

A COLOUR DOPPLER STUDY OF RETROBULBAR BLOOD FLOW PARAMETERS IN PATIENTS OF PRIMARY OPEN ANGLE GLAUCOMA

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ABSTRACT

Background: Present definition of 'Primary Open Angle Glaucoma' considers raised intraocular pressure (IOP) as one of the risk factors for this disease. Association of alterations in ocular blood flow has been considered another risk factor. Moreover the eye being treated for glaucoma could be a part of wider systemic dysfunction of auto-regulation of ocular blood flow. This hypothesis is further backed up with the recognition of normal tension glaucoma as a clinical entity and observation of progressive glaucomatous damage despite IOP control. This study was, thus, undertaken to study retrobulbar blood flow using colour Doppler imaging (CDI) in patients of glaucoma and to see how the control of IOP affected these parameters.

Methods: This is a prospective cohort study involving 43 freshly diagnosed patients of POAG and 30 controls. Peak systolic velocity (PSV) and mean end diastolic velocity (EDV) and resistivity index (RI) were studied in ophthalmic artery (OA), in central retinal artery (CRA) and short posterior ciliary arteries (SPCA). Values were compared with those of normal controls and also pre and post treatment among patients of POAG.

Results: Mean PSV and EDV were found to be significantly low in OA and CRA only in patients of POAG compared to controls. Once target pressure was achieved, blood flow parameters were similar to non glaucomatous eyes.

Conclusions: Blood flow in retrobulbar vessels is reduced among glaucomatous eyes as compared to the normal population. Once target pressure is achieved, blood flow parameters become similar to non glaucomatous eyes suggestive of improved blood flow as a function of reduced IOP. Colour Doppler imaging is not found to be reliable for measuring blood flow in SPCA. Role of RI as a true measure of resistance to blood flow is unclear.

Key Words: Colour doppler imaging, End diastolic velocity (EDV), Peak systolic velocity (PSV), Primary open angle glaucoma, Resistivity index (RI), Retrobulbar blood flow.

INTRODUCTION

With the changed definition of glaucoma, raised intraocular pressure (IOP) is now recognized as one of the main risk factors for primary open angle glaucoma (POAG). The reports from some population based surveys in the US, Europe and Asia¹⁻³ suggest that primary open angle glaucoma (POAG) is associated with alterations in ocular blood flow. These observations support the idea that the eye being treated for glaucoma could possibly be a part of wider systemic dysfunction, particularly of blood flow regulation. This hypothesis is further backed up by observation of progression of disease in certain patients despite the IOP control.⁴

Colour Doppler imaging (CDI) has been widely used in glaucoma to study the alteration in retrobulbar hemodynamics and vascular effects of its treatment. However, there is large quantum of variation among different studies as to which vessels have maximum reduction in velocities of blood flow among patients of POAG.⁵⁻⁷ Moreover, the studies have failed to conclusively say whether reduction in blood flow is a function of raised IOP or is an independent factor contributing to the development of glaucomatous changes in the optic nerve⁸⁻¹³

The present study has been performed to study the retrobulbar blood flow among patients of

POAG using colour doppler imaging and compare these parameters with normal controls and also to assess the effect of IOP control on these blood flow parameters.

MATERIALS AND METHODS

Following approval of the study protocol from the Department and Institutional review board, forty three patients suffering from POAG and 30 healthy matched controls were included. All subjects were asked to sign a written informed consent and underwent a comprehensive ophthalmologic examination. Automated perimetry was performed using Humphery's Field Analyser (HFA-II model 750).

Inclusion criteria for the POAG group were gonioscopically open angles with characteristic optic disc appearance and visual field defects. Depending upon the status of visual fields, the POAG patients were graded into early, moderate and advanced by following the HODAPP Classification based on mean deviation (MD) and additional criteria.¹⁴ Target pressure was then calculated as given in World Glaucoma Association (WGA) guidelines for surgical trials¹⁵ which we extrapolated to this medical trial. The exclusion criteria included normal tension glaucoma (NTG), patients on systemic vasodilators,

uncontrolled hypertension, any ischemic ocular disorder like retinal artery/ vein occlusion, diabetic retinopathy, Eale's disease, myopia of 5D or more, history of glaucoma surgery or any retinal/ optic nerve pathology which could result in visual field defects. Thirty age and sex matched controls were included who had neither POAG nor any of the exclusion criteria.

Retro bulbar blood flow was measured using ultrasound machine made by Philips (Philips HD 11 Ultrasound System, Koninklijke Philips Electronics N.V.). This non-invasive method is based on the back-scattering of ultrasound by the formed elements in the blood vessels. Doppler effect results in frequency shifts, the measurement of which helps to assess blood velocity. Peak systolic flow velocity (PSV) and end diastolic flow velocity (EDV) of the arteries were measured using a 7.5-MHz probe with a pulsed Doppler device in the ophthalmic artery (OA- Fig. 1), central artery of retina (CRA-Fig. 2), and short posterior ciliary arteries (SPCA-Fig. 3).⁷ Colour Doppler imaging was done in lying position with legs uncrossed to avoid influences on venous return. The patients were requested to look straight and the eyelids were kept closed. The trained examiner was seated behind the head of patient while the base of the examiner's hand rested on the patient's forehead, with a finger placed on the patient's cheek. Acoustic coupling gel was applied to provide adequate contact between the probe and skin. The probe was positioned on the closed upper eyelid while avoiding mechanical force on the eyeball as this might increase intraocular pressure thereby changing the perfusion pressure. The anatomy of the eye followed by that of the optic nerve head were identified using the gray scale images in the B-scan mode. Colour Doppler was used to visualize the flow within the vessels and allowed for identification of the appropriate vessels. Care was taken to place the sample volume in the centre of the vessel and to set the angle parallel to the vessel to account for the Doppler angle. In order to obtain measurements that are reliable and reproducible, the specific locations conventionally chosen for measurement, while doing CDI, were used.¹⁶ It is not possible to do independent measurement of central retinal artery (CRA) and vein, using CDI, as they lie close together while passing through the middle of optic nerve. The nasal and temporal short posterior ciliary arteries (NPCA and TPCA) are located on each side of the optic nerve and need to be measured at a position that is close to the optic nerve. It should also be as anterior as possible to avoid receiving noise from the choroid. Colour Doppler imaging could not distinguish individual short posterior ciliary vessels. Therefore, the obtained waveform represented the mass effect produced by a bundle of vessels rather than from individual ciliary vessels. The ophthalmic artery (OA)

lies deep in the orbit. Like in other studies, the parameters of this vessel were measured on the nasal side of the optic nerve, soon after it crossed the optic nerve.

The resistivity index was then calculated as $PSV - EDV / PSV$. All subjects underwent CDI after diagnosis. In POAG patients, anti-glaucoma therapy was initiated and IOP was taken every two weeks till target IOP was achieved and maintained for a period of one month. Following two weeks after achievement of target pressure, provided it was maintained during this period, a repeat CDI was done. Target pressure could be achieved, with medical management, in all subjects recruited in this study and none of the cases were excluded or dropped during the period of study.

STATISTICAL ANALYSIS

For comparison of blood flow of retrobulbar vessels between cases and controls, an independent t-test was applied. To compare retrobulbar blood flow before and after treatment, paired t-test was applied. In patients with field defects present in only one eye, the other healthy eye was excluded from the analysis. In order to find out any inter-ocular difference in ocular blood flow based on the severity of glaucoma, patients with difference in severity of glaucoma in the two eyes were taken up for statistical analysis. A one-way ANOVA was applied to compare the blood flow between early, moderate and advanced glaucoma patients. Statistical evaluations were performed by running the SPSS for Windows (Release 20.0, SPSS, Chicago, IL). P values of less than 0.05 were regarded as statistically significant.

RESULTS

Demographic characteristics and baseline intraocular pressure (IOP) of patients and healthy subjects are given in Table 1. No significant differences between the cases and controls were observed in terms of age and sex distribution. As expected, IOP was higher in patients with POAG than in healthy subjects ($P < 0.0001$; Table 1).

Significantly lower PSV and EDV ($p < 0.05$) were observed in OA and CRA among POAG patients than in the control group. No statistically significant difference in RI was noted between glaucomatous and healthy subjects. Also, there was no statistically significant difference in any blood flow parameters in SPCA between the two groups. On achieving target pressure there was increase in PSV and EDV in both OA & CRA and it was comparable to that of healthy controls (Table 2).

In patients with asymmetric glaucoma ($n=21$), no significant difference in blood flow parameters in the three vessels was found in eyes with early, moderate and advanced glaucoma (Table 3). However, there was statistically significant

improvement in retrobulbar blood flow in terms of PSV in all three vessels and RI in OA in both early and moderate cases after achieving target pressure. Resistivity index in SPCA was also reduced

significantly upon treatment only in early cases. No statistically significant improvement in blood flow was found in advanced category (Table 4).

Table 1: Baseline characteristics of patients and healthy subjects

Parameters	POAG (N=43)	Controls (N=30)	p- Value
Sex (Male/ Female)	23/20	16/14	0.99
	MEAN±SD	MEAN±SD	
Age (Years)	68.4±8.5	68.1±8.6	0.87
IOP (mmHg)	26±2.3	15.3±2.1	<0.0001
OA-PSV	26.8±7.6	30.4±4.8	0.02
OA-EDV	5.9±2.6	7±2.7	0.05
OA-RI	08. ±0.1	0.8±0.1	0.53
CRA-PSV	12.4±3.2	13.8±2.5	0.04
CRA-EDV	4.1±1.6	5.0±1.9	0.02
CRA-RI	0.7±0.1	0.7±0.1	0.65
SPCA-PSV	13.6±3.8	14.6±2.8	0.2
SPCA-EDV	5±2.9	5.2±3.1	0.7
SPCA-RI	0.6±0.1	0.6±0.1	0.5

IOP- intraocular pressure, OA-ophthalmic artery, CRA-central retinal artery, SPCA- short posterior ciliary artery, PSV-peak systolic velocity, EDV- end diastolic velocity, RI- resistivity index and SD- standard deviation.

Table 2: Retrobulbar blood flow velocities of the patients with open angle glaucoma before and after achieving target pressure

Parameters	Poag (baseline)	Poag(after treatment)	P-value
	MEAN ±SD	MEAN ±SD	
IOP (mmHg)	26±2.3	15.2 ± 2.1	<0.0001
OA-PSV	26.8 ± 7.6	31 ± 7.3	<0.001
OA-EDV	5.4± 2.9	6.7 ± 2.9	<0.001
OA-RI	0.8 ± 0.1	0.7± 0.1	0.02
CRA-PSV	12.4±3.2	13.6±3.2	0.03
CRA-EDV	4.2 ± 1.5	4.6 ± 2.1	0.1
CRA-RI	0.7 ± 0.1	0.7 ± 0.1	0.3
SPCA-PSV	13.6±3.8	15.5±3.8	0.001
SPCA-EDV	5±2.9	5.9±2.9	0.001
SPCA-RI	0.6±0.1	0.6±0.1	0.3

IOP- intraocular pressure, OA-ophthalmic artery, CRA-central retinal artery, SPCA- short posterior ciliary artery, PSV- peak systolic velocity, EDV- end diastolic velocity, RI- resistivity index and SD- standard deviation

Table 3: Retrobulbar blood flow velocities in eyes with early, moderate and advanced glaucoma before and after treatment

Parameters	p-value of comparison among early, moderate and advance glaucoma	p-value of comparison among early, moderate and advance glaucoma
	Before Treatment	After Treatment
OA- PSV	0.99	0.89
OA -EDV	0.34	0.78
OA -RI	0.24	0.46
CRA- PSV	0.8	0.6
CRA -EDV	0.66	0.67
CRA -RI	0.75	0.96
SPCA -PSV	0.44	0.83
SPCA -EDV	0.45	0.2
SPCA -RI	0.21	0.14

OA-ophthalmic artery, CRA-central retinal artery, SPCA- short posterior ciliary artery, PSV- peak systolic velocity, EDV- end diastolic velocity and RI- resistivity index

Table 4- A comparison of retrobulbar blood flow parameters before and after treatment in early, moderate and advanced cases of glaucoma

Parameter	Early glaucoma (n = 19)		P value	Moderate glaucoma (n=17)		P value	Advanced (n= 6)		P value
	Before Tt (M+/- SD)	After Tt (M+/-SD)		Before Tt (M+/-SD)	After Tt (M+/-SD)		Before Tt (M+/-SD)	After Tt (M+/-SD)	
OA-PSV	27.9±7.6	31.6±7.3	0.006	28.2±7.2	30.5±8.1	0.05	28.0±4.7	30.6±4.5	0.3
OA-EDV*	5.5	6.9		4.9	6.2		4.3	5.3	
OA-RI	0.8±0.07	0.7±0.1	0.02	0.8±0.1	0.7±0.1	0.03	0.9±0.06	0.8±0.1	0.1
CRA-PSV	11.8±3.2	13.5±3.2	0.007	11.3±2.7	13.2±1.4	0.001	11.1±3.4	12.2±2.5	0.3
CRA-EDV	4.1±1.8	4.3±1.9	0.6	3.7±1.2	4.0±1.4	0.1	3.8±1.1	3.6±0.8	0.8
CRA-RI	0.7±0.1	0.7±0.1	0.9	0.7±0.1	0.7±0.1	0.5	0.6±0.1	0.7±0.1	0.3
SPCA-PSV	14.1±3.5	15.7±2.6	<0.001	13.6±4.1	15.0±3.1	0.05	16.0±5.9	15.5±6.6	0.8
SPCA- EDV*	4.4	6.3		3.5	4.3		3.8	4.2	
SPCA-RI	0.7±0.1	0.6±0.1	0.04	0.7±0.1	0.6±0.1	0.1	0.7±0.1	0.7±0.1	0.6

OA-ophthalmic artery, CRA-central retinal artery, SPCA- short posterior ciliary artery, PSV- peak systolic velocity, EDV- end diastolic velocity, RI- resistivity index, M-mean and SD- standard deviation. (*EDV values of OA and SPCA did not follow normal distribution curve, hence Wilcoxon Signed Rank test applied).

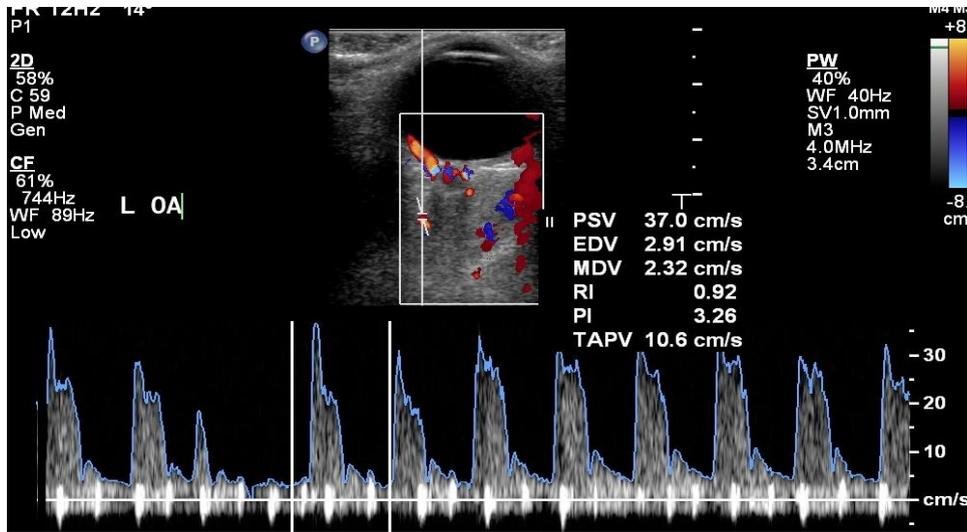


Fig. 1: Colour Doppler image of a patient of glaucoma showing (A) the vessels and (B) the corresponding spectral waveforms for the ophthalmic artery (OA)

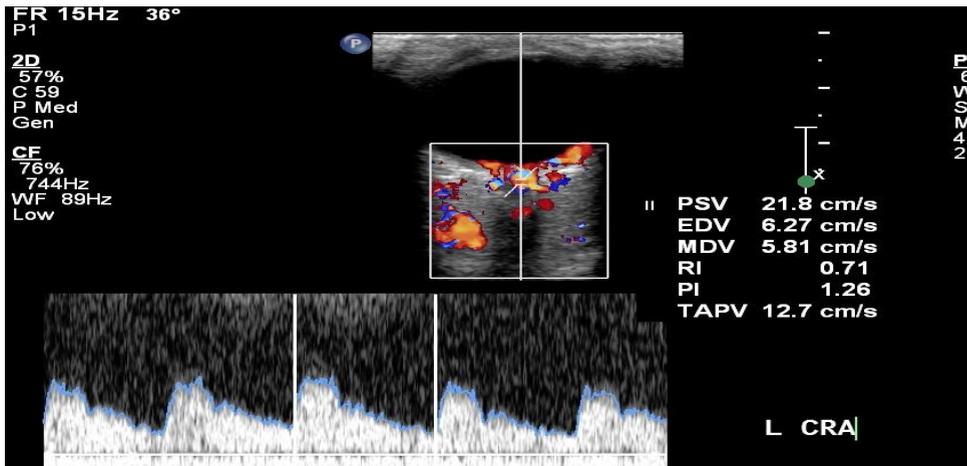


Fig. 2: Colour Doppler Image of a patient of POAG showing (A) the vessels and (B) the corresponding spectral waveforms for the central retinal artery (CRA)

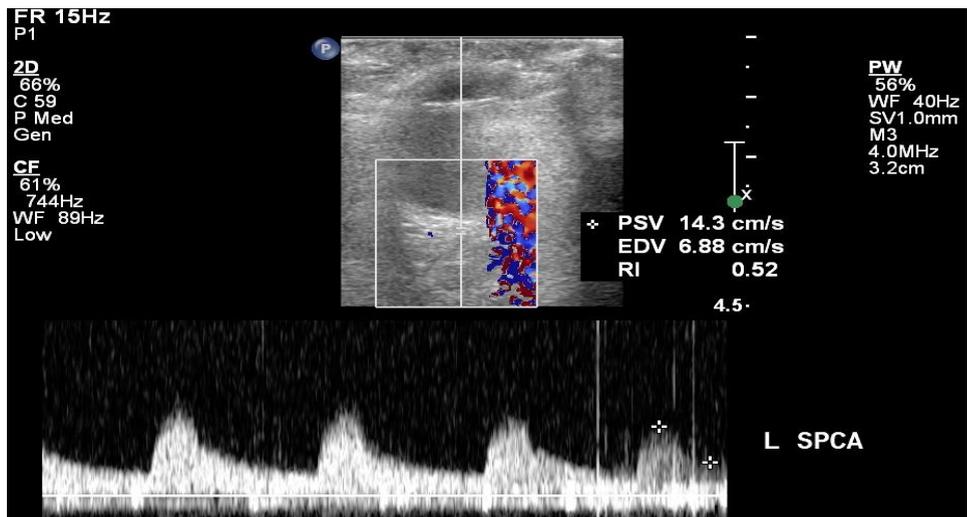


Fig. 3: Colour Doppler image of a patient of glaucoma showing (A) the vessels and (B) the corresponding spectral waveforms for the short posterior ciliary artery (SPCA)

DISCUSSION

A number of studies have been published reporting various aspects of retro bulbar blood flow in patients with various types of glaucomas. Most of these studies have reported that blood velocities are lower and resistivity index is higher in patients with primary open angle glaucoma compared to normal population.¹⁷⁻²⁰

Present study observed statistically significant lower blood flow velocities; both mean Peak Systolic Velocity (PSV) and mean End Diastolic Velocity (EDV) in Ophthalmic Artery (OA) and in Central Retinal Artery (CRA) in 43 untreated patients of POAG compared to normal controls. Similar to our outcome, Januleviciene et al observed statistically significant difference in mean EDV in ophthalmic artery and mean PSV in the central retinal artery between the OAG subjects and the healthy control group.¹² Our findings are also supported by similar studies conducted by Akarsu et al²¹ who reported decreased EDV in all three vessel. Similarly, Brinci et al²² reported an association of decreased flow velocity and increased resistivity index in retro bulbar vasculature of patients suffering from primary open angle glaucoma. However, there is large quantum of variation among different studies as to which vessels have maximum reduction in blood flow velocities in patients of POAG.

In the above mentioned clinical studies, besides reduction in blood flow velocities, increased RI has been reported in all the three vessels. Polska et al, in an experimental study, reported that CDI assessed RI in central artery of retina does not correspond to the actual resistance in retinal vascular.²³ Less data has been published on the reliability of RI in reference to ocular vessels. In reference to retro bulbar vessels, the dependence of RI on the amplitude of pulse pressure has also been reported in certain studies.²⁴⁻²⁶ A reduction in pulse pressure amplitude induced by physiological stimuli was reported to be associated with a decrease in the RI in the OA as well as in posterior ciliary arteries (PCAs).²⁶ In our clinical study, no statistically significant difference was noted in RI in any of the three vessels between POAG cases and controls. Thus concluding that resistivity Index does not correlate with the vascular resistance in ophthalmic artery, central retinal artery or short posterior ciliary arteries. Thus, these findings correlate more with experimental studies and less with the clinical studies mentioned earlier.^{21, 22}

In our study, no statistically significant difference was observed in any of the blood flow parameters among SPCA between cases and controls. Some of the studies have emphasised the importance of altered blood flow parameters in short posterior ciliary arteries in primary open angle glaucoma and its progression.^{21,22,27} Among posterior ciliary arteries

because of small size, tortuous course and uncertain number of vessels within the probing volume, there is high possibility of measurement errors of blood flow parameters. Secondly, there being a number of vessels, study of blood flow by Colour Doppler Imaging is not technically feasible in each individual vessel and the obtained waveform represents the mass effect produced by a group of vessels and not from individual ciliary vessels.

We have observed a statistically significant improvement in blood flow parameters in all three blood vessels following the achievement and maintenance of target pressure in patients of POAG, suggestive of improvement in retro bulbar blood flow as a function of reduced intraocular pressure (IOP). These results are consistent with the results from previous studies.²⁸⁻³⁰

CONCLUSIONS

The present study concludes that there are reduced blood flow velocities; both mean peak systolic velocity (PSV) and mean end diastolic velocity (EDV) in ophthalmic artery (OA) and in central retinal artery (CRA) among patients of primary open angle glaucoma. These blood flow parameters come to normal once the intraocular pressure (IOP) reaches target IOP suggesting that reduced retrobulbar blood flow is probably a function of raised IOP and not an independent factor in the causation of glaucomatous damage. No conclusions could be drawn for short posterior ciliary arteries (SPCA) probably because they have small size, tortuous course and uncertain number of vessels within the probing volume which leads to high possibility of measurement errors of blood flow parameters. Furthermore, there being a number of vessels, study of blood flow by colour doppler imaging is not technically feasible in each individual vessel and the obtained waveform represents the mass effect produced by a bundle of vessels rather than from individual ciliary vessels. Like experimental studies done earlier, our clinical study, has found that resistivity index does not correlate with the vascular resistance in ophthalmic artery, central retinal artery or short posterior ciliary arteries as there is no statistically significant difference noted in RI in any of the three vessels between the cases and controls.

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