patients with glaucoma,[2] anterior ischemic optic neuropathy,[34] venous thrombosis in young individuals,[35] or central serous chorioretinopathy.[36] The findings of the present study demonstrate for the first time that alterations in blood flow regulation occur in the ocular circulation of patients with glaucoma, very similar to those observed in otherwise healthy young but vasospastic subjects.[7] Such an altered vascular regulation might, hypothetically, render the eye more susceptible to variations in intraocular pressure or systemic blood pressure.

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