ORIGINAL RESEARCH

Comparison of Ocular Blood Flow in Glaucomatous Eyes and Nonglaucomatous Eyes at a Tertiary Hospital in South India: A Prospective Case-control Study

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Abstract

Aim: To compare the ocular blood flow in glaucomatous eyes and normal healthy eyes. This study compares open-angle glaucoma patients to healthy adults by measuring various parameters in the ophthalmic artery (OA), central retinal artery (CRA), and short posterior ciliary artery (SPCA).

Materials and methods: A total of 50 glaucomatous eyes and 50 normal eyes were included in a prospective case-control study over 1 year. The color Doppler imaging (CDI) was conducted using a noninvasive linear multifrequency probe with a frequency range of 5–9 MHz. OA, CRA, and SPCA were measured for peak systolic velocity (PSV), end-diastolic volume (EDV), pulsatility index (PI), and resistivity index (RI).

Results: When compared with controls, PSV was decreased in all three vessels, with the results being remarkable only in CRA. The EDV also showed a remarkable decrease in all three vessels. Additionally, all three vessels showed significant increases in PI and RI except OA, p-value < 0.05.

Conclusion: Blood velocity is decreased, and resistive indices are increased in glaucomatous eyes compared with normal eyes. Variations in ocular blood flow could be a cause or consequence of glaucomatous optic neuropathy and are an important predictor of disease progression.

Keywords: Color Doppler imaging, Central retinal artery, End-diastolic volume, Pulsatility index, Resistivity index, Short posterior ciliary artery.

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Introduction

Glaucoma is a group of disorders with unknown etiology, characterized by damage to the optic nerve head with consistent visual field defects where intraocular pressure (IOP) is a modifiable risk factor. Several hypotheses have been postulated to explain the glaucomatous optic neuropathy of which, mechanical theory states the raised IOP is considered a primary risk factor. Reduced optic nerve perfusion contributes to intraneural ischemia according to the ischemic theory. There are several causes of this perfusion, such as the stress of IOP on the blood supply to the nerve or intrinsic processes within the optic nerve.[1] Reduced ocular blood flow and faulty autoregulation with reduced perfusion pressure leads to ischemia of the optic nerve head which plays an important role in glaucomatous damage.[2] It is normal for optic nerve vessels to increase or decrease their tone depending on IOP and blood pressure to maintain a constant blood flow. Diabetes,[3] hypertension,[4] migraine,[5] and peripheral vasospasm[6] inducing diseases like Raynaud's have been associated with the vascular theory contributing to glaucomatous changes. Major sources of blood loss, perioperative hypotension and vascular diseases that affect the carotid and coronary circulation contribute to the circulatory disturbances that cause glaucoma.[7] Ophthalmological circulatory pathologies can be effectively picked up by ultrasound.[8,9] A greater degree of diagnostic discrimination has been achieved with the use of Doppler ultrasound in imaging ocular vasculature due to its ability to measure vascular flow quantitatively, thus allowing statistical analysis of glaucoma whose pathophysiology has been associated with vascular factors.[10–12] Various studies indicate reduced ocular blood flow and disturbed autoregulation in glaucoma patients compared with normal adults. Retrobulbar circulation can be assessed noninvasively with color Doppler imaging (CDI).[13,14] Altered retrobulbar hemodynamics has been seen with newer CDI-related studies in glaucoma patients.[15,16] A long-term study based on a version 3 Heidelberg retinal tomograph has shown that orbital CDI parameters are correlated with the development and progression of glaucomatous damage in the optic nerve head. They have also been correlated to visual field changes to analyze the significance in developing functional damage and to assess progression in a few studies.

The study compares open-angle glaucoma patients to healthy adults by measuring various parameters in the ophthalmic artery (OA), central retinal artery (CRA), and short posterior ciliary artery (SPCA).

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These parameters include peak systolic velocity (PSV), end-diastolic volume (EDV), pulsatility index (PI), and resistivity index (RI).

Materials and Methods

A prospective case-control study was carried out in 50 eyes of 27 open-angle glaucoma patients who visited the glaucoma clinic of the outpatient and inpatient department of ophthalmology. The sample size was calculated after maintaining an α error of 5% and a confidence interval (CI) of 95% using categorical variables in the case-control study population. A total of 50 eyes of 25 age-matched controls without any signs of glaucomatous damage were included from those patients who came for routine eye checkups, and the selection and confounding biases were taken care of. Written informed consent was secured from all individuals, and the study was carried out after Institutional Ethics Committee clearance. No external funding was involved in conducting this study. Data of all patients, including age, sex, duration of glaucoma, use of antiglaucoma medications, history of glaucoma surgeries or lasers, family history of glaucoma, associated systemic illness like diabetes, hypertension, coronary artery disease, and renal disease were obtained by direct patient interviews and by reviewing the medical records. Details of previously taken visual fields, central corneal thickness, and optical coherence tomography glaucoma were recorded. A detailed, systemic evaluation was done. Snellen's chart was used to record visual acuity during the ocular examination. Estimation of intraocular pressure with applanation tonometry, anterior segment examination with slit lamp biomicroscopy, and estimation of the angle of anterior chamber by 4-mirror gonioscopy—classified using modified R P Center classification and optic disc evaluation with stereoscopic 78D lens. Our study population, which included 50 eyes diagnosed with characteristic features of open-angle glaucoma and 50 control eyes with no evidence of glaucoma, underwent CDI for ocular blood flow evaluation. A nonintrusive 5–9 MHz linear multifrequency probe was utilized, and the following blood flow measurements were recorded in the OA, CRA, and SPCA:

- Peak systolic velocity (PSV).
- End diastolic velocity (EVD).
- Pulsatility index (PI).
- Resistivity index (RI).

All these parameters were compared with the normal controls with healthy eyes.

Inclusion Criteria for Cases

- Patients diagnosed to have open-angle glaucoma at presentation with or without systemic illness.
- Elevated IOP or normal IOP under treatment, associated with optic disk and visual field changes.
- Open angles on gonioscopy, including secondary causes.

Inclusion Criteria for Controls

- Normal anterior segment examination on slit lamp biomicroscopy.
- The IOP < 20 mm Hg.
- Normal fundus in slit lamp biomicroscopy with 78D examination.

Exclusion Criteria

- Patients with closed or occlude angles on gonioscopy.
- Retinal vascular pathologies like diabetic retinopathy, vein/artery occlusions, hypertensive retinopathy, and vitreous hemorrhage.

Statistical Analysis

International Business Machines Corporation's Statistical Package for the Social Sciences statistics software 16.0 version was employed to evaluate the data acquired *via* sources. The tools used to interpret the gathered information ranged from descriptive statistics frequency analysis, percentage analysis for categorical variables, mean, and standard deviation (SD) for continuous variables. An unpaired sample *t*-test was utilized as an aid to determine the difference between bivariate samples and independent groups. The *p*-value < 0.05 is the standardized probability value that deems the data as significant or nonsignificant.

Results

We included 50 eyes of 27 open-angle glaucoma patients and 50 eyes of 25 age-matched controls.

Gender showed wide variation in both the groups with female predisposition but was not statistically significant. The mean age in the study population was 56 ± 10 years.

We used color Doppler to image the blood flow pattern in three vessels—CRA, SPCA, and OA. In each vessel, we looked at four parameters—PSV, EDV, PI, and RI. The flow parameters in CRA, short posterior ciliary artery and OA are studied in CDI and are shown in Figures 1 to 3.

The analyzed wave patterns in CRA, short posterior ciliary artery, and OA from CDI are shown in Figures 4 to 6.

After the statistical analysis, it was found that PSV was decreased in OA, CRA, and short posterior ciliary artery compared to controls with *p*-values of 0.076, 0.04, and 0.244, respectively. The PSV reduction in the CRA was statistically significant, with a mean of 9.83 ± 3.41 (Table 1).

End-diastolic volume (EDV) was significantly reduced in all three vessels with a *p*-value of 0.024, 0.031, and 0.005, respectively (Table 1).

Pulsatility index (PI) and RI were increased in all three blood vessels in the glaucoma patients compared to the control population. The results were statistically significant (Table 1).

Discussion

Over the years, ocular blood flow dynamics have been documented to be altered in glaucoma. These changes can further lead to ischemia at the optic nerve head, which in turn alleviates the glaucomatous condition by causing vascular flow alteration and autoregulation failure. Nerve damage in glaucoma progression is often linked primarily to increased ocular pressure. However, certain cases have been documented where normal IOP patients still end up with IOP elevation, which is always considered the primary risk factor for glaucomatous optic nerve damage. This interesting paradoxical fact warrants further research looking into the factors leading to optic nerve damage in glaucoma patients.[17,18]

To date, to explain this phenomenon of optic nerve damage, three different theories have been put forth—mechanical theory, role of neurodegenerative factors and vascular theory.

The Mechanical Theory

It looks at elevated IOP causing compression and back bowing at the level of the lamina cribrosa, which leads to the obstruction of

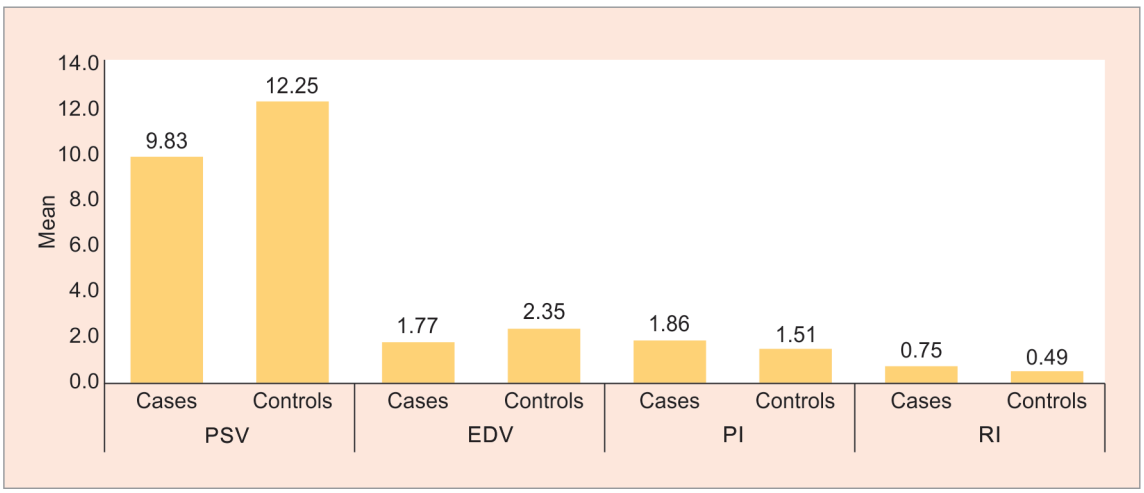

Fig. 1: Flow parameters in central retinal artery

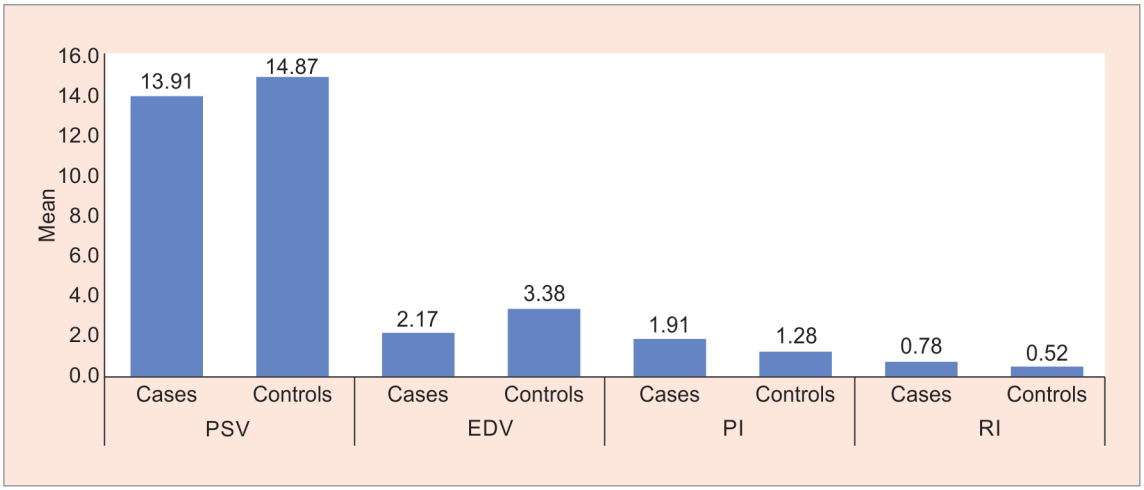

Fig. 2: Flow parameters in the short posterior ciliary artery

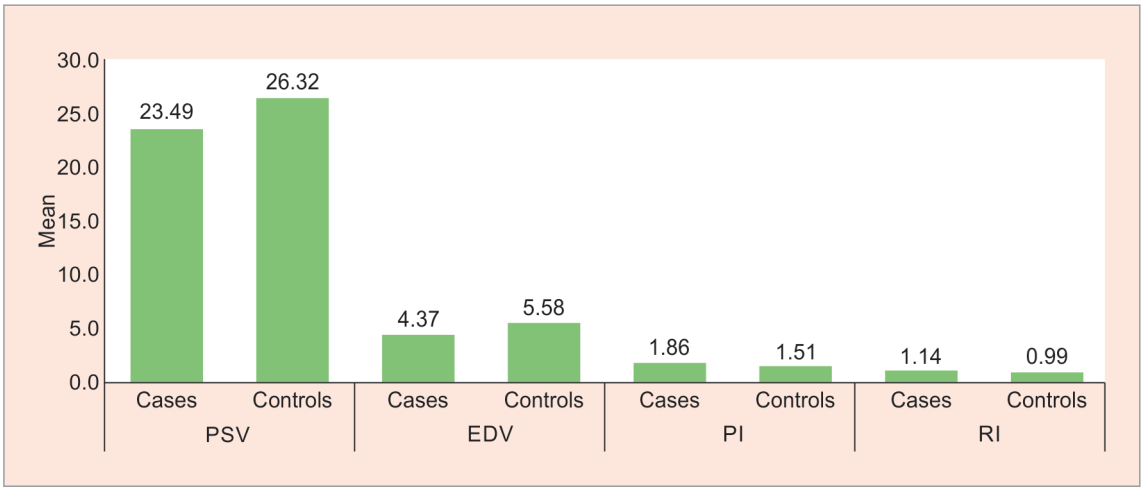

Fig. 3: Flow parameters in ophthalmic artery

axonal transport and, eventually, retinal ganglion cell death, causing optic nerve damage.

Neurodegenerative Factors

Neurodegenerative factors have been studied glutamate—primary optic nerve damage releases glutamate, which acts on receptors and increases intracellular calcium, causing cell death *via* apoptosis, the release of glutamate, and a vicious cycle.[19,20] Nitric oxide moderately reactive free radical-entry within the cell-moderate reactivity of a free radical changing to high reactivity—unstable radicals cause destruction of surrounding components, mainly cellular components and macromolecules.[21]

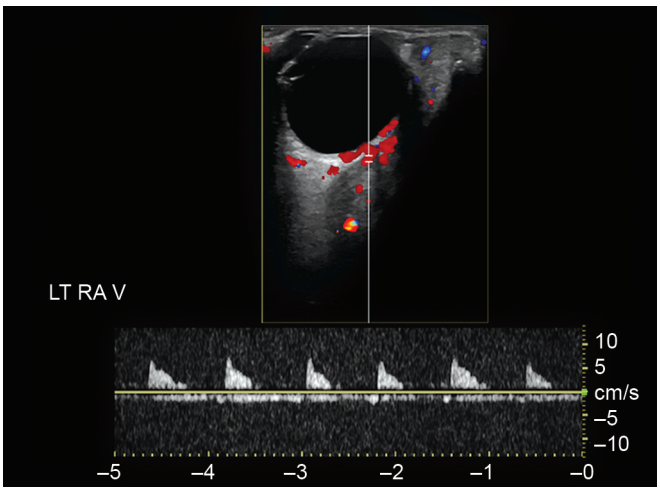

Fig. 4: Wave pattern seen in central retinal artery

The Vascular Theory

It has gained popularity of late as glaucoma has been associated with many vascular disturbances like migraine and peripheral vascular diseases like Raynaud's phenomenon, etc. Vascular theory proposes ischemia to be central to nerve damage and secondary to ocular hypoperfusion or due to intrinsic changes in the optic nerve.[22,23] The hypothesis proposed to explain the pathogenesis of glaucoma progression and damage involves excess production of plasma endothelin-1 (ET-1) in glaucomatous patients. As of yet, the ET-1 increase is thought to be a result of vasospastic stimuli.[24–29]

The evaluation of retrobulbar circulation in the major vessels of the eye can be effectively achieved using CDI.

In our study, we have imaged the OA, CRA, and Short posterior ciliary artery and looked at PSV and EDV. Using these parameters, we have calculated the PI and RI. We compared and analyzed the data against age-matched normal controls.

We found that Peak systolic volume was reduced in all three vessels, but the values were statistically significant only in the CRA ($p = 0.04$). The EDV was reduced in all three vessels, and their results were statistically significant when compared to normal age-matched individuals. Our results are comparable to previous studies that have been done. The CRA and SPCA showed the most consistency in the differences. However, because the SPCA supplies the prelaminar and laminar portions of the optic nerve head, changes to the SPCA are more specific for glaucomatous injury. Any impedance to the blood flow in these regions causes worsening of optic neuropathy. When a patient has glaucoma, which is in the stage of progression, his SPCA often has lower blood flow velocities, as stated by Matthiessen et al.[30] Moreover, detailed analysis of individual vessels is challenging owing to its small size

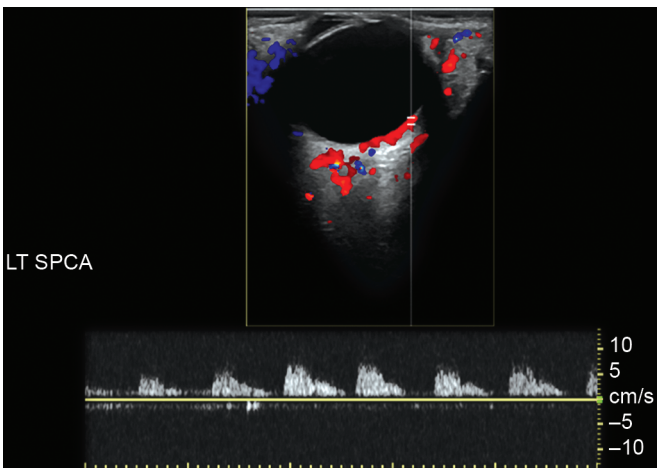

Fig. 5: Wave pattern seen in the short posterior ciliary artery

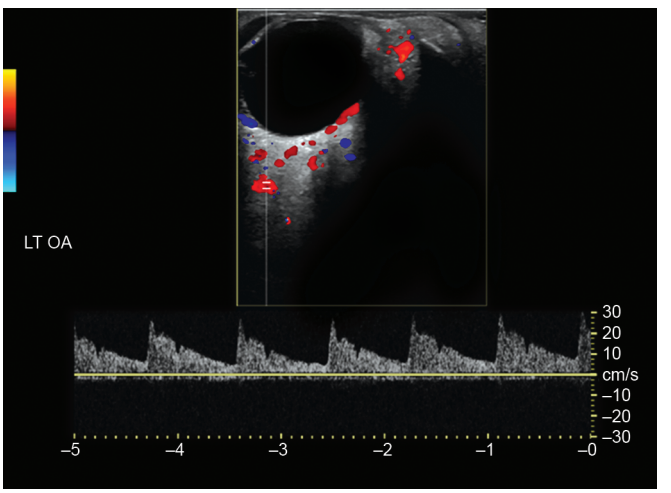

Fig. 6: Wave pattern is seen in the ophthalmic artery

Table 1: Flow parameters in cases and control in all three vessels

Doppler indices	*OA*			*CRA*			*SPCA*		
	Cases	*Control*	*p-value*	*Cases*	*Control*	*p-value*	*Cases*	*Control*	*p-value*
PSV	23.49 ± 7.11	26.32 ± 8.60	0.076	9.83 ± 3.41	12.25 ± 5.96	0.014	13.91 ± 5.03	14.87 ± 2.83	0.244
EDV	4.37 ± 2.25	5.58 ± 3.00	0.024	1.77 ± 1.25	2.35 ± 1.43	0.031	2.17 ± 1.22	3.38 ± 0.72	0.005
PI	1.86 ± 0.59	1.51 ± 0.59	0.003	1.86 ± 0.73	1.51 ± 0.82	0.026	1.91 ± 0.57	1.28 ± 0.50	0.0005
RI	1.14 ± 0.27	0.99 ± 0.47	0.057	0.75 ± 0.11	0.49 ± 0.27	0.0005	0.78 ± 0.08	0.52 ± 0.23	0.0005

and multidirectional nature. A diagnostic aid for this purpose is varying the in sonation angles. As suggested by Matthiessen et al., we discovered through the CRA and SPCA that the PSV and EDV were dramatically decreased.

In all three vessels, the PI and RI dramatically rose, and the findings were statistically significant. After a follow-up period of 48 months, Calvo et al.[31] found that glaucoma advancement in glaucoma patients was accompanied by an RI value greater than 0.75 in the OA.

Jimenez-Aragon et al.[32] looked at the role of color Doppler in the early detection and progression of glaucoma. They imaged the major vessels and analyzed flow parameters through CDI, compared this to Heidelberg retina tomograph 3 images and looked at glaucoma progression. They found that in those groups that had lesser PI and RI, there was a lesser progression. These results are comparable to ours, as we found that the PI and RI indices were higher in the glaucoma groups compared to the normal controls.

Plange et al. suggested the same in their study. According to Birinci et al.[33] a decrease in the supply *via* the posterior ciliary artery results in ischemic damage to the optic nerve's head. According to Cellini et al.,[34] this damage is made worse by the decreased choroidal blood flow that results from higher resistance after the capillary network has been destroyed.

Our results are consistent with the various previously proposed vascular mechanisms that contribute to the development and progression of glaucomatous optic nerve head damage. Capillaries have been known to contribute maximally to vascular resistance within the retinal circulation, and the optic nerve has a rich supply of capillaries. The resistance offered by these capillaries is maximum, and the resistance index is calculated in our study. Our results are suggestive of EDV, PI, and RI values having greater discrepancy or significant differences between the test and control groups as compared to the PSV values.

Retrobulbar hemodynamic changes are a sensitive phenomenon which can easily and frequently be altered in the presence of systemic variables like age,[35] blood pressure,[4] and prevalence of systemic diseases like diabetes mellitus[3] and migraine.[5] These crucial parameters were incorporated into the design of our study.

In their study of pulsatile ocular blood flow in various forms of glaucoma, Shakeel[36] discovered a statistically significant decrease in PSV in CRA and in the EDV in all three major vessels. They also found an increase in the PI and RI that strongly correlated with our results. They also looked at normal-tension glaucoma and primary angle-closure glaucoma, explained the variances found in different types of glaucoma and attributed the change in various parameters to the vascular disturbances that occur in glaucoma. We found similar results as well and agree with the theory they proposed. Our present study compared the parameters only in open-angle glaucoma eyes with the control eyes, hence more specific in the analysis.

Limitations

It is difficult to extrapolate our results to a larger population because the sample size of the study was small, including only 50 eyes of 27 patients. Therefore, in order to accurately establish a stronger association, this sample size may not be adequate. None of these patients were followed up subsequently after initial assessment to look for progression of the disease. Nor did we compare these changes with any structural or functional parameters. Apart from this, instrumental limitation associated with CDI was also noted. Blood velocity can be directly computed *via* CDI; on the contrary, it has limited application in assessing blood flow, which is a product of the speed at which blood is flowing and the area of a blood vessel when the vessel is cut. However, this device does not provide us with precise values as the volume of blood flowing at a particular instance is equivalent to (radius of the vessel)[4] by Poiseuille's law.

Conclusion

Glaucoma is characterized by progressive optic neuropathy, which can be affected by ocular blood flow. PSV and EDV were significantly reduced in open-angle glaucoma patients when compared to the nonglaucomatous eyes.

An increase in pulsatility and resistivity indices will hence lead to a decline in blood velocity in glaucomatous eyes, which is an important marker of disease progression.

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