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Ocular perfusion pressure: distribution and its relationship with glaucoma

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Abstract: *Background and Objectives:* Glaucoma is the second largest causative factor for blindness globally. Despite this, its pathogenesis remains obscure owing to its multi-factorial nature. This study aimed to analyse the distribution of the ocular perfusion pressure (OPP) and assessed its relationship with patients diagnosed with glaucoma along with other noted risk factors. *Methods:* This cross-sectional study was conducted among 284 subjects above the age of 40 years screened during rural medical camps. All participants underwent a comprehensive eye examination, following which the intra ocular pressure (IOP) was measured using the Shiotz tonometer and blood pressure (BP) was recorded. The IOP of patient's right eye was used to calculate mean ocular perfusion pressure (MOPP). Welsh's t-test and Chi-square tests examined the relationship between MOPP and glaucoma diagnosis at $p < 0.05$ significance. *Results:* A significant decrease in the MOPP was observed among glaucoma patients (45.61±12.89 mm Hg) in comparison to normal subjects ($p < 0.05$). In addition, the mean of systolic perfusion pressure (SPP) was found to be significantly higher among subjects with glaucoma (101.55±27.72 mm Hg, $p < 0.05$). Similarly, Diastolic perfusion pressure (DPP)on average was significantly higher in subjects with Glaucoma (51.85±17.45mm Hg,$p< 0.05$). The odds of having glaucoma was 3.284024 (Confidence Interval: 1.4250892-7.567802) times more when diabetes was involved. *Conclusion:* Low mean values of OPP, SPP and DPP are all independent risk factors for glaucoma, thereby providing further evidence of the vascular mechanism involved in multi-factorial pathogenesis of glaucoma.
Keywords: Blindness, Diabetes Mellitus, Glaucoma, Hypertension, Intraocular Pressure.

Introduction

Glaucoma is a progressive type of chronic optic neuropathy affecting millions worldwide which is characterized by destruction of optic nerve axons, retinal ganglion cell death and loss of the visual field[1-2]. As the second largest cause of blindness globally, its incidence is estimated to touch 76 million in 2020and 1.1 billion in 2040[3]. Despite its common occurrence, the exact pathophysiological mechanism causing optic nerve damage has not been adequately explicated as of yet. It has been postulated that the vascular mechanism in the optic nerve head has a salient role to play in the pathogenesis of glaucomatous optic neuropathy [4-5].

In glaucoma, tissue atrophy is often accompanied by degeneration of blood vessels, and subsequent secondary diminution of ocular blood flow. Moreover, blood flow is further reduced if the decline in perfusion pressure (PP) outstrips the auto regulative capacity of the eye. In a milieu where auto regulation has been disrupted, even a small dip in perfusion pressure reduces the ocular blood flow, and an up regulation in signs of damage such as the ischemia inducing hypoxia inducible factor 1-α is observed [5]. Poor blood flow impedes the growth and function of optic nerve head ecosystem owing to the lack of oxygen, ultimately resulting in loss of vision. This theory is reinforced by epidemiological links of glaucoma to vascular risk factors like systemic hypertension, vasospasm, and atherosclerosis [1, 6-7].

Besides the mechanical effect on optic nerve head (ONH), caused by raised intra ocular pressure (IOP), vascular hypothesis suggests that sustained low blood pressure (BP) relative to IOP leads to a corresponding drop

in the mean ocular perfusion pressure (MOPP), thus impairing perfusion of the optic nerve head [5,8-9]. Blood flowing through the capillary mesh of the lamina cribrosa region in the optic nerve is represented by the ocular perfusion pressure [10]. Perfusion pressure refers to the difference between mean arterial BP in the optic nerve head vessels and IOP [5, 11]. Perfusion pressure is also equivalent to the difference between mean arterial pressure and venous pressure in a vascular bed [5, 11].

Intra ocular pressure which is considered a good index of the ocular venous pressure, is currently the most relied upon indicator for the diagnosis, progression of disease and clinical response to therapies in the pipeline [12]. However, multiple types of IOP fluctuations have been reported which range from instantaneous, diurnal to long term. Evidence shows that alcohol, smoking, caffeine consumption, pain and water levels can also cause a temporary change in IOP[13]. With the only measurable factor i.e. IOP, being prone to fluctuation, a complementary and quantifiable risk factor is needed for glaucoma diagnosis.

Expounding this intricate relationship between systemic blood pressure and its effect on optic nerve head perfusion is important to understand the factors affecting glaucoma development. It also aids in having clinical implications given the high prevalence of hypertension and use of BP-lowering treatment among older adults. The aim of this study was to examine the diastolic, systolic, mean arterial and pulse pressure in Indian patients with glaucoma and compare them with that of normal population.

Material and Methods

This prospective, cross-sectional study was conducted over a period of one year (2019-2020) among a rural community in Belagavi at the Department of ophthalmology of a tertiary care hospital and medical research center. The study was conducted after obtaining the ethical clearance from the Institutional Review Board and in accordance to the tenets laid down by the Declaration of Helsinki.

All patients between 40-85 years of age, who were newly diagnosed or antecedently diagnosed cases of glaucoma as noted during screening sessions held in rural areas of Belagavi district in Karnataka were included in the study. However, individuals presenting with acute ocular inflammation; receiving antihypertensive medication or on any drugs that may affect blood pressure or intraocular pressure were excluded to eliminate bias. Therefore, based on convenient random sampling of 300 individuals, the first 284 patients visiting the screening clinic and meeting the aforementioned eligibility criteria and providing informed written consent voluntarily on being explained the study procedures were enrolled. A thorough history of the patient, including patient particulars, ocular complaints, status of systemic diseases and other co-morbidities were duly noted.

Examination and measurement of intraocular pressure: Intraocular pressure in the right eye of enrolled patients resting in the supine position was recorded with a schiotz tonometer (Riester, Germany).Simultaneously the systolic and diastolic blood pressure was recorded by a digital automatic blood pressure monitor (Accusure, India. Blood pressure was assessed using the mean of two measurements with the patient allowed to rest for 10 minutes before the BP recordings. The optic disc was comprehensively evaluated under a direct or indirect ophthalmoscope (Heine, Germany.

Examination and measurement of glaucoma: Patients were diagnosed as glaucoma if two out of the following three parameters were met;

1. Pathologically cupped optic discs- cup-to-disc ratio of 0.6 or more in association with generalized or localized thinning of the neuroretinal rim, notching of the neuro retinal rim, optic nerve head hemorrhages, nerve fiber layer loss, cup- disc asymmetry greater than 0.2, and/or deep cup with prominent lamina cribrosa and bayoneting sign.
2. Visual field defect suggestive of nerve fiber bundle defect such as arcuate scotoma in the central visual fields, nasal step, altitudinal scotoma, paracentral scotoma, and generalized field defects.
3. Intraocular pressure more than 21mm Hg[6].

For persons without glaucoma, the IOP of the right eye was used to calculate perfusion pressure. Patients diagnosed with glaucoma were referred to the tertiary care centre for Visual Fields assessment. Based on the approach described in the Singapore Malay Eye study**,** the IOP in glaucoma patients was determined depending on the affected eye in unilateral cases and on the worse eye in bilateral cases [6].

The following formulas were used to calculate the mean ocular perfusion pressure, SPP and DPP:

Mean arterial BP (MAP) = DBP -1⁄3(SBP - DBP)

Mean ocular perfusion pressure (MOPP) =2⁄3(MAP - IOP)

Systolic perfusion pressure (SPP) = SBP – IOP

Diastolic perfusion pressure (DPP) = DBP – IOP

where SBP is systolic blood pressure, DBP is diastolic blood pressure, MAP is mean arterial pressure and IOP is intraocular pressure.

Statistical analysis: Data analysis was done using R i386 3.5.1 software and summarized as mean± standard deviation (SD) for continuous variables, while categorical variables were presented by a frequency table. Comparison of each continuous variable with glaucoma was done using an independent t-test / Mann-Whitney U test and association between two categorical variables were studied using Chi-square/Fisher test. QQ plot/Shapiro-Wilk's test was used to analyse the normality of variables. A p-value <0.05 was considered as the threshold of significance.

Results

The mean age of this study cohort was 60.96±11.05 years. Among 284 subjects, a female preponderance of 155 (54.77%) subjects over 128 (45.22%) male subjects was seen. Table 1 presents the incidence of glaucoma across selected variables such as age, gender, hypertension, diabetes mellitus, smoking, alcohol and high myopic.

Table-1: Incidence rates of glaucoma across cohort characteristics

Variable		Glaucoma[n (%)]		p-value
		No	Yes	
Age (in years)	< 53	62 (88.57%)	8 (11.43%)	0.8732
	53-61.9	61 (87.14%)	9 (12.86%)	
	62-69.9	64 (88.89%)	8 (11.11%)	
	≥ 70	61 (84.72%)	11 (15.28%)	
	Mean ± SD	60.9±10.9	61.47±12.1	0.7731[t]
Gender	Male	104 (81.25%)	24 (18.75%)	0.005322*
	Female	144 (92.31%)	12 (7.69%)	
Hypertension	No	196 (87.115)	29 (12.89%)	0.8333
	Yes	52 (88.14%)	7 (11.86%)	
Diabetes Mellitus	No	222 (89.52%)	26 (10.48%)	0.005497*[MC]
	Yes	26 (72.22%)	10 (27.78%)	
Smoking	No	237 (86.81%)	36 (13.19%)	0.3758[MC]
	Yes	11 (100%)	0	
Alcohol	No	238 (86.86%)	36 (13.14%)	0.3683[MC]
	Yes	10 (100%)	0	
High Myopic	Yes	248 (87.63%)	35 (12.37%)	-
	No	0	1 (100%)	

MC: Monte-Carlo simulation used to obtain p-value, t: two sample t-test,* indicates significance at p <0.05 level.

Variables such as age, hypertension, smoking and alcohol consumption showed no significant influence on incidence of glaucoma as per Chi-square test. However, gender and presence of diabetes mellitus were found to significantly influence the incidence of glaucoma. Odds of having glaucoma was 3.1006 (Confidence Interval (CI): 1.3748-7.4380) times more for males compared to female patients. While the odds of having glaucoma was 3.284024 (CI: 1.4250892-7.567802) times more for the subjects who were suffering from diabetes mellitus compared to healthy subjects.

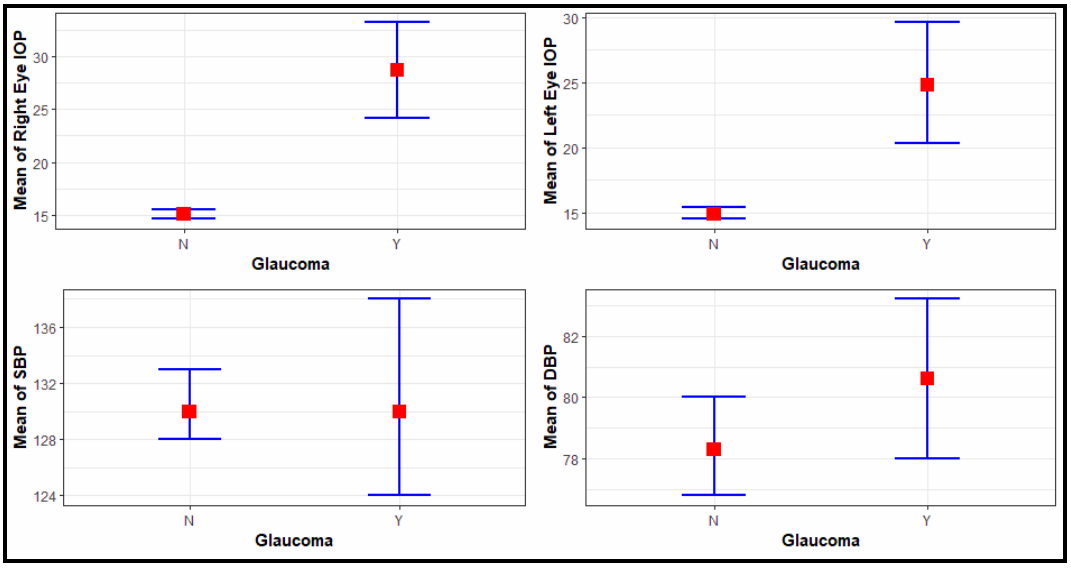
Table2 illustrates the association of the several types of pressures monitored in the study with glaucoma. One-tailed Welch's t-test revealed that the mean of right eye and left eye IOP of normal subjects was significantly lower than that of subjects with glaucoma.

Table-2: Association of varied pressures with Glaucoma

Factors	Glaucoma[mean ± SD]		P-value
	No	Yes	
Right eye IOP (mm Hg)	15.06±3.75	28.73±14.07	<0.0001 ^{Wt*}
Left eye IOP (mm Hg)	14.93±3.59	24.78±14.47	0.000126 ^{Wt*}
Systolic blood pressure (mm Hg)	130.43±21.95	130.28±22.97	0.9607 ^{t}
Diastolic blood pressure (mm Hg)	78.33±12.61	80.58±8.22	0.16 ^{Wt}
Mean arterial blood pressure (mm Hg)	95.69±13.51	97.15±11.65	0.54 ^{t}
Mean ocular perfusion pressure (mm Hg)	53.75±9.48	45.61±12.89	0.0003718 ^{Wt*}
Systolic perfusion pressure(mm Hg)	115.39±22.15	101.55±27.72	0.0004055 ^{*t}
Diastolic perfusion pressure(mm Hg)	63.25±13.58	51.85±17.45	0.0002658 ^{Wt*}

t: two sample t-test, Wt: two sample Welch's t-test,IOP: Intraocular pressure, *indicates significance at p <0.05 level.

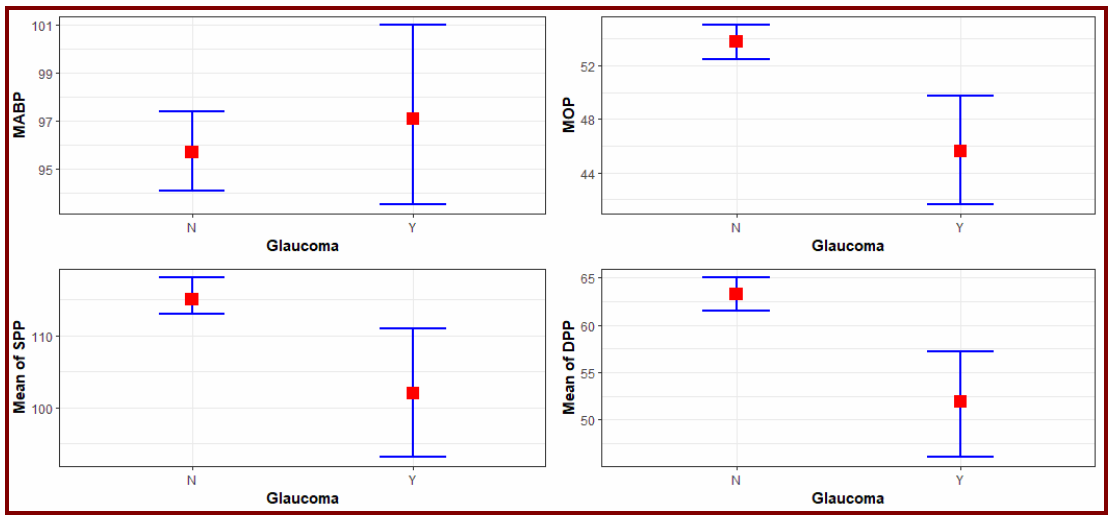
Fig-1: Comparison of Glaucoma (absence –N, presence –Y) with mean values of (A) Right eye IOP (B) Left eye IOP (C) SBP (D)DBP.



Mean of SBP, DBP and arterial blood pressure did not significantly differ among glaucoma and non-glaucoma patients (Figure 1).

Mean ocular perfusion pressure, mean of systolic and diastolic perfusion pressure were significantly more in normal subjects compared to subjects with glaucoma as determined by one tailed Welch's t-test (Figure 2).

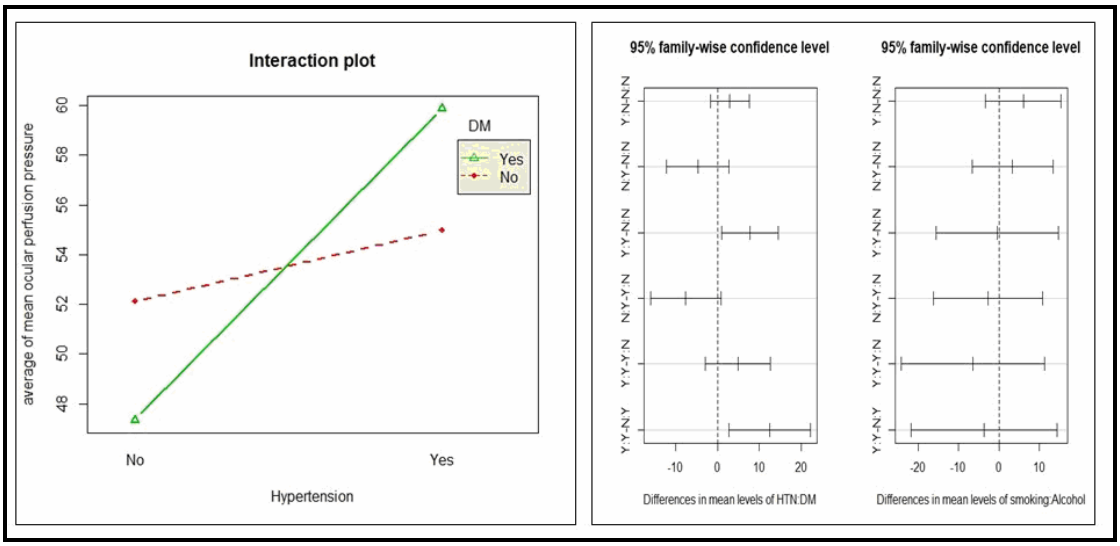
Fig-2: Comparison of Glaucoma with mean values of (A) Arterial Blood Pressure (B) Ocular Perfusion Pressure (C) Systolic Perfusion Pressure (D) Diastolic Perfusion Pressure.



Logistic regression models of studied parameters affirmed the respective odds of developing glaucoma. With a unit increase in the mean arterial blood pressure, the odds of having glaucoma increased by a factor of 1.1263 units whereas a unit increase in the systolic perfusion pressure elicited an increase in the odds of having glaucoma by factor of 0.91472 units.

From Tukey's HSD test, the mean ocular perfusion pressure for the patients having both hypertension and diabetes was found to be 7.7246 times more than the subjects with neither of the two conditions (p=0.0180). Additionally, mean ocular perfusion pressure for subjects with both hypertension and diabetes was 12.4928 times more than the subjects with only diabetes mellitus (p=0.0058). In the absence of diabetes mellitus, there was no significant difference in mean ocular perfusion pressure between the subjects with and without hypertension (p adj=0.3819). Figure 3illustrates the pair-wise interaction effect of hypertension with diabetes mellitus and mean levels of smoking respectively.

Fig-3: Visualisation of interaction effect on Mean ocular perfusion pressure



Discussion

India is home to at least 12.9% of the primary open angle glaucoma (POAG) blindness cases and 12.7% of primary angle closure glaucoma (PACG) blindness cases [14]. Glaucoma has been previously cited to have a myriad of risk factors among which the intra ocular pressure is of particular interest as it serves as a measurable indicator for the progression of this pathology [12]. However IOP values among glaucoma patients are not always consistent [12]. Hence it becomes imperative to delineate the extent and reliability of the relationship between glaucoma and a range of other pressures affecting the eye.

In reference to the prevalence of glaucoma across different demographic sections, gender and patients with diabetes mellitus showed a significant association ($p < 0.05$) with a glaucoma diagnosis in the current study. These observations are in consonance with the findings of Khandelwhal *et al.* who noted a higher prevalence of glaucoma among males (69%), and Zhao *et al.* who on meta-analysis of seven studies found diabetes to significantly increase the risk for glaucoma (Risk ratio: 1.36 (95%, CI=1.24-1.50) [14-15].

Other factors such as age, hypertension, alcohol and smoking failed to demonstrate a notable influence on prevalence of glaucoma ($p > 0.05$) in the present study. Age-related macular degeneration has been documented before, with several studies drawing linear relationship between age and risk of glaucoma. However, age is not a determinative risk factor and is contingent on the frailty of the body caused by an assemblage of health deficits like blood pressure changes, metabolic disorders, dependence and extent of medications consumed and so on[16]. A study by Kang *et al.* and Klein *et al.* demonstrated that smoking and alcohol were not significantly linked to the development of glaucoma respectively as noted in the current study [17-18].

In this community-based study on the rural Belagavi population, a significant decrease in the mean of ocular perfusion pressure coincided with the presence of glaucoma. In congruence to a study by Deb *et al.* who reported a reduction of 31% and 12% in the risk of developing POAG (95% CI = 13-45%, $p = 0.001$) and suspicious glaucoma (95% CI = 2-21%, $p = 0.03$) respectively with a unit increase in MOPP [1]. Similarly, the Barbados Eye study reported a 3.1 fold increase for MOPP below 42 mm Hg [19].

The mean MOPP among glaucoma subjects was 45.61±12.89 mm Hg in the present study in strong agreement with aforementioned studies. Notably, we found that MOPP for the patients who had both hypertension and diabetes is 7 times more than the subjects who do not have diabetes and hypertension. Moreover, mean ocular perfusion pressure for subjects with both hypertension and diabetes is 12 times more than the subjects with only diabetes mellitus. In the absence of diabetes mellitus, hypertension has no independent effect on mean ocular perfusion pressure (MOPP). Thus, this study shows that diabetes and hypertension have a preservative effect on the optic nerve head. This is also evidenced by another study by Raman *et al.* who noted a MOPP of 52.6 ± 9.0 mm Hg among a diabetic population in south India of whom 64% were hypertensive [20].

There exists a convoluted interplay between systemic blood pressure and IOP which in turn decides the OPP tasked with regulating blood flow to the optic nerve [10]. The influence of blood pressure on the development and progression of glaucoma has been postulated to be on the basis of auto-regulative properties possessed by the vascular bed of the optic nerve head. Auto regulation refers to the buffering ability of the eye against fluctuations in perfusion pressures. Failure to auto regulate can alter blood flow, hence facilitating ischemia, neuronal dysfunction, visual field loss and subsequent formation of glaucomatous optic nerve [10].

The mean SPP was found to be significantly elevated among subjects with glaucoma. Cantor *et al.* in their study arrived at an inference congruent to the present study, wherein SPP was significantly linked to higher risk of developing glaucoma [21]. In the current study, DPP on average was significantly higher in subjects with

glaucoma. This result as well is consistent with the work of Cantor *et al.* and with a previous study by Zheng *et al.* who observed that the risk of open angle glaucoma (OAG) is significantly heightened with a dip in DPP values [6, 21.]Mean DPP of 61.4 ± 11.5 mm Hg was noted among patients with glaucoma by Zheng *et al.* which is comparable to the mean DPP of 63.25±13.58 mm Hg seen in the glaucoma patients of our study [6].

The association of OAG with systemic hypertension is a hotly debated topic due to its complex and multi-factorial interaction. Results of some studies such as the Blue Mountain Eye Study and Egna-neumarkt study vouch for the significant association established between open angle glaucoma and hypertension, whereas others like the Barbados Eye Study and Rotterdam study delink presence of systemic hypertension with confirmed OAG [22-25]. This study findings resonate with the latter study as hypertension as a sole factor did not seem to influence development of glaucoma. Deb *et al.* as well as Vijya *et al.* in their research on glaucoma among a south Indian population found no association of POAG with systemic hypertension [1, 26].

When blood pressure drastically falls, it leads to low perfusion pressure, creating an ischemic condition that ultimately damages the optic nerve head [27]. When the blood pressure is highly elevated the vessels become arteriosclerotic and this also tends to create a low perfusion pressure, increasing resistance to blood flow, which hinders the optic nerve from receiving the necessary nutrition [1, 10]. The strength of this study lies in its sizeable population with an almost equivalent gender distribution and the synergistic effect of diabetes and hypertension on incidence of glaucoma. With growing body of epidemiologic literature supporting ocular perfusion pressure as a significant risk factor for open-angle glaucoma, it is time to consider ocular perfusion pressure over intra ocular pressure alone as diagnostic criteria for glaucoma.

Conclusion

This study was instrumental in emphasizing the role of low MOPP, low SPP and low DPP as independent risk factors for glaucoma, providing further evidence of the vascular mechanism in glaucoma pathogenesis. Diabetes mellitus and hypertension seem to synergistically influence the underlying vascular cascade involved.

Recommendations

Monitoring and management of blood pressure should be done along with regular medical/surgical management of glaucoma. The blood pressure has to be maintained within the target range for patients on anti-hypertensives and for cardiac patients. Patients on anti-hypertensive medications as well as patients of hypotension should be regularly screened for glaucoma. In patients with well controlled IOP but progressive glaucomatous optic nerve head damage, blood pressure must be closely monitored and managed.

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