Original Article

Retrobulbar Short Posterior Ciliary Artery Hemodynamics in Patients with Pseudoexfoliation Glaucoma and Primary Open-Angle Glaucoma

Nese Cetin Dogan[1], Nusret Ozdemir[2], Kairgeldy Aikimbaev[3], Emine Ciloglu[1]

[1]Department of Ophthalmology, Adana City Training and Research Hospital, Adana, Turkey, [2]Private Ophthalmology Clinic, Adana, Turkey, [3]Department of Radiology, Cukurova University, Adana, Turkey

Abstract

Purpose: To investigate retrobulbar blood flow changes in the short posterior ciliary arteries (SPCAs) in patients with pseudoexfoliation glaucoma (PEG) and primary open-angle glaucoma (POAG).

Methods: In this prospective study, there were 22 eyes in the PEG group, 28 eyes in the POAG group, and 28 eyes with senile cataract in the control group. Peak systolic velocity (PSV), end-diastolic velocity (EDV), mean velocity (Vm), and resistivity index (RI) parameters of the temporal and nasal SPCAs were compared between the study groups.

Results: Mean temporal PSV, EDV, and Vm value were significantly lower in both the POAG group and the PEG group ($P = 0.049$, $P = 0.004$, $P = 0.020$), respectively. Temporal SPCA RI values were not significantly different between the groups ($P = 0.115$).

Conclusion: There are retrobulbar blood flow changes in glaucomatous compared to nonglaucomatous eyes. However, SPCAs blood flow characteristics are similar between PEG and POAG subtypes.

Keywords: End-diastolic velocity, Primary open-angle glaucoma, Pseudoexfoliation glaucoma, Resistivity index, Short posterior ciliary artery

Address for correspondence: Nese Cetin Dogan, Adana Şehir Eğitim ve Araştırma Hastanesi, Göz Hastalıkları Kliniği, Adana 01160, Türkiye.
E-mail: drnesecetindgn78@gmail.com
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Introduction

Pseudoexfoliation syndrome (PES) is a systemic disease characterized by the abnormal synthesis and extracellular accumulation of elastic fibrillary material in the eye and various other tissues. It is the identifiable leading cause of open-angle glaucoma worldwide.[1] The accumulation of pseudoexfoliation material in the trabecular meshwork, under the inner layers of Schlemm's canal, and in the juxtacanalicular tissue causes an increase in intraocular pressure (IOP) and the development of glaucoma.[2] The extent of this accumulation and damage was shown to be associated with IOP levels and the presence and degree of glaucomatous optic nerve head damage.[2,3] Pseudoexfoliation glaucoma (PEG) characteristically progresses with severe IOP elevation. However, it has been suggested that there may also be other risk factors for the development of glaucomatous damage independent from IOP. Two of these risk factors are impaired retrobulbar and ocular perfusion and abnormal elastic tissue in the lamina cribrosa.[4-6]

Although there are several studies in the literature about blood flow parameters in the ophthalmic artery and central retinal artery, few studies have investigated temporal and nasal short posterior ciliary arteries (SPCAs) hemodynamics in PES.[7] The temporal and nasal SPCAs play an essential role in optic nerve head hemodynamics.[8-11]

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Qualitative, quantitative, or semi-quantitative measurements of retrobulbar hemodynamics can be performed using color Doppler ultrasound (CDUS).[12,13] CDUS is used in the diagnosis and follow-up of diseases that impact ocular blood flow. In this study, changes in retrobulbar blood flow (in the SPCAs) in primary open-angle glaucoma (POAG) and PEG patients were investigated using CDUS, and temporal and nasal SPCA blood flow velocities and resistivity index (RI) values were compared between these patient groups and with a control group.

Methods

This prospective, comparative clinical study was performed according to the Declaration of Helsinki and was approved by the local ethics committee of the Çukurova University Faculty of Medicine (registration number 9/2007). Participants were informed in detail about the study, and informed consent forms were obtained.

Exclusion criteria were nonsenile cataract (e.g., traumatic, metabolic); chronic inflammatory disease such as Behçet's disease, rheumatoid arthritis, Sjögren's syndrome, and systemic lupus; history of ocular surgery; history of long-term topical corticosteroid use; or pathologies such as keratoconus, keratoglobus, keratoconjunctivitis sicca, uveitis, and proliferative diabetic retinopathy or any other retinal pathologies.

Demographic characteristics were recorded for all patients in the study. Patients underwent a complete ophthalmologic examination, including visual acuity, IOP measurement, gonioscopy, and slit-lamp examination. After inducing mydriasis with 1% tropicamide, fundus examination was performed using a 90-diopter aspheric lens. In patients with dense cataract that prevented illumination of the fundus, B-mode ultrasound was used to evaluate the posterior segment. IOP was measured using Goldmann applanation tonometry. Gonioscopic examination of all quadrants was performed using a Goldmann three-mirror contact lens.

All eyes included in the study had stage 3–4 open-angle according to Shaffer staging in gonioscopic examination. Patients with open anterior chamber angle, IOP below 22 mmHg, and no pathology other than senile sclerosis in anterior segment and fundus examination were included in the normal control group. Patients with open anterior chamber angle, IOP values over 22 mmHg measured at different times, glaucomatous changes in the optic nerve head, and typical pseudoexfoliative material (PEM) on the pupillary edge and anterior lens surface in biomicroscopic examination were included in the PEG group. Those with open anterior chamber angle, IOP values of 22 mmHg and above measured at different times, those with glaucomatous damage to the optic nerve head, and those who did not have PEM on the pupillary edge and anterior lens surface in the slit-lamp examination were included in the POAG group. All patients were examined by two experienced clinicians (N.C.D. and E.C.).

In a small number of patients who were using antiglaucoma eye drops, the medications were discontinued 8 weeks before the procedure. The patients included in the study were not using any systemic medication other than antihypertensive. Patients with hypertension were under control with systemic antihypertensive medication.

In all groups, the patients had no known systemic disease other than hypertension. The patients rested for 20 min before the examination. Blood pressure measurements had to be below 140/90 in all patients. The patients were informed that they should not smoke, drink alcohol, and take any other medication on the day of the appointment and 1 day before, and the measurements were made in the morning.

All eyes in the study underwent CDUS measurements by a skilled sonographer (K.A.) to determine retrobulbar blood flow dynamics. A LOGIQ 5 (General Electric Medical Systems, Milwaukee, WI, USA) device and a 10 MHz linear probe were often used for measurement. Wall-filter (24–25 MHz) was used to minimize motion noise in measurements made using virtual convex mode and color mode with 5–6, 7 MHz probe. Measurements were obtained with patients in supine position with head elevated 30°, ample methylcellulose gel between the probe and lid, and the probe was positioned over the lid and globe while applying as little pressure as possible.

The SPCAs originate 10–20 mm posterior to the globe and divide into many branches before encircling the optic nerve in the retrobulbar area. As the extent of these vessels is highly variable, the optic nerve was first located and used as a guide to differentiating the retrobulbar vessels. The evaluation was based on the anterior-most retrobulbar sections in which the characteristic Doppler spectrum of the SPCAs was best observed, and peak systolic velocity (PSV) and end-diastolic velocity (EDV) could be determined. All measurements were performed by the same radiologist who was blind to the patient groups. PSV, EDV, and mean velocity (Vm) in the temporal and nasal SPCA were recorded separately for each eye. Pourcelet's RI was also calculated separately for the flow in each vessel.

Statistical analysis

All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package (IBM Inc., Chicago, IL, USA). Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation. Chi-square test was used to compare categorical variables between the groups. The normality of distribution for continuous variables was confirmed with the Shapiro–Wilk test. For comparison of continuous variables between two groups (i.e., age groups), Mann–Whitney *U* test was used. For comparison of three groups, one-way analysis of variance or Kruskal–Wallis test was used depending on whether the statistical hypotheses were fulfilled or not. For normally distributed data, regarding the homogeneity of variances, Tukey or Games–Howell tests were used for multiple comparisons of groups. For nonnormally distributed data, Bonferroni adjusted Mann–Whitney *U* test

was used for multiple comparisons of groups. The statistical level of significance for all tests was considered to be 0.05.

Results

Seventy-eight eyes of 66 patients with cataract or cataract and glaucoma were prospectively analyzed. Twenty-eight eyes of 23 patients with senile cataract only were included in the control group, 22 eyes of 19 patients were included in the PEG group, and 28 eyes of 24 patients were included in the POAG group.

Of the 66 patients included in the study, 33 were women, and 33 were men. The mean ages of the patients in the control, PEG, and POAG groups were 59.52 ± 9.20, 65.89 ± 8.31, and 59.96 ± 12.47 years, respectively [Table 1].

Mean IOP values in these groups were 13.14 ± 1.73, 23.64 ± 7.81, and 21.68 ± 7.74 mmHg, respectively [Table 1]. All patients had grade 3–4 open angle according to the Shaffer grading system.

Mean values of temporal and nasal SPCA PSV, EDV, Vm, and RI were obtained for all patients. Statistically significant differences were detected between the PEG, POAG, and control groups in terms of temporal SPCA flow velocities (P = 0.049, P = 0.004, P = 0.020, P = 0.115 for PSV, EDV, Vm, RI, respectively) [Table 2] but not for nasal SPCA flow velocity values (P = 0.498, P = 0.634, P = 0.506, P = 0.602, respectively) [Table 3].

Temporal SPCA flow velocity values were significantly lower for all parameters in the PEG and POAG groups compared to controls ($P < 0.05$) [Table 2]. There were no significant differences between PEG and POAG patients [Table 2].

Nasal SPCA flow velocity parameters showed no significant differences between PEG and POAG patients when compared with control [Table 3].

Within-group comparisons by age (≤60 years, >60 years) showed that temporal SPCA EDV and Vm values were significantly lower in patients over 60 years of age in the POAG group (P = 0.018, P = 0.022). No statistically significant age-dependent differences were detected in the other temporal and nasal SPCA flow velocity parameters or RI values [Tables 4 and 5].

Table 1: Clinical and demographic characteristics of the groups

	Control	PEG	POAG	*P*
Age	59.52±9.20	65.89±8.31	59.96±12.47	0.097
Gender, *n* (%)				
Male	11 (47.8)	12 (63.2)	10 (41.7)	0.363
Female	12 (52.2)	7 (36.8)	14 (58.3)	
IOP (mmHg)	13.14±1.73	23.64±7.81	21.68±7.74	<0.001[a,b,c]

[a]P<0.05 for control versus PEG, [b]P<0.05 for control versus POAG, [c]P<0.05 for PEG versus POAG. PEG: Pseudoexfoliation glaucoma, POAG: Primary open-angle glaucoma, IOP: Intraocular pressure

Table 2: Temporal short posterior ciliary artery blood flow velocity values of the groups

Temporal SPCA	Control	PEG	POAG	*P*
PSV	12.69±4.91	8.85±2.88	9.51±3.94	0.049[b]
EDV	4.68±2.14	3.21±1.12	3.26±1.37	0.004[a,b]
Vm	7.69±3.15	5.27±1.98	5.40±2.20	0.020[a,b]
RI	0.626±0.90	0.630±0.08	0.611±0.07	0.115

Minimum *post hoc* power %62, [a]P<0.05 for control versus PEG, [b]P<0.05 for control versus POAG. SPCA: Short posterior ciliary artery, PEG: Pseudoexfoliation glaucoma, POAG: Primary open-angle glaucoma, PSV: Peak systolic velocity, EDV: End-diastolic velocity, Vm: Median velocity, RI: Resistive index

Table 3: Nasal short posterior ciliary artery blood flow velocity values of the groups

Nasal SPCA	Control	PEG	POAG	*P*
PSV	6.83±2.90	6.31±2.21	6.49±2.46	0.498
EDV	2.64±1.05	2.52±0.77	2.51±0.77	0.634
Vm	4.19±1.55	3.84±1.24	3.96±1.53	0.506
RI	0.59±0.12	0.59±0.07	0.61±0.07	0.602

SPCA: Short posterior ciliary artery, PEG: Pseudoexfoliation glaucoma, POAG: Primary open-angle glaucoma, PSV: Peak systolic velocity, EDV: End-diastolic velocity, Vm: Median velocity, RI: Resistive index

Discussion

Pseudoexfoliation was first described in 1917 by Lindberg.[14] Since Lindberg, many studies have been performed, and many theories proposed regarding the structure and pathogenesis of pseudoexfoliation.

The incidence of glaucoma is higher in eyes with PES. Rapid and aggressive progression of glaucomatous damage in some PEG patients despite perfect IOP control has highlighted the importance of vascular pathologies. Numerous studies on this subject have demonstrated vascular abnormalities in glaucoma patients using various techniques.[5,6]

Fundus fluorescein angiography (FFA) studies showing vascular abnormalities and circulation deficits in glaucoma have revealed impaired retinal circulation in addition to reduced perfusion in the optic nerve head, peripapillary retina, and choroid.[15]

Ocular tissues are highly sensitive to fluctuations in systemic pressure and changes in IOP. Hemodynamic autoregulation mechanisms ensure constant blood flow in these tissues. In glaucoma patients, ischemic damage and reperfusion defects are believed to occur as a result of the disruption of these ocular blood flow autoregulation mechanisms.[16] This mechanism explains why low diastolic perfusion pressure is a risk factor for glaucoma development. Ghergel *et al*. reported that in patients whose retrobulbar blood flow parameters are not controlled, lower than average ocular diastolic perfusion pressure was a poor prognostic factor in glaucoma.[17] In the same study, no such correlation was detected in patients with nonprogressive glaucoma or the control group. Findings of decreased blood flow in the optic nerve head capillaries and retina on FFA led

Table 4: Correlation between temporal short posterior ciliary artery blood flow velocity values and age

	Age	Eye (*n*)	PSV	*P*	EDV	*P*	Vm	*P*	RI	*P*
Control	≤60	17	12.57±4.56	0.549	5.03±2.17	0.166	8.08±3.21	0.313	0.6±0.09	0.284
	>60	11	11.47±4.44		3.77±1.16		6.48±2.14		0.65±0.09	
PEG	≤60	8	10.2±2.8	0.176	3.01±0.34	0.331	5.68±1.07	0.398	0.69±0.09	0.612
	>60	14	8.85±3.41		2.94±1.49		5.2±2.13		0.66±0.1	
POAG	≤60	13	10.22±3.37	0.094	3.78±1.33	0.018	6.37±2.07	0.022	0.63±0.09	0.525
	>60	15	8.78±4.91		2.65±1		4.74±2.27		0.67±0.11	

PSV: Peak systolic velocity, EDV: End-diastolic velocity, Vm: Median velocity, RI: Resistive index, PEG: Pseudoexfoliation glaucoma, POAG: Primary open-angle glaucoma

Table 5: Correlation between nasal short posterior ciliary artery blood flow velocity values and age

	Age	Eye (*n*)	PSV	*P*	EDV	*P*	Vm	*P*	RI	*P*
Control	≤60	17	6.69±1.87	0.488	2.77±1.08	0.999	4.35±1.41	0.450	0.59±0.08	0.950
	>60	11	7.22±4.58		2.66±1.1		4.18±2.04		0.59±0.17	
PEG	≤60	8	7.00±1.78	0.035	2.77±0.83	0.151	4.16±1.02	0.063	0.61±0.04	0.176
	>60	14	5.22±1.23		2.24±0.7		3.32±0.92		0.57±0.07	
POAG	≤60	13	6.62±3.07	0.954	2.51±1	0.817	4.19±2.1	0.623	0.62±0.06	0.525
	>60	15	6.47±2.04		2.61±0.59		3.85±1		0.6±0.09	

PSV: Peak systolic velocity, EDV: End-diastolic velocity, Vm: Median velocity, RI: Resistive index, PEG: Pseudoexfoliation glaucoma, POAG: Primary open angle glaucoma

to the concept of optic neuropathy associated with precapillary ischemia.

It is difficult to demonstrate the relationship between altered ocular perfusion and glaucoma progression. First of all, there is no gold standard method to measure ocular blood flow. CDUS imaging is the only system in which a single multifunctional probe is used in all measurements. CDUS is an ultrasonography technique that combines erythrocyte displacement movement velocity with B-scan image. In ocular CDUS, as in other doppler methods, blood flow velocity is determined as the return frequency of the sound waves sent from the probe. CDUS imaging technique allows the examiner to find the desired vessel and selectively measure doppler in a separate window. Flow rate information is graphed according to time. The examiner determines where the current velocity waves peak. In this study, PSV and EDV are calculated. The average current velocity is also calculated from the wave spectrum. The Pourcelot index, also known as the RI, indirectly determines vascular resistance and is based on the analysis of PSV and EDV.[18]

In a study that demonstrated the correlation between abnormal ocular blood flow and glaucoma progression, Yamazaki and Drance compared normotensive glaucoma and POAG patients who did and did not show progression at 5-year follow-up and reported significantly lower PSV and EDV and higher RI in the central retinal artery and SPCAs in normotensive glaucoma groups. However, they detected no significant differences between POAG patient groups with and without progression.[19] In 44 glaucoma patients followed for 7 years, Galassi *et al*. reported significantly lower EDV and higher RI values in the ophthalmic arteries of those with progressive disease.[20] Satilmis *et al*. reported that decreased central retinal artery EDV was associated with progression in 21 POAG patients followed for 4.3 years.[21] Martinez *et al*. reported that of 49 POAG patients followed for 3 years, those with higher RI values in the ophthalmic artery and SPCA exhibited greater progression.[22] Martinez *et al*. reported higher RI values in the ophthalmic artery, central retinal artery, and SPCA in the PEG group compared to the control group. In a study comparing ocular perfusion pressure and hemodynamics in PEG and POAG, Galassi *et al*. observed significantly higher RI values in the PEG patients.[20] Eliaçık *et al*. conducted a 3-month follow-up study evaluating the effect of dorzolamide/timolol fixed combination on retrobulbar hemodynamics in patients with PEG. Their analysis of the ophthalmic artery, central retinal artery, and SPCA revealed significant changes in temporal SPCA PSV and RI values only.[23]

In our study, similar to the literature, we found that temporal SPCA PSV, EDV, and Vm values were significantly lower in PEG patients than in the healthy control group. Nasal SPCA PSV, EDV, and Vm values showed no significant differences. POAG patients also showed significantly lower temporal SPCA flow velocities. When RI values were calculated, there was no significant difference in temporal and nasal SPCA RI values in all groups.

When the effect of age on vascular parameters was evaluated, EDV and Vm values in temporal SPCA in the POAG group were found to be significantly decreased over 60 years of age. In nasal SPCA values, there was a decrease in PSV value only in the PEG group above the age of 60. It is concluded that the significant association of increased IOP values in vascular parameters over 60 years of age is the result of vascular mechanisms in the pathogenesis of glaucoma, in line with the literature.

While significant changes were detected in vascular parameters in the POAG and PEG groups compared to the control group, no significant change was found when these two groups were compared with each other. It is considered that similar vascular mechanisms, excluding PEM, play a role in the development of glaucoma in cases in similar age groups. Larger series of clinical studies are needed to support these results.

The limitations of our study are small sample size, cross-sectional design of the study, and absence of follow-up. These limitations reduce the generalizability of data.

The presence of pseudoexfoliation material is one of the crucial factors influencing ocular hemodynamics. Glaucoma progression is slow; therefore, long-term follow-up periods are needed to correlate blood flow parameters with progression. Local and systemic drugs likely affect the relationship between vascular changes and glaucoma progression. Finally, changes in ocular blood flow velocity pose a risk for the development of glaucoma. In this study, we found that important changes in temporal SPCA hemodynamics occurred in the presence of glaucoma.

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Conflicts of interest
There are no conflicts of interest.

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