EXTENDED REPORT

Retrobulbar haemodynamics and morphometric optic disc analysis in primary open-angle glaucoma

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Background: Previous studies confirmed reduced retrobulbar haemodynamics in primary open-angle glaucoma (POAG).
Aim: To investigate a correlation between retrobulbar haemodynamics and morphometric neuroretinal rim analysis in patients with POAG.
Methods: 51 patients with POAG (mean (standard deviation (SD)) age 65 (11) years) were included in this clinical study. Blood flow velocities (peak systolic velocity (PSV) and end-diastolic velocity (EDV)) of the ophthalmic artery, central retinal artery (CRA), posterior ciliary arteries (PCA) and central retinal vein were measured using colour Doppler imaging (Siemens Sonoline Sienna, Erlangen, Germany). Optic disc morphometry was carried out using scanning laser tomography (Heidelberg Retinal Tomograph II Heidelberg Egineering Heidelberg, Germany). The stereometric parameters of the neuroretinal rim (rim area, rim volume, cup shape measure and retinal nerve fibre layer (RNFL) cross-sectional area) were used for analysis.
Results: The PSV of the CRA was significantly ($p<0.001$) correlated with rim area ($r=0.50$) and rim volume ($r=0.51$). The minimum velocities of the central retinal vein were significantly ($p<0.001$) correlated with rim volume ($r=0.56$) and RNFL cross-sectional area ($r=0.49$). No correlations were found for the flow velocities of the ophthalmic artery and PCAs.
Conclusion: Retrobulbar haemodynamics of the central retinal artery and vein are correlated with the neuroretinal rim damage in POAG.

Ocular haemodynamics have been postulated to be relevant in glaucomatous optic neuropathy, besides mechanical intraocular pressure (IOP)-related optic nerve damage and ganglion cell loss.[1 2] Glaucomatous optic neuropathy results in a reduction of the neuroretinal rim with changes in optic disc morphometry and glaucomatous excavation of the optic nerve head. Histopathological studies investigated a link between neuroretinal rim loss and capillary drop-out in glaucoma.[3 4] A controversial debate is under way as to whether the capillary loss in glaucoma is a primary factor in the disease or a secondary phenomenon. In addition to optic disc changes, systemic and local vascular risk factors have been identified in glaucoma in the past.[5] Systemic and local vascular disease may result in vasosclerosis, capillary dropout, vasospasm and autoregulatory dysfunction contributing to impaired ocular blood flow.[1 5–8] Blood flow velocities of retrobulbar vessels—that is, the central retinal artery, ophthalmic artery, and nasal and temporal short posterior ciliary arteries—can be measured by means of colour Doppler imaging (CDI). CDI is an ultrasound technique combining a simultaneous B mode ultrasound image with Doppler frequency shifts.[9 10] Various studies comparing patients with POAG with controls confirmed reduced flow velocities and increased resistive indices of the ophthalmic artery, central retinal artery and posterior ciliary arteries.[11–15] The relationship between retrobulbar haemodynamics and morphological disc damage—that is, neuroretinal rim loss—has not been evaluated.

This clinical study was carried out to investigate a correlation between retrobulbar haemodynamics in POAG and the morphological disc damage measured using confocal scanning laser tomography. A reduction of retrobulbar flow velocities in POAG related to neuroretinal rim loss of the optic nerve head is postulated.

PATIENTS

Patients with POAG exhibited glaucomatous visual field loss confirmed in at least two visual field examinations. Visual field examinations were carried out with the Humphrey Field Analyzer (Model 750, Humphrey-Zeiss, San Leandro, California, USA) using the achromatic 24–2 full threshold or Swedish interactive thresholding algorithm technique. Glaucomatous visual field loss was defined following the guidelines of the European Glaucoma Society. Field loss was considered significant if: (a) the glaucoma hemifield test was abnormal; (b) three points were confirmed with $p<0.05$ probability of being normal (one of which should have $p<0.01$), not contiguous with the blind spot; or (c) corrected pattern standard deviation (CPSD) was abnormal, with $p<0.05$.[16] IOP was measured using Goldmann applanation tonometry. All patients with POAG had at least two IOP readings >21 mm Hg in their medical history. Patients with diabetes mellitus, visual acuity of <20/40 or media opacities preventing image acquisition with retinal tomography were excluded from the study. Adherence to the Declaration of Helsinki for research involving human beings was confirmed. Informed consent was obtained from all patients.

A total of 51 patients with POAG (M 30, F 21; mean (standard deviation (SD)) age 65 (11) years) were included in this clinical study. One eye of each patient was randomly selected for analysis. Table 1 presents the clinical data. Forty two patients with POAG were on topical IOP lowering drugs (β blockers, carbonic anhydrase inhibitors, prostaglandins, sympathomimetics, pilocarpine or combinations; mean (SD)

Abbreviations: CDI, colour Doppler imaging; CPSD, corrected pattern standard deviation; CRA, central retinal artery; EDV, end-diastolic velocity; IOP, intraocular pressure; PCA, posterior ciliary arteries; POAG, primary open-angle glaucoma; PSV, peak systolic velocity; RNFL, retinal nerve fibre layer

Table 1 Clinical data of the patients with POAG (n = 51), mean (SD)

Age (years)	64.6 (10.8)
IOP (mm Hg)	18.3 (4.3)
Mean deviation (dB)	−10.2 (8.1)
Pattern standard deviation (dB)	7.1 (3.9)
Systolic blood pressure (mm Hg)	142 (20)
Diastolic blood pressure (mm Hg)	82 (10)
Heart rate (beats/min)	68 (13)

IOP, intraocular pressure.
Values are given as mean (SD).

number of therapeutic agents 1.7 (1.2)). According to the patients' medical history, 25 patients were treated for systemic arterial hypertension, 12 patients had a systemic vascular disease (ie, myocardial infarction, cerebrovascular disease or peripheral arterial occlusive disease) and 8 patients had a history of systemic vasospasms (ie, cold hands or feet or migraine). Thirteen of the patients with POAG did not receive any systemic drugs.

METHODS

All patients with POAG had a detailed ophthalmological examination, visual field testing, CDI of their retrobulbar blood vessels and a confocal scanning laser imaging of the optic disc.

Blood flow velocities of retrobulbar vessels were measured by means of CDI using a 7.5-MHz linear phased-array transducer (Siemens Sonoline Sienna, Germany). The transducer was gently placed on the closed upper eyelid using a coupling gel, taking care to minimise pressure on the globe. All patients were in supine position during the examination. CDI allows blood velocity measurements of the ophthalmic artery, the central retinal artery (CRA), and the temporal short posterior ciliary arteries and nasal short posterior ciliary arteries. The peak systolic velocity (PSV) and the end-diastolic velocity (EDV) were obtained from the Doppler-shifted spectral waves of each artery. The resistive index (Pourcelot's ratio) was calculated ((PSV−EDV)/PSV) to characterise peripheral vascular resistance of the vessels studied. Additionally, the maximum and minimum velocities of the central retinal vein were evaluated.

The Heidelberg Retina Tomograph (HRT II, Heidelberg Engineering, Heidelberg, Germany) is a confocal scanning laser ophthalmoscope for quantitative analysis of the optic nerve head topography with high optical resolution. The three-dimensional topographic measurements are based on the superficial reflection of a diode laser (675 nm). After confocal detection of the reflected light, a topographic map of the optic disc is calculated. The observer defines the border of the optic nerve head (Elschnig scleral ring) with a contour line. A standard reference plane based on the contour line divides the cup from the rim of the optic nerve head. The standard reference plane is based on the assumption of a nerve fibre layer thickness of 50 μm at the level of the papillomacular bundle (at 350–356°). The Heidelberg Retina Tomograph generates a topographic map of the optic disc and calculates stereometric parameters for quantitative optic disc analysis. The stereometric parameters rim area, rim volume, cup shape measure and retinal nerve fibre layer (RNFL) cross-sectional area were used for analysis.

Correlations were tested using the Fisher's r to z test after Bonferroni's multiple comparison correction. A p value <0.001 was regarded as significant.

RESULTS

Table 2 presents the flow velocities and resistive indices of the ophthalmic artery, the CRA, the PCA, and the maximum and minimum velocities of the central retinal vein.

Table 2 Flow velocities (peak systolic velocity and end-diastolic velocity) and resistive indices of the ophthalmic artery, central retinal artery, posterior ciliary arteries and central retinal vein

OA PSV (cm/s)	32.7 (12.8)
OA EDV (cm/s)	7.0 (2.9)
OA RI	0.75 (0.25)
CRA PSV (cm/s)	7.9 (2.1)
CRA EDV (cm/s)	2.3 (0.6)
CRA RI	0.70 (0.06)
PCA PSV (cm/s)	7.2 (1.5)
PCA EDV (cm/s)	2.5 (0.6)
PCA RI	0.65 (0.07)
Central retinal vein maximum velocity (cm/s)	3.6 (0.8)
Central retinal vein minimum velocity (cm/s)	2.4 (0.8)

CRA, central retinal artery; EDV, end-diastolic velocity; OA, ophthalmic artery; PCA, posterior ciliary arteries; PSV, peak systolic velocity; RI, resistive indices.
Values are given as mean (SD).

Table 3 presents the stereometric parameters of the optic disc evaluated with the scanning laser ophthalmoscope (Heidelberg Retina Tomograph II).

The peak systolic velocities of the CRA were significantly correlated with rim area ($r = 0.50$) and rim volume ($r = 0.51$). The minimum velocities of the central retinal vein were significantly correlated with rim volume ($r = 0.56$) and RNFL cross-sectional area ($r = 0.49$). The correlation of the PSV of the CRA with RNFL cross-sectional area ($r = 0.39$), the correlation of the EDVs of the CRA with rim area ($r = 0.40$) and rim volume ($r = 0.39$), and the correlation of the minimum velocities of the central retinal vein with rim area ($r = 0.39$) did not reach significance after Bonferroni's adjustment for multiple comparisons.

Haemodynamic parameters of the ophthalmic artery and of the PCAs, and the resistive indices of the CRA were not correlated with stereometric parameters of the optic disc. The cup shape measure was not correlated with retrobulbar haemodynamics. Table 4 presents the correlation coefficients. Flow velocities of retrobulbar vessels were not significantly correlated with age or IOP, except the resistive indices of the ophthalmic artery (correlation with age: $r = 0.30$; $p = 0.031$). The IOP before CDI measurements was not correlated with the morphological disc parameters.

DISCUSSION

Flow velocities of the CRA and of the central retinal vein are significantly correlated with the size of the neuroretinal rim of the optic disc in POAG. Flow velocities decrease with increasing optic disc damage in glaucoma.

Reduced EDVs and increased resistive indices of the ophthalmic artery, the CRA and PCA have been reported in patients with POAG compared with controls.[11–15] PSVs of the CRA and short PCA were found to be reduced in some studies.[12 15 17 18] Satilmis *et al*[19] reported a correlation of EDVs of the CRA with the rate of progression in glaucoma in a retrospective study. Reduced flow velocities of the CRA in patients with asymmetric POAG were found in eyes with more severe visual field loss.[20] A reduction in flow velocities

Table 3 Stereometric parameters of the HRTII used for analysis

Rim area (mm^2)	1.03 (0.43)
Rim volume (mm^3)	0.21 (0.15)
Cup shape measure	−0.05 (0.07)
Retinal nerve fibre layer cross-sectional area (mm^2)	0.86 (0.43)

Values are given as mean (SD).

Table 4 Correlation coefficients and p levels of the retrobulbar haemodynamics and stereometric parameters of the optic disc

	Rim area	Rim volume	Cup shape measure	RNFL cross-sectional area
OA PSV (cm/s)	0.19	0.12	−0.23	−0.08
OA EDV (cm/s)	0.11	0.02	−0.17	−0.15
OA RI	0.09	0.10	−0.19	0.01
CRA PSV (cm/s)	0.50; p<0.001	0.51; p<0.001	−0.29	0.39; p=0.005
CRA EDV (cm/s)	0.40; p=0.004	0.39; p=0.005	−0.18	0.25
CRA RI	0.09	0.08	−0.11	0.11
PCA PSV (cm/s)	0.04	−0.03	−0.19	−0.11
PCA EDV (cm/s)	0.19	0.10	−0.29	−0.06
PCA RI	−0.18	0.15	0.13	0.04
Central retinal vein minimum velocity (cm/s)	0.39; p=0.005	0.56; p<0.001	−0.33	0.49; p<0.001
Central retinal vein maximum velocity (cm/s)	0.15	0.11	−0.10	0.08

CRA, central retinal artery; EDV, end-diastolic velocity; OA, ophthalmic artery; PCA, posterior ciliary arteries; PSV, peak systolic velocity; RI, resistive indices.
A p value < 0.001 was considered significant after Bonferroni's adjustment for multiple comparisons.

of the CRA may be caused by an increase in vascular resistance related to vasoconstriction or vasospasm, vasosclerosis, reduction in the cross-section of the vessel diameters (eg, capillary loss) or rheological factors. In addition, a reduction in both PSVs and EDVs may be interpreted as a decrease in volumetric flow related to an increase in vascular resistance.[21] Previous studies confirmed a correlation of EDVs of the CRA with the retinal arteriovenous passage time assessed by fluorescein angiography [22] and with the extent of capillary non-perfusion of the optic nerve head—that is, fluorescein-filling defects in patients with normal-tension glaucoma.[23] A reduction in retinal vessel diameters may also account for an increase in retinal vascular resistance.[24]

In this study, flow velocities of the CRA were related to the neuroretinal rim loss in POAG. No correlations were found for the ophthalmic artery or for the short PCA. Glaucoma is characterised by glaucomatous optic neuropathy and ganglion cell loss at the level of the retina. Thus, a reduction of retinal ganglion cells may be associated with a reduction of retinal blood flow either as a primary vascular disease or as a secondary down regulation. Furthermore, the superficial capillaries of the optic nerve head are perfused by the CRA, and capillary drop-out at the level of the superficial neuroretinal rim and prelaminar region is a well-known phenomenon in glaucoma.[7] However, the flow velocities of the PCA that are relevant for optic disc perfusion in the prelaminar and laminar regions were not correlated with the rim loss in our study. This could be due to a higher intraindividual variability in CDI measurements of these vessels resulting in lower reliability.[25] Jonas *et al*[26] found a correlation of laser Doppler flowmetry measurements of the neuroretinal rim with the rim area of the optic nerve head in a cohort of patients with normal tension glaucoma and age-matched controls. The laser Doppler parameter ''flow'' decreased with increasing neuroretinal rim loss.

In addition to the reduced flow velocities of the CRA, we found a significant correlation of the minimum velocities in the central retinal vein with the neuroretinal rim of the optic disc. A reduction in the central retinal vein flow velocities could be related to a venous congestion, possibly at the level of the lamina cribrosa. In 1997, Kaiser *et al*[13] reported decreased flow velocities of the central retinal vein in POAG. Previous studies found decreased retinal arteriovenous passage times in patients with POAG[27] and normal tension glaucoma.[28] The prolonged retinal transit times may reflect an increased vascular resistance related to altered retinal microcirculation or a venous congestion. Consequently, an increase in the central retinal venous pressure[29–31] related to decreased flow velocities in the central retinal vein could decrease ocular perfusion. Morgan studied central retinal vein pulsation pressures in glaucoma. The ophthalmodynamometric force required to induce venous pulsation was correlated with the severity of glaucomatous visual field damage.[32] This phenomenon may be explained by several pathologies. An increased venous pulsation pressure may be due to an increased cerebrospinal fluid[33] or orbital pressure,[34] or increases in arterial blood pressure—that is, altered upstream resistance or an increase in downstream resistance of retinal veins.[32 35] However, Hayreh[29] stated in 2001 that there is little valid evidence so far that central retinal vein pressure plays any significant part in the optic nerve head blood flow and in ischaemia of the optic nerve. Future studies have to elucidate the pathogenetic role of central retinal venous outflow pressure and retinal vein flow velocities in glaucoma, and possible implications for retinal and optic nerve head blood flow.

To summarise, the reductions in flow velocities of the CRA and the central retinal vein emphasise the decreased retinal blood flow in POAG. The flow velocities of the CRA and the central retinal vein are considerably correlated with the morphological disc damage in patients with POAG. In contrast with considerations of optic nerve head blood flow changes in glaucoma, a reduction in flow velocities of the central retinal vessels and the correlation with morphological disc damage in glaucoma hint at altered retinal haemodynamics associated with neural tissue loss at the level of the retinal nerve fibre layer. Prospective longitudinal studies need to confirm a prognostic value of reduced retrobulbar haemodynamics in POAG.

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