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Ocular haemodynamics in pseudoexfoliative and primary open-angle glaucoma

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Abstract

Objective   To compare the retrobulbar haemodynamic parameters in the ophthalmic artery (OA) and short posterior ciliary arteries (SPCA) in pseudoexfoliative and primary open-angle glaucoma patients.

Subjects and methods   fourty-three eyes from 43 patients with pseudoexfoliative glaucoma (PXE) and 31 eyes from 31 patients with primary open-angle glaucoma (POAG) who met the inclusion/exclusion criteria were included in this prospective cross-sectional study. Colour Doppler imaging measurements, peak systolic velocity (PSV), and end-diastolic velocity (EDV) were assessed in the OA and posterior ciliary arteries (PCA). Pourcelot resistivity indices (RI) were calculated. Visual function was assessed using the 24-2 Swedish Interactive Threshold Algorithm (SITA). The main outcomes of the study were PSV, EDV, and RI in the OA and SPCA.

Results   In POAG patients, PSV and EDV were significantly lower in the OA, $P = 0.003$ and $P < 0.001$ respectively, and in the PCA, $P = 0.003$ and $P < 0.001$ respectively, when compared with the PXE group. The RI was significantly higher, $P < 0.001$, in both vessels, in the POAG group.

Conclusion   The results of this study have found reduced PSV and EDV and increased RI in the retrobulbar vessels of POAG patients when compared with PXE patients.

Eye (2008) **22,** 515–520; doi:10.1038/sj.eye.6702676; published online 15 December 2006

Introduction

Although elevated intraocular pressure (IOP) has been identified as a major risk factor for glaucoma progression,[1–3] there is also increasing evidence that disturbed ocular blood flow (OBF) is a primary and independent risk factor for glaucoma progression.[4–6]

However, the question of whether the impact of ocular blood flow is similar, in the different types of glaucoma, remains.

Many different studies, using different types of instruments, suggested that on average ocular blood flow (OBF) is decreased in some glaucoma patients, especially in normal-tension glaucoma (NTG) and in primary open-angle glaucoma (POAG) patients with progressive visual field damage.[6–8]

Pseudoexfoliation syndrome is an age-related disorder of the extracellular matrix characterized by production and progressive accumulation of small, white deposits of a fibrillar extracellular material in many ocular and extraocular tissues.

The prevalence of pseudoexfoliation syndrome in POAG populations is much higher than in age-matched nonglaucomatous ones.

Several blood flow disturbances have been reported in patients with pseudoexfoliative glaucoma (PXE).[9,10] However, another study did not find differences between eyes with exfoliative glaucoma and normal controls.[11]

Our aim was to compare the value of colour Doppler imaging (CDI) measurements, peak systolic velocity (PSV), end–diastolic velocity (EDV), and Pourcelot resistivity indices (RI) in the ophthalmic artery (OA) and posterior ciliary arteries (PCA) between patients with PXE and patients with primary POAG.

Subjects and methods

This prospective cross-sectional study included 43 eyes of 43 patients with PXE and 31 eyes of 31 patients with POAG examined during the period from January 2003 to April 2004 in our clinic.

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The study was approved by the local ethic committee. All patients were included in this study during the initial clinical open-angle glaucoma (OAG) diagnosis and had never previously been treated for glaucoma. The Doppler measurements were performed by the same experienced observer who was masked to the clinical diagnosis. All patients were fully informed about the details of the study protocol. Written informed consent was obtained from all subjects at the beginning of the study in accordance with the Declaration of Helsinki principles.

Each subject underwent a standard ophthalmic examination, including review of medical history, best-corrected visual acuity, and slit-lamp examination of the anterior segment with dilated pupils, with the aim to detect pseudoexfoliation, IOP measurement using Goldmann aplanation tonometry, gonioscopy, dilated funduscopic examination using a 78-diopter lens, stereoscopic optic disc photography, and three automated perimetry using the 24-2 Swedish Interactive Threshold Algorithm (SITA) (Carl Zeiss Meditec Inc., Dublin, CA, USA).

For glaucoma diagnosis, three visual field examinations were performed, two within 1 month of the beginning of the study.

Glaucomatous field defects were defined according to the following guidelines: as a minimum of one location in the paracentral or nasal step regions corresponding to sectors 1 or 2, or to the inferior 3 location in sector 3 of the Glaucoma Hemifield Test[12] exhibiting repeatable abnormality at the $P < 0.5\%$ level by pattern deviation probability analysis; or as two or more locations situating in a cluster exhibiting repeatable abnormality at the $P < 2\%$ level, or lower, by pattern deviation probability analysis excluding any location in the cluster that was situated in the opposite horizontal hemifield.

Patients were included if one or both eyes exhibited mild or moderate visual field defects in terms of the classification of Hodapp *et al*[13] and modified for the program 24-2 and the SITA standard algorithm by Litwak.[14]

Patients with unreliable visual field assessment (false negatives, false positives, or fixation losses exceeding 30%) were excluded.

Patients receiving systemic medications that affect IOP or systemic blood pressure were ineligible unless the patient's medication dosages were stable ≥6 months before the screening visit.

Only one eye that fulfilled all inclusion criteria and none of the exclusion criteria was designed as the study eye; in the case where both eyes from the same patient fulfilled all inclusion criteria, and none of the exclusion criteria, the study eye was chosen randomly. Table 1 summarizes the main inclusion and exclusion criteria.

Central corneal thickness (CCT) was measured using an ultrasonic pachymeter (Corneo-gage plus 2, Sonogage, Cleveland, OH, USA). One drop of benoxinate was applied to the eye before the measurement was being taken. Six measurements were carried out and the average was recorded. All readings were performed by one observer trained in the technique.

Systolic (SBP) and diastolic (DBP) blood pressures were measured on the upper arm by sphygmomanometry. Heart rate was measured by palpation of radial pulse. These parameters were measured every 10 min and all of them remained constant in each individual throughout all examinations.

Mean arterial pressure (MAP) was calculated as $DBP + \frac{1}{3}(SBP-DBP)$.

Ocular perfusion pressure (OPP) was calculated as $\frac{2}{3}MAP-IOP$.

All CDI examinations were performed (model SSA-340, Toshiba Medical Systems, Tustin, CA), USA by the same experienced observer.

A 7.5 MHz vector-array transducer was applied to the closed eyelid using a coupling gel and care was taken care to avoid any pressure to the eye itself. During the examination, subjects were in supine position, with the head tilted forward at about a 30° angle. Details of the technique have been previously published.[15]

Measurements of the OA flow were performed approximately 10–15 mm posterior to the globe, where the echographic signals are stronger. The SPCA images were taken temporally and nasally to the optic nerve just behind the posterior pole to the eye globe. The angle between transducer and orientation of the vessels was corrected.

Peak systolic velocity (PSV) and end diastolic velocity (EDV) were measured in the OA and medial and lateral PCA. Although medial and lateral PCA were individually assessed, the mean value of both was used for the statistical analysis.

The PSV and EDV were used to calculate the Pourcelot RI according to the following equation: $RI = PSV - EDV/PSV$.

Statistical analysis

Sample size was calculated for an α level of 0.05, two sides, a power of 90%, and a minimal detectable difference in means of 5% between groups. For the purpose of statistical analysis, only one randomly chosen eye was included for patients with bilateral affliction.

Results are expressed as a mean (standard deviation). In order to establish an initial comparison, the Fisher exact test was used to evaluate the significance of the differences between groups in categorical variables (gender, race, diagnosis, and systemic medication). The

Table 1 Inclusion and Exclusion criteria

Inclusion criteria	Exclusion Criteria
⩾40 years of age	Presence of any form of glaucoma other than OAG
Clinical diagnosis of OAG in at least one eye with or without pseudoexfoliation	Any concurrent infectious/noninfectious conjunctivitis, keratitis, or uveitis in either eye
Glaucomatous visual field defect	Any abnormality preventing reliable applanation tonometry in study eye(s)
IOP⩾22 mmHg	Patients previously treated with anyone anti-glaucoma treatment (antiglaucoma medications, argon laser trabeculoplasty, and/or ocular filtering surgical intervention)
Willingness to comply with the investigator's and protocol indications	Progressive retinal or optic nerve disease due to any cause
Visual acuity⩾0.4 (EDTRS scale[a]) in both eyes	Asthma or other obstructive pulmonary disease
Spherical refractive error between +3.00 and −6.00 dioptres	Cardiogenic shock, 2 or 3 degree atrioventricular block, sinus bradycardia, or heart failure
	Diabetes with any sign of retinopathy (Haemorrhages, hard and/or soft exudates, macular oedema
	Systemic medications that affect IOP or systemic blood pressure were ineligible unless the patients' medication dosages were stable ⩾6 months before the screening visit
	Pregnant or nursing women

Abbreviations: EDTRS, Early Treatment Diabetic Retinopathy Study; OAG, open-angle glaucoma.
[a]See Ferris et al.[31]

difference between the study groups in the quantitative variables was analysed with the one-way analysis of variance (ANOVA). A P-value <0.01 was considered statistically significant. Analysis was performed using SPSS 12.0.[16]

Results

Demographic and clinical characteristics of the study population are shown in Table 2. No significant differences were found with respect to SBP and DBP between the two groups. However, the mean age was higher in the PXE group, $P<0.001$.

The MD and PSD of the visual field were significantly worse in the PXE group, $P<0.001$, than in the POAG group.

The IOP was significantly higher, $P<0.0001$, in the PXE group. There was no significant difference in CCT between the two study groups.

In the POAG group, the PSV and EDV were significantly lower in the OA, $P=0.003$ and, $P<0.001$, respectively, and PCA, $P=0.003$ and $P<0.001$, respectively, when compared with the PXE patients group (Table 3).

The RI was significantly higher, $P<0.001$, in both vessels, in the POAG group (Table 3).

Discussion

The results of this study have found reduced PSV and EDV and increased RI in the retrobulbar vessels of POAG patients when compared with PXE patients.

In POAG patients, our results are consistent with those previously reported in which retrobulbar blood flow reductions are greater in the eye with more damage.[17,18] However, our study failed to confirm this assumption in the PXE group.

There are relatively few studies that have evaluated the haemodynamic parameters of PXE patients. Our findings dissent from the findings reported by Yüksel et al,[19] who reported that some haemodynamic parameters in the retrobulbar vessels were altered in patients with PXE, even with pseudoexfoliation syndrome without glaucoma.

Yüksel et al[19] reported lower PSV and EDV and higher RI in both OA and PCA than our group. It may be argued that the differences between the results of the Yüksel study and our results may be due to the use of topical therapy in the Yüksel study. Although several papers have reported systemic and ocular vascular alterations in patients with pseudoexfoliation syndrome,[20–23] our results suggested that the OBF alterations were stronger in the POAG patients group.

The well-recognized parameter in the pathogenesis of PXE is increased IOP.[24,25] Pseudoexfoliation is also believed to be an important independent risk factor in patients with ocular hypertension.[26,27]

Limitations of this study exist that warrant consideration. It is possible that the differences between the two study groups in age, IOP, and visual field damage may justify the differences in blood flow parameters between POAG and PXE patients. However, Harris et al,[28] using CDI, found that in healthy subjects the ophthalmic arterial EDV decreased and RI rose with

Table 2 Baseline characteristics

	GPEX	GPAA	F-ratio	P-value
Number	43	31		
Age (years)				
Mean (SD)	74.4 (4.7)	67.5 (7.7)	23.65	<0.001
95% CI	(73.0–75.9)	(64.6–70.2)		
Range	63–81	49–80		
SBP (mmHg)				
Mean (SD)	143.3 (6.4)	142.9 (7.0)	0.05	0.823
95% CI	(141.3–145.2)	(140.3–145.5)		
Range	135–160	135–160		
DBP (mmHg)				
Mean (SD)	70.2 (7.2)	73.1 (7.5)	2.68	0.106
95% CI	(68.0–72.5)	(70.3–75.8)		
Range	55–85	60–90		
IOP (mmHg)				
Mean (SD)	29.3 (2.3)	23.9 (1.4)	141.16	<0.001
95% CI	(28.6–30.0)	(23.4–24.4)		
Range	26–35	22–27		
OPP (mmHg)				
Mean (SD)	43.5 (4.3)	48.3 (4.4)	22.00	<0.001
95% CI	(42.2–44.8)	(46.7–49.9)		
Range	33.3–54.7	40.7–56.7		
MD (dB)				
Mean (SD)	−8.2 (1.6)	−5.4 (1.2)	73.55	<0.001
95% CI	(−8.7−−7.8)	(−5.8−−4.9)		
Range	−12.3−−6.0	−8.4−−3.4		
PSD (dB)				
Mean (SD)	6.4 (0.8)	4.8 (0.7)	79.22	<0.001
95% CI	(6.1–6.6)	(4.6–5.0)		
Range	5.1– 8.0	3.5–6.5		
CCT (μm)				
Mean (SD)	548.1	550.5	0.177	0.676
95% CI	(541.4–554.8)	(540.8–560.1)		
Range	504–589	503–596		
Systemic medications				
High blood pressure	14 (32.5%)	9 (29%)		0.984
Cardiovascular disease	7 (16.3%)	3 (9.6%)		0.595
Diabetes	6 (14.0%)	7 (22.5%)		0.558

Abbreviations: 95% CI, 95% confident interval; CCT, central corneal thickness (μm); DBP, diastolic blood pressure (mmHg); IOP, intraocular pressure; MD, mean defect (dB); NA, not applicable; OPP, ocular perfusion pressure (mmHg); PSD, pattern standard deviation (dB); SBP, systolic blood pressure (mmHg); SD, standard deviation.
P-values were calculated comparing the parameters at baseline between the two study groups (one-way ANOVA test); *P*-values were considered statistically significant if lower than 0.05.
[a]Fisher's exact test. *P*-values were considered statistically significant if lower than 0.05.

advancing age. Furthermore, Gallassi *et al*[29] found that in normal subjects the flow velocities of all considered vessels progressively decline whereas RI values increase with advancing age. Glaucomatous eyes with uncontrolled IOP and with visual field worsening showed a statistically significant decrease in the EDV flow velocities and an increase in the resistivity index value in ciliary arteries.[29] Geyer *et al*,[30] using the Langhams pneumotonometer, reported that for younger women the pulsatile ocular blood flow (POBF) was significantly higher than for older women.

Table 3 Comparison of retrobulbar haemodynamic parameters between POAG and PXE

	PXE	POAG	F-ratio	P-value
PSV OA (cm/s)				
Mean	36.4 (1.8)	35.0 (2.0)	9.51	0.003
95% CI	(35.8–37.0)	(34.3–35.8)		
EDV OA (cm/s)				
Mean	9.7 (1.5)	7.4 (1.2)	50.81	<0.001
95% CI	(9.2–10.2)	(6.9–7.8)		
RI OA				
Mean	0.733 (0.040)	0.789 (0.037)	37.81	<0.001
95% CI	(0.721–0.745)	(0.776–0.803)		
PSV PCA (cm/s)				
Mean	14.9 (0.8)	14.2 (0.9)	9.77	0.003
95% CI	(14.6–15.1)	(13.9–14.6)		
EDV PCA (cm/s)				
Mean	5.3 (0.7)	4.0 (0.6)	68.13	<0.001
95% CI	(5.1–5.5)	(3.8–4.2)		
RI PCA				
Mean	0.643 (0.038)	0.719 (0.038)	69.79	<0.001
95% CI	(0.632–0.656)	(0.705–0.737)		

Abbreviations: EDV, end-diastolic velocity; OA, ophthalmic artery; PCA, posterior ciliary arteries; POAG, primary open-angle glaucoma; PSV, Peak systolic velocity; PXE, pseudoexfoliative glaucoma; RI, resistance index.
P-values were calculated comparing the parameters at baseline between the two study groups (one-way ANOVA test).
P-values were considered statistically significant if lower than 0.01.

Although the PXE subjects were older, with increased IOP and more visual field damage than POAG patients, the ocular blood flow alterations were higher in the POAG patients group.

Therefore, we suggest different pathogenic mechanisms for POAG and PXE. Further research investigating the relationship between ocular blood flow – IOP and visual field deterioration, and longitudinal follow-up in the same population could be helpful in determining the relative value of each for early prediction of glaucomatous damage.

Acknowledgements

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