Blood-flow Velocities of the Extraocular Vessels in Patients With High-tension and Normal-tension Primary Open-angle Glaucoma

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• PURPOSE: To evaluate blood-flow parameters in three different groups of patients with primary open-angle glaucoma.

• METHODS: Hemodynamic parameters in the ophthalmic artery, central retinal artery, central retinal vein, and lateral and medial short posterior ciliary arteries were evaluated by color Doppler imaging in 237 patients with primary open-angle glaucoma and 124 age-matched normal control subjects. Group A consisted of 56 patients with primary open-angle glaucoma with treated intraocular pressure higher than 20 mm Hg; group B, of 103 patients with primary open-angle glaucoma with progression of glaucomatous damage despite intraocular pressure of 21 mm Hg or less; and group C, of 78 patients with normal-tension glaucoma.

• RESULTS: All patients showed a significant decrease in end-diastolic velocities ($P < .01$) and a significant increase in resistivity index ($P < .05$) in all arteries measured. Peak-systolic velocities were normal in the ophthalmic artery in all three groups. In the central retinal artery and the short posterior ciliary arteries, however, patients in groups B and C had significantly reduced peak-systolic velocity ($P < .05$) compared with normal control subjects. Peak-systolic velocity in group A did not differ significantly from that of normal control subjects. Maximal and minimal blood-flow velocities in the central retinal vein were significantly lower in groups B and C ($P < .001$) compared with normal control subjects. In group A, only minimal blood-flow velocity was significantly reduced ($P < .05$).

• CONCLUSIONS: Hemodynamic parameters in the extraocular vessels are altered in patients with glaucoma. Reduced blood-flow velocities may be secondary as well as contributory to glaucomatous damage.

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PHENOMENOLOGICALLY, PRIMARY OPEN-ANGLE glaucoma is a syndrome of a progressive optic neuropathy characterized by optic nerve head excavation, visual-field defects, and other psychophysical alterations. Although elevated intraocular pressure is the main cause of such damage, the existence of normal-tension glaucoma and the weak correlation between progression and the level of intraocular pressure[1] indicate that other factors might also be involved in the pathogenesis of glaucomatous damage. Most theories concerning the pathogenesis can be grouped in two broad categories: those identifying mechanical mechanisms and those identifying vasogenic mechanisms. Although increased intraocular pressure is a clear risk factor, glaucomatous optic nerve damage can develop at virtually any level of intraocular pressure. Besides age and demographic and genetic factors, vascular and rheologic factors are

the main ones that have been reported in the literature.[2-13]

First reports on reduced blood-flow velocity in the ophthalmic artery in patients with glaucoma were based on transcranial Doppler ultrasound.[14-16] Recent studies performed with color Doppler imaging[17-23] also reported reduced peak-systolic velocity, reduced end-diastolic velocity, and an increased resistivity index in the ophthalmic artery.[24-27] Some researchers, however, reported no statistically significant difference between patients with glaucoma and normal control subjects with regard to the maximum and average velocities in the ophthalmic and carotid arteries.[28] Others found that those eyes with uncontrolled intraocular pressure and eyes with visual-field deterioration had a significant decrease in end-diastolic velocity, resulting in an increase in the resistivity index in the posterior ciliary arteries.[29] Several authors found no statistically significant difference in the blood-flow velocity measurements between patients with high-tension glaucoma and those with normal-tension glaucoma.[24,25,30]

In the present study, we investigated blood-flow parameters in three different groups of patients with glaucoma. Blood-flow velocities and the resistivity index in the ophthalmic artery, central retinal artery, central retinal vein, and one lateral and one medial short posterior ciliary artery were compared with those of normal control subjects.[31,32]

PATIENTS AND METHODS

A TOTAL OF 237 PATIENTS WITH GLAUCOMA AND 124 age-matched normal control subjects were included in this prospective study. All patients were inpatients of the University Eye Clinic, Basel, Switzerland. The normal control subjects were healthy volunteers, measured at a public fair (Mustermesse, Basel), which we partially reported previously.[31,32] In all groups, only one eye per subject was chosen randomly for analysis. Every patient and volunteer was informed by the examining ophthalmologist about the scientific character of the examination and could freely decide to participate or not.

Group A included patients with primary open-angle glaucoma (n = 56) with definitive glaucomatous damage who were hospitalized because the referring ophthalmologist felt that they had intraocular pressure that was too high while under medical treatment (above 20 mm Hg). Group B included patients with open-angle glaucoma (n = 103) referred because of progression of visual-field damage in spite of medically well-controlled or borderline intraocular pressure. The diurnal tension curve over 2 days for these patients did not show intraocular pressure of more than 21 mm Hg in either eye. Group C included patients with normal-tension glaucoma (n = 78). Untreated intraocular pressure over a 2-day diurnal-tension curve for these patients did not exceed 21 mm Hg.

The grouping of patients with high-tension glaucoma is arbitrary and is based on prior findings that the two groups might not have identical risk factors for developing glaucomatous damage.[6] Excluded were patients with eye diseases other than glaucoma or mild cataract, patients with previous filtering surgery, and patients with diabetes mellitus or other severe systemic and cardiovascular diseases. Neither a history of abnormal blood pressure nor a history of treatment of hypertension or hypotension was a criterion for inclusion or exclusion. The patients maintained the same local and systemic medication as before hospitalization.

Blood-flow velocity was measured by means of a Siemens Quantum 2000 (Siemens Albis AG, Zurich, Switzerland) using a 7.5-mHz linear phased-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, subjects were in the supine position, with the head tilted forward at about a 30-degree angle. The ophthalmic artery, the central retinal artery and vein, and one lateral and one medial short posterior ciliary artery were examined following a standard protocol, as described previously.[31,32] If more than one short posterior ciliary artery could be visualized, the velocity was measured in the largest one. The proximal and distal portions of the vessel were imaged as well as possible to determine the Doppler flow angle. We traced the ophthalmic artery nasally from the optic nerve after their crossing. Strong signals are routinely detectable on this side, and measurements were performed approximately 10 to 15 mm posterior to the globe in every subject. The central retinal artery and the accompanying vein can be depicted within the anterior part of the optic nerve

Table 1. Demographic Data of the Normal Control Subjects and Three Groups of Patients With Glaucoma

	Normal Control Subjects	Patients With Glaucoma		
		Group A	Group B	Group C
No.	124	56	103	78
Gender (F/M)	60/64	32/24	47/56	44/34
Smoker	17	9	8	10
Systolic BP (mm Hg ± SEM)	136 ± 1.7	134 ± 2.3	127 ± 1.5	128 ± 1.7
Diastolic BP (mm Hg ± SEM)	77 ± 0.9	73 ± 1.4	75 ± 0.9	73 ± 1.0
Pulse (beats/min ± SEM)	70 ± 0.6	72 ± 1.3	69 ± 1.2	69 ± 1.0
IOP (mm Hg ± SEM)	—	22 ± 0.9	18 ± 0.3	16 ± 0.3

BP = blood pressure; IOP = intraocular pressure; SEM = standard error of the mean.

shadow, about 2 to 3 mm behind the surface of the disk. Lateral and medial from the optic nerve shadow, the short posterior ciliary arteries can be depicted. Their locations are more variable than those of the other vessels. Because of their small size, it was not always possible to determine whether a colored pixel on the image represents a single vessel. However, characteristic Doppler spectra can be obtained from the posterior ciliary arteries with higher diastolic flow velocities because of the low resistance in the choroid, which they supply. All the color Doppler imaging measurements were performed by the same experienced ophthalmologist (H.J.K.) in patients with glaucoma and healthy volunteers. During the approximately 30-minute examination, systolic and diastolic blood pressure as well as heart rate were measured every 5 minutes.

Mean values and SEM were calculated for peak-systolic velocity (PSV), end-diastolic velocity (EDV), and resistivity index (RI) (RI = [PSV - EDV] / PSV) in the arteries, and for maximal velocity and minimal velocity in the central retinal vein. Blood-flow velocity and resistivity index of each glaucomatous group were compared with those of normal control subjects by means of an analysis of variance and among the glaucomatous groups with an unpaired *t* test. Correction of *P* values for multiple comparison was performed with a Tukey honest significant difference test for unequal sample sizes.[33] Blood pressure, heart rate, and intraocular pressure were compared by an unpaired *t* test.

Table 2. Number and Percentage of Patients Receiving Systemic Medication

	No. (%)		
	Group A	Group B	Group C
ACE-blocker	6 10.8	5 4.9	8 10.2
Ca^{++}-blocker	3 5.4	21 20.4	9 11.5
Beta-blocker	3 5.4	7 6.8	4 5.1
Dipyridamole	0 0	3 2.9	1 1.3
Fludrocortisone	1 1.8	1 1	3 3.9
Mg	2 3.6	6 5.8	8 10.2
ASA	1 1.8	12 11.7	3 3.9

ACE-blocker = angiotensin-converting enzyme blocker; Mg = magnesium sulfate; ASA = acetylsalicylic acid.

RESULTS

THE MEAN AGE ± SD OF NORMAL CONTROL SUBJECTS was 58.4 ± 15.7 years; of group A, 61 ± 17.7 years; of group B, 65.6 ± 13.6 years; and of group C, 61.1 ± 15.4 years. There were no statistically significant differences. The demographic data of the study population are listed in Table 1. Systolic blood pressure was statistically significantly lower in groups B and C ($P <$

Table 3. Blood-flow Parameters of Normal Control Subjects and Three Different Groups of Patients With Glaucoma

	(Mean ± SEM)			
	Normal Control Subjects	Group A	Group B	Group C
Ophthalmic artery				
PSV (cm/sec)	38.9 ± 0.5	38.28 ± 1.7	36.38 ± 1.1	35.87 ± 1.1
EDV (cm/sec)	9.15 ± 0.2	7.76 ± 0.5	7.83 ± 0.3	7.68 ± 0.3
RI	0.75 ± 0.006	0.79 ± 0.009	0.78 ± 0.006	0.78 ± 0.008
Central retinal artery				
PSV (cm/sec)	11.1 ± 0.1	10.63 ± 0.4	9.05 ± 0.2	9.24 ± 0.2
EDV (cm/sec)	3.23 ± 0.07	2.42 ± 0.1	2.15 ± 0.08	2.29 ± 0.1
RI	0.70 ± 0.005	0.76 ± 0.009	0.75 ± 0.006	0.75 ± 0.008
Central retinal vein				
MAX (cm/sec)	−4.58 ± 0.08	−4.37 ± 0.1	−3.87 ± 0.1	−4.29 ± 0.1
MIN (cm/sec)	−3.33 ± 0.06	−2.97 ± 0.1	−2.83 ± 0.07	−2.84 ± 0.1
Lateral posterior ciliary artery				
PSV (cm/sec)	11.12 ± 0.1	11.71 ± 0.3	10.28 ± 0.3	9.77 ± 0.2
EDV (cm/sec)	3.57 ± 0.08	3.11 ± 0.1	2.93 ± 0.1	2.91 ± 0.1
RI	0.68 ± 0.005	0.74 ± 0.01	0.71 ± 0.007	0.70 ± 0.009
Medial posterior ciliary artery				
PSV (cm/sec)	11.27 ± 0.1	11.49 ± 0.4	9.65 ± 0.2	10.46 ± 0.3
EDV (cm/sec)	3.57 ± 0.08	3.05 ± 0.1	2.74 ± 0.1	2.81 ± 0.1
RI	0.68 ± 0.005	0.74 ± 0.01	0.71 ± 0.007	0.71 ± 0.009

EDV = end-diastolic velocity; MAX = maximal velocity; MIN = minimal velocity; PSV = peak-systolic velocity; RI = resistivity index.

.01) than in the normal subjects. Diastolic blood pressure was statistically significantly reduced in groups A and C ($P < .05$) compared with the normal subjects. Pulse rate was not statistically different within the study population. As expected, intraocular pressure was statistically significantly different among groups A, B, and C ($P < .0001$).

In group A, 75% of patients were using topical beta-blockers in both eyes; 32.1% were using pilocarpine in the right eye and 35.7%, in the left eye; 16.1% were using alpha-agonists in the right eye and 14.3%, in the left eye; and 26.8% took systemic acetazolamide. In group B, 71% of patients were using topical beta-blockers in both eyes; 35% were using pilocarpine in the right eye and 38.8%, in the left eye; 9% were using topical alpha-agonists; and 9% were on systemic acetazolamide. In group C, 21.8% were using topical beta-blockers and 9%, pilocarpine in both eyes. No patient was receiving topical alpha-agonists or systemic acetazolamide. The percentage of other systemic treatment in the patients of each group is given in Table 2.

Mean values ± SEM of blood-flow parameters in normal control subjects and the three glaucomatous groups are listed in Table 3. The results of the statistical analysis are given in Table 4.

In the ophthalmic artery, the peak-systolic velocity was not significantly different among normal subjects and patients with glaucoma. The peak-systolic velocities, however, were statistically significantly lower in the central retinal artery and posterior ciliary arteries of patients in groups B and C ($P < .05$, t test) but not in group A. The difference in peak-systolic velocity in the lateral short posterior ciliary artery between normal subjects and group B, however, did not reach statistical significance in the Tukey honest significant difference test.

All three groups of patients with glaucoma had statistically significantly lower end-diastolic velocities in all arteries measured than did normal subjects ($P < .01$, t test). The difference in the ophthalmic artery, lateral short posterior ciliary artery, and medial short posterior ciliary artery, however, was not statistically significant in the Tukey honest significant difference

Table 4. Comparison of Blood-flow Parameters in Normal Control Subjects and Blood-flow Parameters in the Three Groups of Patients With Glaucoma

	Control Subjects Compared With Group A		Control Subjects Compared With Group B		Control Subjects Compared With Group C	
	P Value*	*P* Value†	*P* Value*	*P* Value†	*P* Value*	*P* Value†
Ophthalmic artery						
PSV	NS	NS	NS	NS	NS	NS
EDV	$P < .01$	NS	$P < .01$	$P < .02$	$P < .01$	$P < .03$
RI	$P < .01$	NS	$P < .01$	NS	$P < .05$	NS
Central retinal artery						
PSV	NS	NS	$P < .001$	$P < .001$	$P < .001$	$P < .001$
EDV	$P < .001$	$P < .001$	$P < .001$	$P < .001$	$P < .001$	$P < .001$
RI	$P < .001$	$P < .001$	$P < .001$	$P < .001$	$P < .001$	$P < .001$
Central retinal vein						
MAX	NS	NS	$P < .001$	$P < .001$	$P < .001$	NS
MIN	$P < .05$	NS	$P < .001$	$P < .001$	$P < .001$	$P < .002$
Lateral posterior ciliary artery						
PSV	NS	NS	$P < .01$	NS	$P < .001$	$P < .007$
EDV	$P < .01$	NS	$P < .001$	$P < .001$	$P < .001$	$P < .002$
RI	$P < .001$	$P < .001$	$P < .001$	$P < .01$	$P < .001$	$P < .01$
Medial posterior ciliary artery						
PSV	NS	NS	$P < .001$	$P < .001$	$P < .001$	$P < .01$
EDV	$P < .01$	NS	$P < .001$	$P < .001$	$P < .001$	$P < .001$
RI	$P < .001$	$P < .001$	$P < .001$	$P < .004$	$P < .001$	$P < .05$

*P values based on an unpaired *t* test.

†Corrected *P* values for multiple comparison based on the Tukey honest significant difference test.

EDV = end-diastolic velocity; MAX = maximal velocity; MIN = minimal velocity; NS = not significant; PSV = peak-systolic velocity; RI = resistivity index.

test comparing normal subjects and patients from group A.

Resistivity indices were statistically significantly higher in all groups of patients with glaucoma in all vessels measured ($P < .05$, *t* test). The difference in the ophthalmic artery, however, was not statistically significant by the Tukey honest significant difference test.

In the central retinal vein, the maximal blood-flow velocities were statistically significantly lower in groups B and C ($P < .001$, *t* test), and the minimal blood-flow velocities were statistically significantly lower in all patients with glaucoma compared with normal control subjects ($P < .05$, *t* test). For the maximal blood-flow velocities, the differences were not statistically significant in the Tukey honest significant difference test comparing normal subjects and groups A and C. For the minimal blood-flow velocities, the difference was not statistically significant in the Tukey honest significant difference test in group A.

In the ophthalmic artery, no significant difference in blood-flow parameters among the patients with glaucoma could be observed. However, patients in groups B and C had statistically significantly lower peak-systolic velocities in the central retinal artery ($P < .01$) and posterior ciliary arteries ($P < .05$) compared with group A. The end-diastolic velocities and resistivity index were not statistically different in these vessels. In the central retinal vein, patients in groups B and C had statistically significantly lower maximal blood-flow velocities than did patients in group A ($P < .05$, *t* test). Performing the Tukey honest significant difference test, the difference did not reach statistical significance. The minimal blood-flow velocities in the central retinal vein were not statistically different among patients with glaucoma. Patients in group B (progressing primary open-angle glaucoma) had blood-flow parameters similar to those of the patients in group C (normal-tension glaucoma). The *P* values are given in Table 5. The

Table 5. Comparison of Blood-flow Parameters Among the Three Groups of Patients With Glaucoma

	Group A Compared With Group B		Group A Compared With Group C		Group B Compared With Group C	
	P Value*	*P* Value†	*P* Value*	*P* Value†	*P* Value*	*P* Value†
Ophthalmic artery						
PSV	NS	NS	NS	NS	NS	NS
EDV	NS	NS	NS	NS	NS	NS
RI	NS	NS	NS	NS	NS	NS
Central retinal artery						
PSV	$P < .001$	$P < .003$	$P < .01$	$P < .02$	NS	NS
EDV	NS	NS	NS	NS	NS	NS
RI	NS	NS	NS	NS	NS	NS
Central retinal vein						
MAX	$P < .01$	NS	$P < .05$	NS	$P < .05$	NS
MIN	NS	NS	NS	NS	NS	NS
Lateral posterior ciliary artery						
PSV	$P < .05$	$P < .05$	$P < .01$	$P < .01$	NS	NS
EDV	NS	NS	NS	NS	NS	NS
RI	NS	NS	$P < .05$	NS	NS	NS
Medial posterior ciliary artery						
PSV	$P < .001$	$P < .001$	$P < .001$	$P < .05$	NS	NS
EDV	NS	NS	NS	NS	NS	NS
RI	NS	NS	NS	NS	NS	NS

*P values based on an unpaired *t* test.
†Corrected *P* values for multiple comparison based on the Tukey honest significant difference test.
EDV = end-diastolic velocity; MAX = maximal velocity; MIN = minimal velocity; NS = not significant; PSV = peak-systolic velocity; RI = resistivity index.

differences in treatment among groups was not considered in this analysis.

DISCUSSION

THIS STUDY HAS SHOWN THAT AT LEAST SOME HEMODYnamic parameters in the extraocular vessels are significantly different in patients with glaucoma compared with normal control subjects. Furthermore, patients with glaucoma seem to represent a heterogeneous population that might not be identical in terms of vascular parameters.

On the arterial side, peak-systolic velocities are more influenced in smaller vessels than in larger vessels, and end-diastolic velocities are relatively more reduced than peak systolic velocities are. This explains the increased resistivity indices in the patients with glaucoma. Group B, the patients with progression despite normalized intraocular pressure, and group C, the patients with normal-tension glaucoma, had larger changes than did group A, the patients with increased intraocular pressure despite treatment. This latter group was only slightly different from the normal subjects. The same pattern could be found in the central retinal vein. There is no definitive explanation for these findings in blood-flow parameters. It might be that confounding factors, such as medication or intraocular pressure, have a hidden influence.

Interpretation of changes in blood-flow velocity and the resistivity index is difficult. It appears that the reduced end-diastolic velocity may mainly be caused by an increase in vascular resistance, either by elevated intraocular pressure or by increased vascular tone. A decrease in end-diastolic velocity is a sensitive indicator of downstream impedance.[34,35] Small arterioles are the site where blood flow encounters the greatest resistance. Therefore, the resistance in the arterioles is the regulatory mechanism that determines the amount of blood flowing into an organ. We would like to emphasize that color Doppler imaging

permits measurement of blood-flow velocity only and not of the volume of blood flow. Calculation of blood flow would require knowledge of the diameter of the vessel, as well. Currently, we cannot accurately measure the diameters of vessels as small as the extraocular vessels. However, blood velocity provides reasonable information on blood flow within the vessel.

One limitation of this study is that all patients with glaucoma were measured while they were inpatients, whereas the healthy control group was measured outside the hospital, but by the same examiner with the same instrument under otherwise similar conditions.

Reduced blood flow in patients with glaucoma does not automatically indicate that this is causal for glaucomatous damage. However, the fact that patients with glaucoma do have reduced blood-flow velocity in other parts of the body, as for example from the heart to the carotid artery, from the carotid artery to the ophthalmic artery,[36] or in the peripheral circulation as measured by capillary microscopy,[37] makes it unlikely that these alterations in circulation are only secondary to the glaucomatous damage. That such vascular alterations are on the average more pronounced in untreated patients with normal-tension glaucoma than in treated patients with high-tension glaucoma indicates that glaucoma therapy is not the major cause for these findings. From this study, we conclude that circulation is reduced in the extraocular vessels in some patients with glaucoma. Further studies are necessary to elucidate the cause of this reduction.

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