SCIENTIFIC REPORT

Glaucoma progression is associated with decreased blood flow velocities in the short posterior ciliary artery

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Background: An altered perfusion of the optic nerve head has been proposed as a pathogenic factor in glaucoma.

Aim: To investigate potential differences in the ocular haemodynamics of patients having glaucoma with progressive versus stable disease, as well as healthy volunteers.

Methods: Peak-systolic velocity (PSV), end-diastolic velocity (EDV) and resistivity index in the short posterior ciliary artery (SPCA), central retinal artery (CRA) and ophthalmic artery were recorded in 114 consecutive patients having glaucoma with an intraocular pressure (IOP) ≤ 21 mm Hg, as well as in 40 healthy volunteers, by colour Doppler imaging (CDI).

Results: Of the 114 patients with glaucoma, 12 showed glaucoma progression (follow-up period: mean 295 (standard deviation (SD)) (18) days). CDI measurements in these patients showed decreased PSV and EDV in the SPCA ($p < 0.001$ and $p < 0.05$, respectively) and decreased PSV in the CRA compared with patients with stable glaucoma and healthy controls ($p < 0.05$). No differences in flow velocities were found for the ophthalmic artery. IOP and systemic blood pressure was similar in all the three groups.

Conclusions: Progressive glaucoma is associated with decreased blood flow velocities in the small retrobulbar vessels supplying the optic nerve head. The detected difference could represent a risk factor for progression of glaucomatous optic neuropathy.

Besides increased intraocular pressure (IOP),¹ a disturbed microcirculation at the level of the optic nerve head as well as a primary neurodegenerative component are thought to contribute to glaucomatous optic neuropathy.^{2,3} To gain insight into the pathophysiological relevance of haemodynamic disturbances on the course of disease progression, in this study it was hypothesised that there are differences in haemodynamics of patients having glaucoma with progressive versus stable disease, which are independent of IOP and systemic blood pressure.

PATIENTS AND METHODS

The study was approved by the local ethics committee and was carried out in accordance with the Declaration of Helsinki.

Participants

One hundred and fourteen consecutive patients with glaucoma were enrolled in the trial between January 2002 and June 2004. Inclusion criteria were IOP persistently ≤ 21 mm Hg (applanation tonometry and circadian evaluation) with IOP-lowering treatment, characteristic cupping of

the optic disc, glaucomatous visual field defects, refractive error between -4.0 and $+4.0$ D, and informed consent. In addition, 40 healthy volunteers controls were also observed. Exclusion criteria for this group were cardiovascular diseases, including diabetes mellitus, ocular pathology except cataract or pseudophacia, and refractive error higher than ± 4.0 D.

Study protocol

Patients were subjected to visual field testing, funduscopy and measurement of IOP. If the patients met the inclusion criteria, they were enrolled in the trial. All examinations were repeated 3–6 months later to determine the progression status of the disease. In addition, colour Doppler imaging (CDI) was carried out at this time point.

Diagnosis of glaucoma and assessment of progression

The diagnosis of glaucoma was based on the assessment of an experienced ophthalmologist (MK). Glaucoma progression was defined as an increase in the cup:disc (C:D) ratio of the optic nerve head assessed clinically in conjunction with a concomitant decrease of the mean deviation in visual field testing (Humphrey 30-2 protocol). All funduscopy examinations at any time point were carried out by the same experienced glaucoma specialist (MK). Progression of visual field was determined by comparison of each test spot with previous visual field recordings.

Colour Doppler imaging

CDI was carried out with a Sonoline Elegra Advanced System (Siemens, Erlangen, Germany) using a phased-array transducer type 7.5L40 (Siemens, Erlangen, Germany) at 6.5 MHz, as described previously in detail.^{4,5} Peak-systolic velocity (PSV) and end-diastolic velocity (EDV) can be determined directly; the resistivity index (RI) is calculated automatically by the CDI software, using the equation $RI = (PSV - EDV) / PSV$.

Blood pressure

Blood pressure was measured before the CDI examination using the method of Riva-Rocci.

Statistical analysis

One eye (randomly chosen) of each patient was taken into account in the statistical analysis. An analysis of variance model was applied. The independent variable was the affiliation to the three study groups: stable glaucoma, progressive glaucoma and control groups. Dependent variables were the Doppler readouts, PSV, EDV and resistivity

Abbreviations: CDI, colour Doppler imaging; CRA, central retinal artery; EDV, end-diastolic velocity; IOP, intraocular pressure; PSV, peak-systolic velocity; SPCA, short posterior ciliary artery

Table 1 Ophthalmological data at initial and follow-up examination

	Control group (n = 40)	Stable glaucoma (n = 102)		Progressive glaucoma (n = 12)	
		Initial examination	Follow-up examination	Initial examination	Follow-up examination
Best-corrected visual acuity (decimal)	0.94 (0.03)	0.88 (0.07)	0.92 (0.02)	0.85 (0.6)	0.96 (0.03)
Intraocular pressure (mm Hg)	14.9 (0.5)	15.3 (0.7)	14.4 (0.3)	16.6 (1.2)	14.9 (0.8)
Visual field mean deviation (dB)	Not determined	-4.15 (0.510)	-4.18 (0.52)	-4.44 (1.34)	-6.30 (1.30)*
Cup:disc ratio	0.26 (0.02)	0.75 (0.02)	0.75 (0.02)	0.55 (0.09)	0.73 (0.06) *
Females:males	24:16	69:33		6:6	
Age at Doppler examination (years)	51.9 (21.9)	62.9 (11.4)		60.9 (10.5)	

*Significant difference between initial and current examination ($p < 0.05$).
Values are mean (SEM) unless specified.

index. The Games–Howell test was chosen as a retrospective analysis test. Values of $p < 0.05$ were considered to be significant. Data are shown as mean (standard error of mean (SEM)).

RESULTS

Over an average follow-up period of 295 (18) days, 12 of the 114 patients with glaucoma (10.5%) showed progression of visual field defects (mean deviation -4.44 (1.34) ν -6.30 (1.30); $p < 0.05$; table 1) and cupping of the optic disc (C:D ratio 0.55 (0.09) ν 0.73 (0.06); $p < 0.05$; table 1); 102 (89.5%) patients were stable with these parameters (table 1). IOP and best-corrected visual acuity were statistically similar and normal in all the three study groups and did not change during the follow-up period (table 1). Table 2 gives a detailed overview of the Doppler and blood pressure measurements. Briefly, the PSV and EDV in the short posterior ciliary artery (SPCA) were significantly lower in the patient group with progressive glaucoma ($p < 0.001$ for PSV; $p < 0.05$ for EDV). In the central retinal artery (CRA), only the PSV was reduced significantly in the progressive glaucoma group ($p < 0.05$). No difference was detected in blood flow velocities of the ophthalmic artery. For all three vessels no difference was found between the stable glaucoma group and the controls. Resistivity index in all three vessels did not differ in the three study populations (table 2). Diastolic and systolic blood pressure were similar in all groups (table 2; fig 1).

After completion of the study protocol, 57 patients from the stable group and 6 patients from the progressive glaucoma group returned to the Hamburg glaucoma laboratory 254 (14) days after the CDI measurement. At this time point, mean deviation of the visual field remained unchanged in the stable glaucoma group (-4.44 (0.83); not significant (NS)), but was further decreased in the progressive glaucoma group (-7.41 (2.03); $p < 0.05$).

DISCUSSION

The presented data indicate that patients with progressive glaucoma have reduced ocular blood flow velocities in the retrobulbar vasculature when compared with patients with stable glaucoma and controls. These differences were most pronounced in the SPCA and partially present in the CRA. No significant difference was found in the ophthalmic artery.

Several previous studies using various methods have aimed at eliciting the changes of ocular perfusion in patients with glaucoma. Most of these trials focused on a comparison between healthy people and people with glaucoma,^{6–8} or on a comparison between patients with primary open-angle glaucoma and those with normal-tension glaucoma.^{9, 10} Briefly, the findings of these studies indicate a reduction in the ocular perfusion in patients with glaucoma, but no distinct difference between normal tension and primary open-angle glaucoma. It also remains unclear whether these changes are of a primary nature and relevant for disease

Table 2 Colour Doppler imaging results and blood pressure measurements of the three study groups

	Control group (n = 40)	Stable glaucoma (n = 102)	Progressive glaucoma (n = 12)
SPCA			
PSV (cm/s)	10.8 (0.6)	9.5 (0.3)	6.6 (0.5)*
EDV (cm/s)	2.4 (0.2)	2.4 (0.1)	1.8 (0.2)*
Resistivity index	0.77 (0.01)	0.72 (0.03)	0.73 (0.01)
CRA			
PSV (cm/s)	10.0 (0.6)	9.4 (0.3)	7.2 (0.6)*
EDV (cm/s)	1.9 (0.1)	1.7 (0.1)	1.6 (0.3)
Resistivity index	0.80 (0.01)	0.81 (0.01)	0.79 (0.03)
Ophthalmic artery			
PSV (cm/s)	30.9 (1.5)	30.6 (0.8)	30.5 (2.6)
EDV (cm/s)	3.7 (0.2)	3.7 (0.2)	4.0 (0.9)
Resistivity index	0.87 (0.01)	0.87 (0.01)	0.87 (0.02)
Blood pressure			
Systolic (mm Hg)	128 (9)	129 (2)	126 (5)
Diastolic (mm Hg)	83 (6)	78 (1)	79 (2)

CRA, central retinal artery; EDV, end-diastolic velocity; PSV, peak-systolic velocity; SPCA, short posterior ciliary artery.

*Significant differences between the groups ($p < 0.05$).
Values are mean (SEM).

Figure 1 Box plot of peak systolic velocity and end-diastolic velocity in the short posterior ciliary artery (A), in the central retinal artery (B) and in the ophthalmic artery (C). Control, group of healthy volunteers; progr., progressive glaucoma group; stable, stable glaucoma group. * $p < 0.05$.

progression, or if they are a secondary characteristic of glaucomatous optic neuropathy. If a reduced ocular perfusion is a risk factor for glaucoma, these changes should be most pronounced in progressive glaucoma.

An association between changes in retrobulbar haemodynamics and progressive visual field damage has been observed in previous studies.^{11–13} In keeping with our results, Yamazaki *et al*¹¹ did not detect a reduction in retrobulbar blood flow parameters in patients with stable visual fields when compared with healthy people, whereas patients having glaucoma with progression in visual field defects had decreased blood flow velocities in the CRA and SPCA. Other groups found changes in the flow velocities of the ophthalmic artery^{12–14} and the CRA.^{15–16} Regarding study design, these previous studies differ from the present trial in two ways. Firstly, the present study investigates a large series of consecutive patients with glaucoma, whereas the other studies report on selected, partially retrospectively recruited patient collectives. Secondly, the effects observed in the present study are most likely independent of IOP and blood pressure, as both are similar in all the three study groups. Thus,

the detected differences in blood flow velocities could be interpreted as a primary, possibly causative factor for the deterioration of morphological and functional glaucoma parameters. The further prospective follow-up of about half of the study population confirmed the progression of glaucomatous damage in the group with reduced blood flow velocities, and underlining the hypothesis of an altered ocular blood flow as a possibly primary risk factor for disease progression.

The presented data also support the postulate that haemodynamic disturbances in glaucoma primarily occur at the level of the optic nerve head¹⁷ as changes in blood flow velocities were detected in the SPCA and the CRA. Besides feeding into the retinal and choroidal circulation, these two vessels constitute the Haller–Zinn Circle—the main blood supply to the optic nerve head.

Interestingly, there was a difference in the cup:disc ratio between the progressive glaucoma and the stable glaucoma groups at the initial examination. This could be a statistical artefact as there is a pronounced difference in the size of the groups, which is due to the consecutive recruitment of patients.

Compared with previous work^{12–14} the present data do not show a difference in resistivity index between the three groups. On the one hand, this is surprising as it is assumed that the disturbance of ocular haemodynamics is marked by increased vascular resistance. On the other hand, the reliability of the resistivity index to indicate vascular resistance is unclear.¹⁸ Thus, the interpretation of resistivity index results has to be carried out with extreme care.

Potential bias might be introduced in this study by the local anti-glaucoma treatment of the patients. All patients with glaucoma were treated and received, on average, one or two active agents (data not shown). In our experience, only dorzolamide has a marked effect on retrobulbar haemodynamics,^{19–21} which was applied in 30 patients of this study. Although this treatment might influence retrobulbar blood flow, the comparable distribution of its application in patients of both the stable and progressive glaucoma groups should not compromise the major conclusions of the study.

In summary, the presented data indicate that retrobulbar blood flow velocities are altered independently from IOP and systemic blood pressure in patients with progressive glaucoma, which could represent a primary risk factor for disease progression.

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REFERENCES

- Goldmann H. Open-angle glaucoma. *Br J Ophthalmol* 1972;**56**:242–8.
- Harris A, Sergott RC, Spaeth GL, et al. Colour Doppler analysis of ocular vessel blood velocity in normal-tension glaucoma. *Am J Ophthalmol* 1994;**118**:642–9.
- Flammer J, Orgul S, Costa VP, et al. The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res* 2002;**21**:359–93.
- Matthiessen ET, Zeitz O, Richard G, et al. Reproducibility of blood flow velocity measurements using colour decoded Doppler imaging. *Eye* 2004;**18**:400–5.
- Zeitz O, Matthiessen E, Richard G, et al. Estimation of choroid perfusion by colour Doppler imaging vs. other methods. *Ultrasound Med Biol* 2002;**28**:1023.
- Nicolela MT, Walman BE, Buckley AR, et al. Ocular hypertension and primary open-angle glaucoma: a comparative study of their retrobulbar blood flow velocity. *J Glaucoma* 1996;**5**:308–10.
- Schmidt KG, Ruckmann AV, Mittag TW, et al. Reduced ocular pulse amplitude in low tension glaucoma is independent of vasospasm. *Eye* 1997;**11**:485–8.
- Butt Z, McKillop G, O'Brien C, et al. Measurement of ocular blood flow velocity using colour Doppler imaging in low tension glaucoma. *Eye* 1995;**9**:29–33.
- Kaiser HJ, Schoetbau A, Stumpf D, et al. Blood-flow velocities of the extraocular vessels in patients with high-tension and normal-tension primary open-angle glaucoma. *Am J Ophthalmol* 1997;**123**:320–7.
- Butt Z, O'Brien C, McKillop G, et al. Colour Doppler imaging in untreated high- and normal-pressure open-angle glaucoma. *Invest Ophthalmol Vis Sci* 1997;**38**:690–6.
- Yamazaki Y, Drance SM. The relationship between progression of visual field defects and retrobulbar circulation in patients with glaucoma. *Am J Ophthalmol* 1997;**124**:287–95.
- Schumann J, Orgul S, Gugleta K, et al. Interocular difference in progression of glaucoma correlates with interocular differences in retrobulbar circulation. *Am J Ophthalmol* 2000;**129**:728–33.
- Zink JM, Grunwald JE, Piltz-Seymour J, et al. Association between lower optic nerve laser Doppler blood volume measurements and glaucomatous visual field progression. *Br J Ophthalmol* 2003;**87**:1487–91.
- Galassi F, Sodi A, Ucci F, et al. Ocular hemodynamics and glaucoma prognosis: a colour Doppler imaging study. *Arch Ophthalmol* 2003;**121**:1711–5.
- Gherghel D, Orgul S, Gugleta K, et al. Relationship between ocular perfusion pressure and retrobulbar blood flow in patients with glaucoma with progressive damage. *Am J Ophthalmol* 2000;**130**:597–605.
- Satilmis M, Orgul S, Doubler B, et al. Rate of progression of glaucoma correlates with retrobulbar circulation and intraocular pressure. *Am J Ophthalmol* 2003;**135**:664–9.
- Flammer J, Pache M, Resink T. Vasospasm, its role in the pathogenesis of diseases with particular reference to the eye. *Prog Retin Eye Res* 2001;**20**:319–49.
- Polska E, Polak K, Luksch A, et al. Twelve hour reproducibility of choroidal blood flow parameters in healthy subjects. *Br J Ophthalmol* 2004;**88**:533–7.
- Zeitz O, Vilchez SE, Matthiessen ET, et al. Volumetric colour Doppler imaging: a useful tool for the determination of ocular blood flow in glaucoma patients? *Eye* 2006;**20**:668–73.
- Zeitz O, Matthiessen ET, Reuss J, et al. Effects of glaucoma drugs on ocular hemodynamics in normal tension glaucoma: a randomized trial comparing bimatoprost and latanoprost with dorzolamide [ISRCTN18873428]. *BMC Ophthalmol* 2005;**5**:6.
- Klemm M, Zeitz O, Reuss J, et al. Therapy of normal tension glaucoma: effect of brinzolamide on ocular haemodynamics. *Klin Monatsbl Augenheilkd* 2003;**220**:330–3.