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EFFECTS OF VALSALVA MANOEUVER ON GLAUCOMA PATIENTS: STUDY OF VASCULAR HYPOTHESIS

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ABSTRACT

PURPOSE: The research was done to study the changes in Intraocular Pressure (IOP), Ocular Perfusion Pressure (OPP), and Ocular Blood Flow (OBF) which occur after doing Valsalva manoeuver, in patients of Primary Open Angle Glaucoma (POAG) and Ocular Hypertension (OHT) and to compare the above findings with healthy individuals.

METHODS: Three groups were studied: healthy controls (n=36), POAG not on medications (n=34) and OHT not on medications (n=27), with a total of 95 study subjects who underwent measurements of IOP, OPP and OBF pre and post Valsalva manoeuvre by colour doppler.

RESULTS: There was significant rise in IOP in all the groups ($p<0.001$), with POAG showing the highly significant rise as compare to all other groups. There was significant fall in OPP in POAG ($p=0.005$), OHT ($p=0.016$) and controls ($P=0.040$) but the change was small and insignificant in between the groups. OBF measurements, showed significant fall in retrobulbar arterial velocities ($p<0.001$) and rise in resistivity index ($p<0.001$) in all the groups. There was significant correlation between the rise in IOP and fall in OPP in POAG ($r= -0.41$, $p=0.019$). There was significant correlation in POAG between MD of Visual field and PSV of SPCA ($r=0.382$, $p=0.031$), EDV of SPCA ($r=0.740$, $p<0.001$) and RI of SPCA ($r= -0.445$, $p=0.011$).

CONCLUSION: The study showed that Valsalva manoeuvre has detrimental effects on IOP, OBF and MD of visual fields in patients of glaucoma and glaucomatous damage can be correlated with reduced OBF parameters and increased RI.

KEYWORDS : Colour dopper, Glaucoma, intraocular pressure, ocular blood flow, ocular perfusion pressure, Valsalva manoeuver

1. INTRODUCTION

Glaucoma is a family of multifactorial optic neuropathies characterized by loss of retinal ganglion cells (RGCs) leading to typical optic nerve head (ONH) damage and distinctive visual field defects. The well-established risk factor for glaucoma is elevated **Intraocular Pressure (IOP).**[1]

The primary target for slowing down the progression of disease is to control the IOP, but despite reducing IOP few patients keep on progressing. Several studies implicated vascular risk factors in the pathogenesis of glaucoma. This vascular hypothesis is based on the premise that abnormal perfusion and the subsequent ischemia of the ONH play a major role in the glaucomatous damage.[1]

The main blood supply of the Optic Nerve Head (Figure: 1) is from posterior ciliary artery circulation along with some contribution from retinal circulation.[2] Within the eye, **autoregulation** is defined as local vascular constriction or dilation causing vascular resistance to reciprocally increase or decrease, thereby maintaining a constant nutrient supply in response to perfusion pressure changes.[3] It is an attempt to keep blood flow constant despite changes in **ocular perfusion pressure (OPP).** A decrease in OPP may significantly decrease the **ocular blood flow (OBF)** in the absence of vascular autoregulation.[4]

Colour Doppler Imaging (CDI) is a noninvasive technique for testing ocular blood flow in retrobulbar vessels and its use dates back to the 1980s.[5] Accounting for its low cost, high reliability, repeatability and easy availability, this method has gained popularity in a short time.[5]

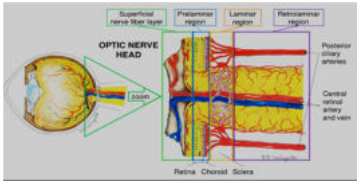


Figure 1: Anatomy and vascular supply of the optic nerve head (ONH). The ONH includes the superficial nerve fiber layer, the prelaminar region, the laminar region, and the retrolaminar region.[6]

The Valsalva manoeuver (VM) is performed by moderately exhaling against a closed airway. The VM is frequently performed during daily activities, including heavy lifting, vomiting, straining, forceful coughing, and sneezing. There are four phases to the Valsalva manoeuvre.[7] In the phase 1 of Valsalva, as the intrathoracic pressure rises, blood gets squeezed from aorta and there occurs a rise in arterial pressure. In phase 2, the raised intrathoracic pressure reduces the venous return which causes a short term fall in mean arterial pressure (MAP), but this fall in MAP is limited by reflex tachycardia and peripheral vasoconstriction. In phase 3, on release of glottis, the intrathoracic pressure drops which restores the venous return and the MAP rebounds rapidly. In phase 4, to counteract this rebound, there is a reflex bradycardia.

The original Valsalva manoeuver (VM) was first described by Mario Antonio Valsalva,[8] and the research method was then standardized by Levin, where subjects were asked to blow into a tube and to maintain a pressure of 40 mmHg for 10 s.[9,10] After further evaluation of the effects of varying the parameters, Benarroch et al. suggested use of 15 s strain phase during the VM.[11]

In normal subjects it has been shown that the pulsatile OBF is significantly reduced during Valsalva and is proportional to the rise in IOP.[12]

We designed this study to investigate the effect of the Valsalva manoeuvre on ocular blood flow in normal individuals, patients with primary open angle glaucoma and ocular hypertension and also to study the correlation of glaucomatous damage with the vascular insult detected through ocular blood flow.

2. METHODS

This is a hospital based cross sectional observational study.

2.1. PATIENTS

Three cohorts of individual attending Glaucoma Clinic of Department of Ophthalmology, GSVM Medical College and LLR Hospital,

Kanpur, Uttar Pradesh were recruited, POAG (n=32), OHT (n=27) and healthy control (n=36) on the basis of following definition. POAG were identified as patients with open anterior chamber angle, glaucomatous optic nerve head changes, visual field defect and an IOP of more than 21mmHg recorded on atleast two occasions. OHT as patients with open anterior chamber, with normal optic disc, normal visual fields and an IOP of more than 21mmHg. For controls, healthy volunteers with normal optic disc, normal visual fields, i.e., MD <-2.0 dB on HVF analyser and normal IOP were recruited.

Worse eye per patient was selected. Patients on antiglaucoma drugs, angle closure glaucoma, congenital glaucoma, secondary glaucoma, with history of any ocular trauma or eye surgery (except cataract surgery), with cardiovascular disorders and with history of any neurological disorder were excluded.

The study was approved by the ethical review committee (Institutional Review Board) of our own institution; Ref. No: EC/BMHR/2020/44, Dated: 17-09-2020; and was conducted in accordance with Good Clinical Practice within the tenets of the Helsinki's agreement. Each patient/subject was required to sign an informed consent statement before being enrolled into the study and prior to any study measurements being taken.

2.2. HISTORY & EXAMINATION

The patients were subjected to detailed history and comprehensive examination.

UCVA and BCVA were taken using Snellen's chart. Detailed slit lamp examination was done and angle of the anterior chamber was assessed by gonioscopy done using Sussman four mirror goniolens. Fundus examination was done by +90 D to observe any ONH changes.

IOP was measured using Applanation tonometer, Perkin's hand held tonometer was used to measure IOP in supine position.

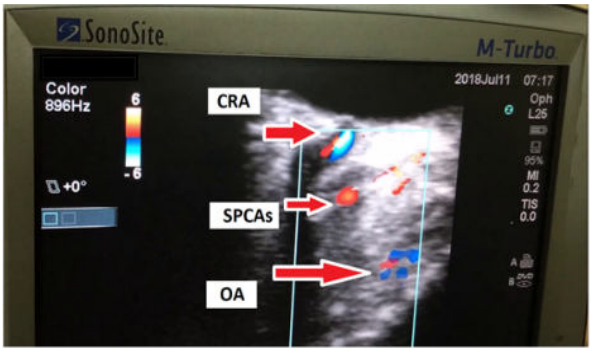


Figure 2: Pulsations of retrobulbur arteries as seen on CDI

OBF parameters were recorded via 13.5-MHz probe by colour doppler machine (Sonosite. Inc). Three retrobulbar arteries, namely, Central retinal artery(CRA), Ophthalmic artery(OA), and Short posterior ciliary artery(SPCA) were identified by their pulsations (Figure: 2) and ocular blood flow parameters, Peak Systolic Velocity(PSV), End Diastolic Velocity(EDV) and Resistivity Index(RI) was automatically calculated by the machine.

Visual fields, as predictor of glaucomatous damage, were assessed by Humphrey's Visual Field Analyser.

BP was recorded using mercury sphygmomanometer in supine position, for calculating mean arterial pressure (MAP) and OPP. OPP is given by formula **2/3(MAP-IOP)**, Where mean arterial pressure **(MAP)=Diastolic BP+[1/3(Systolic BP-Diastolic BP)]**

Then the subjects were asked to carry out Valsalva manoeuver. They were instructed to exhale forcibly with nose pinched closed through a mouth piece connected to an aneroid manometer to a pressure of 30-35 mm of Hg for 15 secs. The final readings for IOP, OPP and OBF were again recorded in supine position as previously described.

2.3. STATISTICAL ANALYSIS

Data was collected and enter in Excel Spreadsheet for statistical analysis. GraphPad InStat 3.1 of GraphPad software, Inc., California, U.S.A., was used for applying tests of significance. Paired 't' test was used to compare between two variables within the group. Two sample 't' test was used to compare between variables between the groups. Spearman's correlation coefficient was used to study association between variables. Probabilities are two-tailed and considered statistically significant if $p<0.05$.

3. RESULTS

A total of 95 subjects were enrolled in the study which included 32 diagnosed patients of POAG, 27 diagnosed patients of OHT and 36 healthy volunteers or controls.

Table 1 enlists the demographic data, and table 2 summarizes the average baseline parameters of the subjects.

Table 3,4 and 5 depict the changes in the baseline parameters post Valsalva manoeuver in patients of POAG, OHT and Controls.

In POAG, there was highly significant rise in post Valsalva IOP ($p<0.001$) along with PSV and EDV of CRA, SPCA, and OA ($p<0.001$). There was highly significant fall in RI of CRA, SPCA and OA ($p<0.001$) but only mildly significant fall in OPP ($p=0.04$).

In OHT and Controls, there was highly significant rise in post Valsalva IOP ($p<0.001$) along with PSV and EDV of CRA, SPCA, and OA ($p<0.001$). There was highly significant fall in RI of CRA, SPCA and OA ($p<0.001$) and significant fall in OPP ($p=0.005$, $p=0.01$).

There was highly significant correlation between the rise in IOP and fall in OPP in POAG, ($r = -0.41$, $p=0.019$), in OHT ($r = -0.48$, $p=0.012$) and in Control ($r = -0.51$, $p=0.002$).

Glaucomatous damage recorded as MD of Visual field was correlated with ocular blood flow parameters using Spearman rank correlation to detect any significant relationship between the two.

Chart 1 depicts the correlation between MD of visual field and EDV of SPCA in the form of scatter diagram.

In POAG, there was significant correlation between MD of Visual field and PSV of SPCA ($r = 0.382$, $p=0.031$), highly significant correlation between MD of Visual field and EDV of SPCA ($r = 0.742$, $p< 0.001$) and significant correlation between MD of Visual field and RI of SPCA ($r = -0.445$, $p=0.011$).

Table 1: Demographic Data

	CONTROL	POAG	OHT
AGE GROUP	**N=36**	**N=32**	**N=27**
• 41-50	19	17	14
• 51-60	15	13	12
• >60	2	2	1
SEX			
• MALES	20	18	19
• FEMALES	16	14	8

Table 2: Mean Baseline Characteristeic

	POAG (n=32)	OHT (n=27)	CONTROL (n=36)
VISUAL ACUITY (logMAR BCVA)	0.60±0.2 SD	0.25±0.12 SD	0.24±0.1 SD
MD VISUAL FIELDS (dB)	-6.56dB±1.88 SD	-1.48±0.42 SD	-1.45dB±0.40 SD
MEAN IOP (mmHg)	29.15±3.37 SD	28.91±3.35	15.57±2.04 SD
MEAN OPP(mmHg)	44.30±3.47 SD	45.34±4.92 SD	53.26±3.52 SD
OBF PARAMETERS			
• **PSV(CRA)**	10.54±2.36 SD	12.33±2.23 SD	11.26±5.40 SD
• **PSV (OA)**	31.17±4.00 SD	32.3±4.24 SD	33.49±6.41 SD
• **PSV (SPCA)** **(cm/sec)**	10.29±2.39 SD	16.03±3.64 SD	12.13±2.91 SD
• **EDV(CRA)**	3.36±0.95 SD	4.01±1.31 SD	3.70±0.84 SD
• **EDV(OA)**	8.23±1.94 SD	10.29±1.40 SD	10.51±2.85 SD
• **EDV(SPCA)** **(cm/sec)**	3.09±1.12 SD	4.71±1.04 SD	3.98±0.98 SD

• **RI(CRA)**	0.68±0.09 SD	0.67±0.08 SD	0.66±0.06 SD
• **RI(OA)**	0.74±0.06 SD	0.68±0.04 SD	0.67±0.11 SD
• **RI(SPCA)**	0.70±0.07 SD	0.7±0.04 SD	0.66±0.07 SD

Table 2: Changes In Iop, Opp And Obf In Poag Post Valsalva

PARAMETERS		PRE VALSALVA	POST VALSALVA	T-VALUE	P-VALUE	INFERENCE
IOP	MEAN	29.15	31.28	33.3	<0.0001	HIGHLY SIG.
	SD	3.37	3.37			
OPP	MEAN	44.3	43.73	2.998	0.0053	SIG.
	SD	3.47	3.05			
PSV(CRA)	MEAN	10.54	8.02	10.07	<0.0001	HIGHLY SIG.
	SD	2.35	1.72			
PSV(OA)	MEAN	31.17	27.63	19	<0.0001	HIGHLY SIG.
	SD	3.99	4.06			
PSV(SPCA)	MEAN	10.29	8.01	16.95	<0.0001	HIGHLY SIG.
	SD	2.39	2.71			
EDV(CRA)	MEAN	3.36	2.22	14	<0.0001	HIGHLY SIG.
	SD	0.95	0.78			
EDV(OA)	MEAN	8.23	6.62	16.84	<0.0001	HIGHLY SIG.
	SD	1.98	1.66			
EDV(SPCA)	MEAN	3.09	1.99	13.81	<0.0001	HIGHLY SIG.
	SD	1.12	1			
RI(CRA)	MEAN	0.68	0.72	7.53	<0.0001	HIGHLY SIG.
	SD	0.09	0.08			
RI(OA)	MEAN	0.74	0.76	11.3	<0.0001	HIGHLY SIG.
	SD	0.06	0.06			
(RI(SPCA)	MEAN	0.7	0.76	7.06	<0.0001	HIGHLY SIG.
	SD	0.6	0.66			

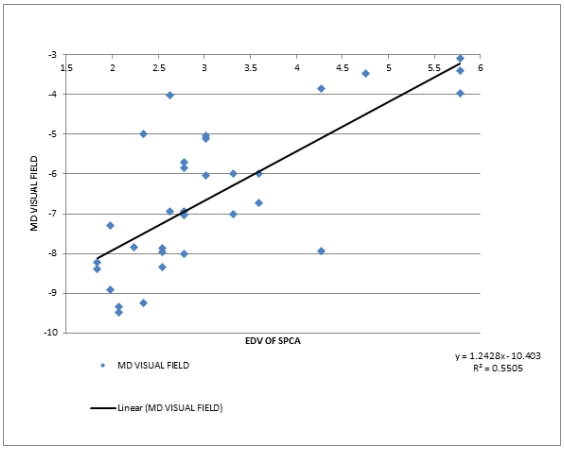
Table 3: Changes In Iop, Opp And Obf In Oht Post Valsalva

PARAMETERS		PRE VALSALVA	POST VALSALVSA	T-VALUE	P-VALUE	INFERENCE
IOP	MEAN	28.91	30.68	19.97	<0.0001	HIGHLY SIG.
	SD	3.35	3.45			
OPP	MEAN	45.33	45.04	2.59	0.016	SIG.
	SD	4.93	4.94			
PSV (CRA)	MEAN	12.33	9.23	24.38	<0.0001	HIGHLY SIG.
	SD	2.23	2.38			
PSV(OA)	MEAN	32.3	27.91	20.53	<0.0001	HIGHLY SIG.
	SD	4.24	3.6			
PSV(SPCA)	MEAN	16.03	12.52	20.07	<0.0001	HIGHLY SIG.
	SD	3.64	3.7			
EDV(CRA)	MEAN	4.03	2.31	17.3	<0.0001	HIGHLY SIG.
	SD	1.31	1.06			
EDV(OA)	MEAN	10.29	7.78	28.7	<0.0001	HIGHLY SIG.
	SD	1.4	1.19			
EDV (SPCA)	MEAN	4.71	3.04	18.73	<0.0001	HIGHLY SIG.
	SD	1.04	0.78			
RI(CRA)	MEAN	0.68	0.76	8.3	<0.0001	HIGHLY SIG.
	SD	0.08	0.07			
RI(OA)	MEAN	0.68	0.73	12.97	<0.0001	HIGHLY SIG.
	SD	0.04	0.04			
(RI(SPCA)	MEAN	0.7	0.75	11.97	<0.0001	HIGHLY SIG.
	SD	0.04	0.04			

Table 4: Changes In Iop, Opp And Obf In Control Post Valsalva

PARAMETERS		PRE VALSALVA	POST VALSALVA	T-VALUE	P-VALUE	INFERENCE
IOP	MEAN	15.57	17.13	42.29	<0.0001	HIGHLY SIG.
	SD	2.03	2.02			
OPP	MEAN	53.26	53.04	2.13	0.04	MILD SIG.
	SD	3.53	3.5			
PSV(CRA)	MEAN	11.26	8.76	10.97	<0.0001	HIGHLY SIG.
	SD	5.4	3.54			
PSV(OA)	MEAN	33.49	29.7	14.96	<0.0001	HIGHLY SIG.
	SD	6.41	5.93			
PSV(SPCA)	MEAN	12.12	9.65	19.42	<0.0001	HIGHLY SIG.
	SD	2.91	2.5			
EDV(CRA)	MEAN	3.7	2.27	15.35	<0.0001	HIGHLY SIG.
	SD	0.83	0.6			
EDV(OA)	MEAN	10.51	7.52	16.34	<0.0001	HIGHLY SIG.
	SD	2.85	2.16			
EDV (SPCA)	MEAN	3.98	2.39	13.21	<0.0001	HIGHLY SIG.
	SD	0.98	0.62			
RI(CRA)	MEAN	0.66	0.73	10.59	<0.0001	HIGHLY SIG.
	SD	0.06	0.07			
RI(OA)	MEAN	0.67	0.73	11.02	<0.0001	HIGHLY SIG.
	SD	0.11	0.1			
(RI(SPCA)	MEAN	0.66	0.75	8.84	<0.0001	HIGHLY SIG.
	SD	0.07	0.06			

Chart 1: Correlation Between Md Visual Field And Edv Of Spca In Poag



4. DISCUSSION

In our study, total of 95 subjects were evaluated out of which most patients, 52.8 %, were in 41-50 years age group whereas, 41.7 % were in 51-60 years and 5.5 % in >60 years age group. In our study, out of 95 evaluated subjects, the overall prevalence in males was 55.6% and females were less being 44.4 %. A large difference between male and female ratio was in the OHT group, i.e., around 7:3 ratio where males outnumbered females.

In our study the resting IOP among the groups was highest in the POAG (29.15±3.37 mm Hg) than in OHT(28.91±3.35 mm Hg) and lowest in the Control (15.57±2.03 mm Hg). Post Valsalva, there occurred a significant rise in IOP ($p<0.001$) in all the groups, with POAG showing the highly significant rise as compare to all other groups. The rise in IOP with Valsalva correlated with the study of Aykan U et al[13] who showed that in healthy individuals IOP rises with Valsalva. Significant rise in IOP in POAG group with Valsalva did not correlated with the study of Khan JC et at[14] who showed that IOP fell in POAG patients with Valsalva. The increase in IOP can be explained from the fact that during phase 2 of Valsalva, the intrathoracic venous pressure increase is transmitted through the jugular, orbital and vortex veins to the choroid. It causes a vascular engorgement and increase in the choroidal volume leading to an increase in IOP. The increase in episcleral venous pressure may be an additional mechanism for the IOP increase.

In our study, the resting OPP was slightly lower in the POAG (44.3±3.47 mm Hg) than OHT (45.33±4.93 mm Hg) and within normal range (53.26±3.53 mm Hg) in the control group. This can be explained by the fact that the OPP depends on many systemic and ocular factors and one of them being IOP. As the patients of POAG and OHT taken in our study are not on any pressure lowering medications and taking the formula of OPP= 2/3(MAP-IOP) into consideration, the higher the IOP, the lesser is the OPP. Post Valsalva, there occurred a mildly significant decrease in OPP in Controls ($p=0.04$) and significant fall in OPP in OHT ($p=0.016$) as well as in POAG ($p=0.005$). This fall in OPP among the groups correlated with the study of Sun L et al (2020)[15] who showed that in the phase II of Valsalva there occurs a significant fall in OPP in the study subjects. Although in our study the change was small and insignificant between the groups. This insignificance can be due to the small sample size.

In our study, among the ocular blood flow parameters, the average resting blood flow velocities, PSV and EDV in CRA and SPCA were highest in the OHT group, except EDV and PSV in OA, which were highest in Control. POAG showed lower blood velocities values as compared to control and OHT accounting for the chronic vascular dysregulation leading to decreased ocular blood flow. The higher values in OHT can be explained by the mechanism of autoregulation. With rising IOP the OBF tends to decrease but there occurs a compensatory mechanism to maintain the OBF, which is reflected as higher blood flow velocities in OHT patients. With progression of disease, the blood flow decreases chronically due to loss of autoregulation and reflected as lower blood flow velocities in POAG patients. Post Valsalva, there was a highly significant fall ($p<0.001$) in the blood flow velocities in all the groups. This fall in blood flow velocities post Valsalva correlated with the study of Garhöfer G et al[16] and Khan JC et al[14] who showed that POBF fell during Valsalva in POAG and healthy individuals with the greatest predictor being the resting value of POBF. In our study the fall in blood flow velocities and was significantly higher in the OHT group as compared to other groups, this can be explained by the fact that the changes are reflected apparently more in the blood flow velocities with higher resting values.

Significant rise in RI of CRA, OA, SPCA ($p<0.001$) was seen all the three groups post Valsalva, with resting value of RIs being highest in POAG, than in OHT than in control. Formula for RI is calculated as RI = (PSV − EDV)/PSV and as in POAG due to chronic disease progression the observed blood flow velocities are least as compared to the other two groups, hence the resistance to the blood flow also becomes higher. Although the change in RIs was significant between the groups, no gradation could be deduced among the groups regarding rise in RI. This was a limitation and could be due to lesser sample size. Establishment of any significant relationship requires further studies with larger sample size.

Correlation between the rise in IOP and fall in OPP as calculated by Spearman Rank Correlation was highly significant in control ®= -0.51, p=0.002), POAG (r= -0.41, p=0.019) and in OHT (r= -0.48, p=0.012), which suggested that the change in OPP post Valsalva is in proportion with the change in IOP and as IOP rises, OPP falls.

Significant correlation was also found between the PSV, EDV and RI of SPCA and MD visual fields in the POAG group as calculated by Spearman Rank Correlation. There was significant correlation between PSV of SPCA and MD visual fields ($r = 0.382$, $p=0.030$) and highly significant between EDV of SPCA and MD visual fields ($r = 0.740$, $p< 0.001$), i.e., the more negative the MD visual field the lesser was the blood flow velocities of SPCA. There was significant correlation between RI of SPCA and MD visual fields ($r = -0.445$, $p=0.011$), i.e., the more negative the MD visual field the greater was the RI of SPCA. This correlation helps to conclude that the visual field damage is related to the decreased OBF, and that glaucomatous damage is linked to the vascular pathogenesis.

5. CONCLUSION

- Valsalva causes rise in IOP and RI of OBF parameters and fall in OPP and ocular blood flow velocities in POAG, OHT as well as in healthy individuals.
- OBF is significantly reduced in POAG and the lower the OBF, the greater is the visual field damage detected. Hence this proves that vascular dysgenesis in POAG is linked to glaucomatous damage.
- OBF as measured by CDI can be a considered parameter for deciding the aggressiveness of treatment in patients of glaucoma.
- The inverse correlation between IOP and OPP in our study explains that by decreasing IOP, OPP can be increased. Hence direct measurement of OPP is as important as IOP in the management plan of glaucoma.
- Valsalva or valsalva like manoeuvres like squats, weightlifting, trumpet playing and various yogasanas (positions of adho-mukha svanasana, uttanasana, halasana, viparita karani)should be discontinued in POAG and OHT patients as the vascular pathogenesis of ONH ischemia is linked to decreased OBF and can lead to progression in glaucomatous damage.

6. REFERENCES

1. Cherecheanu AP, Garhofer G, Schmidl D, et al. Ocular perfusion pressure and ocular blood flow in glaucoma. *Curr Opin Pharmacol*. 2013;13(1):36-42.
2. Hayreh SS. Blood supply of the optic nerve head and its role in optic atrophy, glaucoma, and oedema of the optic disc. *Br J Ophthalmol*. 1969;53(11):721-48.
3. Harris A, Ciulla TA, Chung HS, et al. Regulation of retinal and optic nerve blood flow. *Arch Ophthalmolol*. 1998;116:1491–5.
4. Leske MC, Heijl A, Hyman L, et al. Predictors of long-term progression in the Early manifest glaucoma trial. Ophthalmol. 2007 ;114(11):1965-72.
5. Benavente-Pérez A, Hosking SL, Logan NS, et al. Ocular blood flow measurements in healthy human myopic eyes. *Graefes Arch Clin Exp Ophthalmol.* 2010 Nov;248(11):1587-94.
6. Prada D, Harris A, Guidoboni G, Siesky B, Huang AM, Arciero J. Autoregulation and neurovascular coupling in the optic nerve head. *Surv Ophthalmol.* 2016 Mar-Apr;61(2):164-86.
7. Korner PI, Tonkin AM, Uther JB. Reflex and mechanical circulatory effects of graded valsalva maneuvers in normal man. *J Appl Physiol.* 1976;40:434–40.
8. Jellinek EH. The Valsalva manoeuvre and Antonio Valsalva (1666-1723). *J R Soc Med.* 2006;99(9):448–51.
9. Palamar M, Dag MY, Yagci A. The effects of Valsalva manoeuvre on ocular response analyzer measurements. *Clin Exp Optom.* 2015;98(5):447–50.
10. Albert BL, M. D. A simple test of cardiac function based upon the heart rate changes induced by the valsalva maneuver. *Am J Cardiol.* 1966;18(1):90–9.
11. Benarroch EE, Opfer-Gehrkin TL. Low. PA. Use of the photoplethysmographic technique to analyze the Valsalva maneuver in normal man. *Muscle Nerve*. 1991;14:1165–72.
12. Shuman JS, Massicotte EC, Connolly S, et al. Increased intraocular pressure and visual field defects in high resistance wind instrument players. *Ophthalmol.* 2000; 107:127–33.
13. Aykan U, Erdurmus M, Yilmaz B, et al. Intra ocular pressure and ocular pulse amplitude variation during the Valsalva maneuver. *Graefes Arch Clin Exp Ophthalmol.*2010;248:1183-6.
14. Khan JC, Hughes EH, Tom BD, et al. Pulsatile ocular blood flow: the effect of the Valsalva manoeuvre in open angle and normal tension glaucoma: A case report and prospective study. *Br J Ophthalmol*. 2002;86(10):1089-92.
15. Sun L, Chen W, Chen Z, et al. Dual effect of the Valsalva maneuver on autonomic nervous system activity, intraocular pressure, Schlemm's canal, and iridocorneal angle morphology. *BMC Ophthalmology.* 2020 Jan;20(1):5.
16. Garhöfer G, Fuchsjäger-Mayrl G, Vass C, et al. Retrobulbar blood flow velocities in open angle glaucoma and their association with mean arterial blood pressure. *Invest Ophthalmol Vis Sci*. 2010;51(12):6652-7.