Research Article
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Doppler ultrasonography of ocular blood flow in non-glaucoma versus primary open angle glaucoma subjects at the university of Nigeria teaching hospital, Enugu

Abstract

Purpose: To evaluate and compare the ocular blood flow in non-glaucoma versus primary open-angle glaucoma (POAG) subjects attending the ophthalmic clinic of University of Nigeria Teaching Hospital (UNTH) Enugu using Doppler ultrasonography.

Methods: A cross-sectional comparative study was adopted. Fifty-Eight POAG and 58 non-glaucoma subjects were recruited. Information on their socio-demographic and clinical profiles was obtained via an interviewer-administered questionnaire. Ocular Doppler Imaging was performed on all the Subjects. Peak systolic volume, End diastolic volume, mean flow velocity and Resistive Index (RI) of the central retinal artery and ophthalmic artery were recorded. Data were analysed using the SPSS version 21. Person correlation was used to determine the relationship between the Doppler indices and demographic and clinical variables. The level of significance was at $p < 0.05$.

Results: The subjects were mainly males, 71(61.7%), with an age range of 40 to 79 years. The POAG Subjects lived with glaucoma for 5.57±4.2 years, and mainly on medical treatment 52(89.7%) with beta-blockers and prostaglandin analogues. The RI was significantly higher (p=0.01) in POAG subjects. A significant positive relationship (P = 0.014) was observed between RI and intraocular pressure (IOP) of the POAG subjects.

Conclusion: In POAG subjects, RI was significantly higher; as the IOP increased there was an increase in RI translating to a sub-optimal ocular blood flow. Interventions aimed at modifying the RI would therefore be synergistic with IOP lowering measures. Additionally, RI assessment may offer a new target for glaucoma case finding.

Keywords: ocular blood flow, glaucoma, doppler indices, black population

Volume 13 Issue 2 - 2023

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Received: May 15, 2023 | **Published:** May 26, 2023

Introduction

Globally, glaucoma is the leading cause of avoidable, irreversible blindness, affecting about 64.3 million people, with a prevalence of 3.54% in those aged between 40-80 years.[1] The prevalence of POAG is highest in Africa (4.2%).[1] In Nigeria, it accounted for 16.7% of blindness and is the leading cause of functional low vision.[2] The mechanisms underlying the development and progression of glaucoma remain uncertain.[3] Several risk factors have been implicated with IOP being the only modifiable risk factor. However, it has become increasingly clear that blood supply compromise also plays a significant role in glaucomatous optic neuropathy.[4] Despite the various current approaches to glaucoma treatment aimed at maintaining target intraocular pressure, there are still documented evidence of progressive optic disc cupping and visual field loss within a normal range of intraocular pressure.[5] Consequently, management of glaucoma beyond IOP control has been proposed.[6]

Retinal blood flow assessment using Doppler ultrasonography has been investigated by several studies.[7–12] Compromised ocular blood flow was observed in eyes with POAG in Canada,[7] Europe,[8,9] Asia[10] and elsewhere in Nigeria.[11,12] However, the few Nigerian studies[11,12] were among the south-western population. None has been conducted in the South-east, which harbours predominantly the ethnic Igbos with the highest prevalence (7.77%) of glaucoma in Nigeria[13] and a risk factor for glaucoma blindness.[14] This study, therefore, sought to investigate the possible variations in the ocular blood flow to the optic nerve head in POAG and non-glaucomatous subjects among Igbo ethnic groups within Southeast Nigeria. It is hoped that findings from this study would contribute to the management guideline for glaucoma and may offer a new target for glaucoma case finding and treatment in the study area and elsewhere with similar settings.

Study area- The study was conducted at Ophthalmology and Radiology Departments, University of Nigeria Teaching Hospital (UNTH), Ituku Ozalla, Enugu State, South-Eastern Nigeria. UNTH serve mainly the Enugu State population and the other South-Eastern States, as well as South-South Nigeria and beyond.

Study population- This comprised POAG and non-glaucoma subjects, who attended the Eye clinic at UNTH from January to June 2019.

Study design- This was a cross-sectional, descriptive, prospective and comparative study involving 58 consecutive consenting POAG patients and 58 non-glaucoma subjects, who met with the inclusion criteria. Information on their socio-demographic and clinical profiles was obtained via an interviewer-administered questionnaire.

Inclusion criteria- for POAG subjects- Patients who are 40 years and above, clinically diagnosed with POAG by the glaucoma specialists and with transparent ocular media. Inclusion criteria for non-glaucoma subjects- Patients who are 40 years and above, with simple refractive errors or presbyopia with transparent ocular media and no other ocular pathology who consented to participation.

Exclusion criteria-patients with ocular congenital abnormalities, retinopathies, on systemic medication affecting blood flow, with cataracts or corneal opacity precluding posterior segment assessment. Patients who did not give consent, aged less than 40 years. Patients with cardiovascular diseases such as carotid occlusive disorders, atherosclerosis, hypertension, Diabetes mellitus. Glaucoma suspects and all patients clinically diagnosed with secondary glaucoma and angle-closure glaucoma.

Minimum sample size determination

The sample size for each arm of this study was determined with the following formula[15]

$$S = \frac{2\alpha^2 \left(Z\beta + Z\alpha 2 \right)^2}{\left(d_1 - d_2 \right)^2}$$

$$Difference^2 = \left(d_1 - d_2 \right)^2$$

S=Minimum sample size of each of the study groups.

α = Probability of making type one error.

β = Probability of making type two error

Zα2 = level of significance of type one error probability; determined from a statistical table based on the value of the level of significance α; for this study was set at 0.05, the ninety-five (95%) confidence interval =1.96 for a two-tailed test(standard normal deviate)

Zβ = type two error probability corresponding to standard normal deviate for a stated power of the study to detect a significant difference.

For this study, a power of 90 was used therefore Zβ = 1.28 σ = 2, Standard deviation of the outcome variable in glaucoma subjects. d1-d2 = difference in the means of glaucoma and normal subjects.21

Adding 10% attrition (5.22), the minimum sample size = 57.39.

Therefore, a total of 116 persons comprising 58 glaucoma and 58 normal subjects were recruited as the study participants.

Sampling technique: To obtain the required sample size, consecutive enrolment was used. All consecutive, consenting patients who met the inclusion criteria were enrolled on the study until the estimated sample size was obtained for the two groups.

Ethical approval: The study was conducted with ethical approval from the Institutional review board of the University of Nigeria teaching Hospital Enugu (certificate number: NHREC/05/01/2008B-FWA00002458-1RB00002323). All procedures were performed in line with 1964 Helsinki Declaration for human subjects (as amended).

Study procedure: subjects diagnosed with POAG were evaluated for eligibility and recruited into the study, as well as the non-glaucoma subjects. After obtaining consent, the pre-tested, structured questionnaire comprising of two sections:- socio-demographic and clinical sections was administered by the researchers. Thereafter, each subject had the following examinations: Intraocular pressure was measured using a Goldman applanation tonometer. The prism was disinfected with isopropyl alcohol 70% rinsed in sterile water and wiped dry with a clean swab. After checking the graduation and setting the calibrated dial to 10mmHg, the patient was seated comfortably at the slit-lamp, a local anaesthetic drop was instilled in the lower fornix of the conjunctiva. After a while, the tear-film was stained with a fluorescein strip. With the patient looking straight ahead, the prism was gradually placed to rest gently on the centre of the patient's cornea, the calibrated dial on the tonometer was turned clockwise until the inner edges of the semi-circles in the prism head were seen to touch. The reading on the dial was then noted and recorded.

Ocular Doppler ultrasonography of the ophthalmic and central retinal arteries was done using the Nemio XG ultrasound machine (Model no.SSA-580A) with an 11 MHz curvilinear transducer and Doppler facility at the Radiology department. The subject was placed in a supine position on a couch, with gaze directed at a marked spot on the ceiling. With the eyelids closed, and the gaze maintained, the power level of the ultrasound machine was set at 10% which is equivalent to 16- 1 mw/cm2, the safety limit. The ultrasound transducer was applied to the closed eyelids using a coupling gel (K-Y jelly). The right eye of the subjects in both groups was used for the study. Greyscale imaging was performed routinely in every subject to obtain an overview of the orbital anatomy. Axial and sagittal planes were included during the real-time scanning. Pulsed Doppler ultrasonography was performed with the gain optimized such that colour would be seen within the vessels without any colour artefacts, allowing the detection of low velocities. The sample volume depth was set at 40mm when imaging the ophthalmic artery (OA).

The Doppler sample gate of 2mm was placed at the centre of the detected vessels to image the spectral pattern. As orbital vessels were frequently parallel to the ultrasound beam, an angle correction of 600 was used when needed and the colour box steering would sometimes be required to attain this. A low wall filter setting was used. To examine the OA, the sample volume was oriented nasally and superior to the optic nerve, as the OA is lateral to and abuts the visible hypo reflective stripe representing the nerve, while the central retinal artery (CRA) was imaged in the shadow of the optic nerve, the sample was placed about 3mm behind the surface of the optic disc. The Peak Systolic Velocity (PSV) and End Diastolic Velocity (EDV) values were obtained by taking the velocity reading at the peak of the spectral wave pattern and that at the wave trough, respectively. Three readings of each artery were obtained and the average is taken to minimize intra observer error.

Doppler ultrasonography indices

i. Peak systolic velocity (PSV) is the maximum peak systolic velocity (PSV) normal = 32.35 ± 10.41 for OA and 9.4 ± 2.2 for CRA.

ii. Mean flow velocity (MFV) is the mean of the peak frequency, peaks envelope which outlines all the frequency peaks forming a single signal in one cardiac cycle, normal is 16.35 ± 2.94

iii. End Diastolic flow velocity (EDV) is the minimum flow velocity at the end of the diastolic phase before the next cardiac cycle, (EDV) normal = 8.19 ± 3.64 for OA and 2.0 - 4.0 for CRA.

iv. Resistive Index (RI) is calculated as the Porcelouts[16] ratio for OA and CRA as (PSV-EDV)/PSV and normal is 0.73.

Data management- Data was coded and analysed using the statistical package for social sciences version 20. The descriptive statistics – frequency, percentage, mean, range and standard deviation were used to summarise the data. Means of continuous variables were compared using a student t-test between the two groups. Pearson correlation was used to test the relationships between the Doppler indices and IOP of the two groups – POAG and non-glaucoma subjects, as well as between indices and demographic variables. A p-value <0.05 was regarded as statistically significant.

Results

The participants have mainly married males, civil servants and traders, with at least primary school education within the age range of 40 to 79 years. There was no significant difference in the socio-demography of the two groups, Table 1.

The POAG subjects lived with glaucoma for 5.57±4.2 years and were mainly on medical treatment with beta-blockers and prostaglandin analogues (Table 2). The MFV and RI were observed to be significantly higher in POAG subjects while comparing the Doppler indices between the two groups, (Table 3). There was no difference in PSV and EDV between the two groups (Table 3). There was a significant positive relationship between the IOP and RI of the POAG participants (P = 0.014), which implied that as the IOP increases, there is an expected increase in the RI of the POAG subjects (Table 4).

There was no significant gender difference in the Doppler indices, IOP and BP between the two groups, table 5 and there was no significant relationship between age and all the variables in the Doppler indices, IOP and BP in both study groups, (Table 6).

Table 1 Socio-demographic characteristics of the non-glaucoma (N) and glaucoma (G)

Demographic characteristics	N=58	G=58	Total=116	Chi-Square	df	P-value
Age group						
40 – 49yrs	18 (31.0)	15 (25.9)	33 (28.4)	1.46	4	0.834
50 – 59yrs	20 (34.5)	17 (29.3)	37 (31.9)			
60 – 69yrs	10 (17.2)	12 (20.7)	22 (19.0)			
70 – 79yrs	10 (17.2)	14 (24.1)	24 (20.7)			
Gender						
Male	37 (64.9)	34 (58.6)	71 (61.7)	0.327	1	0.568
Female	21 (36.2)	24 (41.4)	45 (38.8)			
Marital status						
Single	1 (1.7)	3 (5.2)	4 (3.4)	4.185	4	0.382
Married	47 (81.0)	49 (84.5)	96 (82.8)			
Divorced	5 (8.6)	1 (1.7)	6 (5.2)			
Separated	1 (1.7)	2 (3.4)	3 (2.6)			
Widowed	4 (6.9)	3 (5.2)	7 (6.0)			
Educational level						
Primary	19 (32.8)	17 (29.3)	36 (31.0)	2.731	3	0.435
Secondary	12 (20.7)	15 (25.9)	27 (23.3)			
Tertiary	9 (15.5)	14 (24.1)	23 (19.8)			
None	18 (31.0)	12 (20.7)	30 (25.9)			
Occupation						
Civil servant	15 (25.9)	15 (25.9)	30 (25.9)	5.687	7	0.577
Trading	12 (20.7)	13 (22.4)	23 (21.6)			
Farming	3 (5.2)	6 (10.3)	9 (7.8)			
Artisan	4 (6.9)	6 (10.3)	10 (8.6)			
Unemployment	1 (1.7)	3 (5.2)	4 (3.4)			
Driver	5 (8.6)	2 (3.4)	7 (6.0)			
Retiree	15 (25.9)	9 (15.5)	24 (20.7)			
Housewife	3 (5.2)	4 (6.9)	7 (6.0)			
Tertiary	9 (15.5)	14 (24.1)	23 (19.8)			
None	18 (31.0)	12 (20.7)	30 (25.9)			
Occupation						
Civil servant	15 (25.9)	15 (25.9)	30 (25.9)	5.687	7	0.577
Trading	12 (20.7)	13 (22.4)	23 (21.6)			
Farming	3 (5.2)	6 (10.3)	9 (7.8)			
Artisan	4 (6.9)	6 (10.3)	10 (8.6)			
Unemployment	1 (1.7)	3 (5.2)	4 (3.4)			
Driver	5 (8.6)	2 (3.4)	7 (6.0)			
Retiree	15 (25.9)	9 (15.5)	24 (20.7)			
Housewife	3 (5.2)	4 (6.9)	7 (6.0)			

The POAG subjects lived with glaucoma for 5.57±4.2 years and were mainly on medical treatment with beta-blockers and prostaglandin analogues.

Table 2 Ocular profile of the POAG patients

Ocular Profile		Frequency
Types of treatment		
Medical	52	89.70%
Surgical	6	10.30%
Types of Surgical treatment		
Trabeculectomy	6	5.20%
Others	0	0.00%
*Drugs received		
Beta-blockers	54	61.40%
Alpha -2 agonist	2	2.30%
Prostaglandin analogues	27	30.70%
Systemic Carbonic anhydrase inhibitor	5	5.70%
Years of living with Glaucoma		
0 – 5years	31	53.40%
6 – 10years	18	31.00%
11 – 20 years	7	12.10%

*multiple responses.

The mean IOP in POAG subjects (17.8 ±3.4mmHg) was significantly higher than in non-glaucoma subjects (15.2 ±3.3mmHg), p = 0.000.

Table 3 Comparison of the doppler ultrasound indices among the non-glaucoma (N) and glaucoma (G) subjects

	G	N		
Doppler Indices	Mean ±SD	Mean ±SD	t-value	P-value
PSV(cm/s)	39.99±17.67	36.56 ±14.98	-1.128	0.262
EDV(cm/s)	15.21±8.18	15.82±8.95	0.379	0.705
MFV(cm/s)	18.39±4.71	15.09±2.53	4.702	0.000*
RI(cm/s)	0.92±0.18	0.85±0.110	-2.719	0.008*

• Significant. N= non- glaucoma subjects, G= glaucoma subjects

Table 4 Correlation between IOP and other doppler indices of the two groups (N= non- glaucoma subjects, G= glaucoma

		N	G
Parameters	Test	IOP	IOP
PSV	Pearson correlation	0.037	0.042
	P-value	0.785	0.756
	N	57	57
EDV	Pearson correlation	0.076	-0.1
	P-value	0.574	0.459
	N	57	57
MFV	Pearson correlation	-0.007	0.113
	P-value	0.957	0.403
	N	57	57
RI	Pearson correlation	0.14	0.322
	P-value	0.299	0.014*
	N	57	57

Table 5 Gender differences in IOP, doppler indices and BP between the non-glaucoma (N) and glaucoma (G) subjects

	N	G						
Parameters	**Males**	**Females**	**T**	**P-value**	**Males**	**Females**	**T**	**P-value**
Average IOP	15.50±3.31	14.89±3.22	0.688	0.49	18.35±3.80	18.65±4.63	2620	0.794
PSV (cm/s)	40.32±18.85	39.52±16.23	0.168	0.867	39.48±14.58	31.48±14.46	2.051	0.05
EDV (cm/s)	15.09±7.96	15.40±8.64	-0.1444	0.886	16.68±8.90	14.79±9.03	0.763	0.449
PI (cm/s)	2.73±1.37	2.15±1.04	1.744	0.087	2.33±0.96	2.40±1.02	0.258	0.797
MFV(cm/s)	19.02±5.70	17.51±2.64	1.204	0.234	14.89±2.73	15.37±2.17	0.669	0.506
RI (cm/s)	0.93±0.20	0.91±0.13	0.49	0.626	0.86±0.12	0.82±0.09	1.307	0.197
Systolic BP (mm/Hg)	115.00±9.92	113.33±11.67	0.586	0.561	119.19±10.37	121.00±8.52	0.479	0.634
Diastolic BP(mm/Hg)	71.06±6.45	68.75±7.97	1.173	0.247	75.14±8.37	74.00±8.83	0.973	0.335
Sys/Dia	2.72±0.91	2.75±1.03	-0.106	0.916	2.65±0.79	2.45±0.68	0.688	0.494

N= Non- glaucoma subjects, G= Glaucoma subjects, sys= systolic, dia= diastolic.

Table 6 Correlation between age and IOP, doppler indices and BP of the non-glaucoma (N) and glaucoma (G) groups

		N	G
Parameters	**Test**	**Age (years)**	**Age (years)**
Average IOP	Pearson correlation	-0.092	-0.008
	P-Value	0.495	0.951
	N	57	57
PSV(cm/s)	Pearson correlation	0.057	-0.154
	P-Value	0.67	0.247
	N	58	58
EDV(cm/s)	Pearson correlation	0.066	-0.118
	P-Value	0.624	0.379
	N	58	58
PI(cm/s)	Pearson correlation	-0.081	0.049
	P-Value	0.545	0.714
	N	58	58
MFV(cm/s)	Pearson correlation	-0.22	0.1
	P-Value	0.097	0.455
	N	58	58
RI(cm/s)	Pearson correlation	0.121	0.001
	P-Value	0.366	0.995
	N	58	58
Systolic BP(mmHg)	Pearson correlation	0.118	0.239
	P-Value	0.379	0.071
	N	58	58
Diastolic BP(mmHg)	Pearson correlation	0.043	0.148
	P-Value	0.751	0.266
	N	58	58
Systolic/Diastolic	Pearson correlation	-0.08	-0.02
	P-Value	0.552	0.883
	N	58	58

N, non- glaucoma subjects; G, glaucoma subjects

Discussion

The participants have mainly married males within the age range of 40 to 79 years. These demographic characteristics are similar to a Nigerian study[11] Males from this study population sought eye care more than females, probably the male folk seems to be more economically empowered than females in the study environment. Appropriate public health measures and universal access to eye care should therefore be promoted by the stakeholders. The POAG subjects lived with glaucoma for 5.57±4.2SD years, and were mainly on medical treatment, with their mean IOP significantly higher than in non-glaucoma subjects. This ocular profile is similar to a study in Nigeria[11] but contrasts with the Canadian study[3] which studied the angle-closure glaucoma subjects as well.

Citation: Markson NO, Onwubiko SN, Zuadae NN et al. Doppler ultrasonography of ocular blood flow in non-glaucoma versus primary open angle glaucoma subjects at the university of Nigeria teaching hospital, Enugu. *Adv Ophthalmol Vis Syst.* 2023;13(2):58–63. DOI: 10.15406/aovs.2023.13.00441

In this study, while comparing the Doppler indices, there was no difference in PSV and EDV between the two groups. This contrasts with the reports of the south-western Nigerian studies[11,12] where these indices were significantly reduced in the POAG group. However, the RI which was significantly higher in POAG subjects, in this study agreed with their findings and other varied populations across the globe, North America, Europe, and Asia.

The Japanese study[17] found no difference in RI, probably because their study subjects were POAG and normal pressure glaucoma patients without a control group. The higher RI in POAG subjects implies sub-optimal blood flow to the optic nerve. The fact that RI is a ratio[16] an absolute value derived from PSV and EDV independent of the Doppler angle makes it a more useful index for comparison among studies. There was a significant positive relationship between the IOP and RI of the POAG participants, in this study. This was similar to the observations made elsewhere in Nigeria and Europe which suggests direct impedance to the ocular blood flow by elevated IOP. In consonance, Singh et al.[19] reported that when target pressure was achieved, the reduced ocular blood flow parameters in POAG subjects became similar to those of the non-glaucomatous eyes suggesting improved ocular blood flow as a function of reduced IOP.

In this study, there was no age and gender difference or relationship with the Doppler indices of the groups. Comparatively, indices suggestive of reduced ocular blood flow in males would have been expected in this study population, where the male gender is a documented risk factor for glaucoma blindness.[14] However, other studies did not explore this finding, precluding a robust discussion. Future studies should therefore investigate the influence of these variables on ocular blood flow.

Conclusion

The RI of the central retinal artery was significantly higher in POAG subjects and a significant positive relationship was observed between their RI and IOP. As the IOP increased there was an increase in RI translating to a sub-optimal ocular blood flow. Interventions aimed at modifying the RI would therefore, be synergistic with IOP lowering measures. Additionally, RI assessment may offer a new target for glaucoma case finding. Study strength and weakness: The study is the first to highlight the fact that RI assessment may offer a new target for glaucoma case finding among the Ibos, the ethnicity with the highest risk of glaucoma blindness in Nigeria. However, challenges with the cost of Doppler ultrasonography limited a larger sample size, which would have implied a better generalizability of the study results. In POAG subjects, RI was significantly higher; as the IOP increased there was an increase in RI translating to a sub-optimal ocular blood flow. Interventions aimed at modifying the RI would therefore be synergistic with IOP lowering measures.

Ethics approval

Ethical approval for the study was obtained from the Health Research and Ethics Committee of the University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu (NHREC/05/01/2008B-FWA00002458-1RB00002323). Research involving human participants: All procedures were performed in line with 1964 Helsinki Declaration for human subjects (as amended).

Acknowledgments

None.

Conflicts of interest

The authors declares that there are no conflicts of interest.

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