Original Article

TRANSLATIONAL&PRACTICAL MEDICINE

DOI: 10.51271/JTPM-0014

J Transl Pract Med 2022; 1(2): 43-48

Ocular pulse amplitude and hemodynamy in controlled asymmetric glaucoma: a cross-sectional study

Mustafa Civelekler

University of Health Sciences of Gülhane Education and Research Hospital, Ophthalmology Service, Ankara, Turkey

Cite this article as: Civelekler M. Ocular pulse amplitude and hemodynamy in controlled asymmetric glaucoma: a cross-sectional study. J Transl Pract Med 2022; 1(2): 43-48.

ABSTRACT

Aim: The aim of this study was to explore the relationship between glaucoma severity, ocular pulse amplitude (OPA) and hemodynamic variables.

Material and Method: Thirty-one Asymmetric primary open-angle glaucoma (POAG) cases (one eye with better-MD, fellow eye with worst-MD) who applied to the glaucoma outpatient clinic of Gulhane Military Medical Faculty Hospital between January 1, 2006 and June 30, 2007 were included in this cross- sectional study. Patients using beta-blockers or alphaadrenergic agonists were excluded. The patients went on using glaucoma medications. Asymmetricity was assessed if a visual field mean deviation (MD) difference ≥6 decibel existed between the eyes. Mean MD and pattern standard deviation, diurnal OPA and intraocular pressure(IOP) (7 am, 9 am, 11 am, 1 pm, 3 pm, 5 pm, 7 pm, 9 pm, 11 pm, 1 am, 4 am), central corneal thickness, peak systolic velocity (PSV), end diastolic velocity (EDV), PSV/EDV, pulsatility index (PI), resistivity index (RI) for internal carotid artery and ophthalmic artery were measured with color Doppler ultrasonography.

Results: The differences in mean diurnal IOP and mean diurnal OPA between the eyes were statistically insignificant. Each diurnal IOP and OPA values and coefficient of variability of diurnal IOP and OPA were statistically insignificant between the groups. There was no significant difference in PSV, EDV, PSV/EDV, PI and RI between the better-MD and worse-MD eyes. The correlations between mean IOP/mean OPA, each diurnal IOP/OPA values were insignificant.

Conclusion: These results suggest that ocular hemodynamy is affected after a critical point in the evolution of glaucoma. The severity of glaucoma is not directly related to pulsatile ocular blood flow.

Keywords: Ocular pulse amplitude, Glaucoma, ophthalmic artery, intraocular pressure, visual field test

INTRODUCTION

Primary open-angle glaucoma (POAG) is a multifactorial disease presenting with optic nerve damage and visual field defects. Intraocular pressure (IOP) increase is the most significant risk factor although it is not sine qua non such as in normotensive glaucoma. However, other risk factors such as systemic hypotension with nocturnal pressure drops, vasospasm, low perfusion pressure and cardiovascular diseases are associated with increased prevalence of glaucoma (1). Related to the development of non-invasive techniques for ophthalmic hemodynamic investigation in recent years, vascular factors were studied to explore the significance of ocular blood flow in the pathogenesis of glaucoma (2-9). One of these techniques is based on continuous IOP recording by means of dynamic contour tonometry (DCT) allowing the measurement of the pressure wave (pulse amplitude) of the ocular pulsation during a cardiac cycle. Many studies have investigated the role of vascular insufficiencies around the optic nerve head, retrobulbar hemodynamics such as blood flow velocities in the central retinal artery, ophthalmic artery and short posterior ciliary arteries and retinal vessel diameters (5, 10, 11).

Asymmetric cases carry a significant importance for the investigation of POAG. In this study, we aimed to explore the causes of asymmetricity in view of hemodynamic changes. The article in the literature with the same aim generally focuses on asymmetric cases with one non-glaucomatous eye and the fellow eye with glaucoma. However, we think that affecting variables can be investigated in a better way using correlations to explore their effects to a disease process in the asymmetrically affected cases rather than in affected and unaffected cases. For this reason, this study included patients with bilateral glaucoma with asymmetric visual field loss. Furthermore, the studies in the literature focused on

Corresponding Author: Mustafa Civelekler, mcivelekler@yahoo.com

Received: 25.08.2022 **Accepted:** 18.09.2022

the glaucoma patients after having a washout period for anti-glaucoma medication or newly-diagnosed glaucoma cases. For this reason, those studies explored the hemodynamic changes without the effect of any medication. However, in this study, we aimed to report the relation between ocular pulse amplitude and hemodynamy in glaucoma patients during anti-glaucoma medication.

MATERIAL AND METHOD

Asymmetric POAG cases who applied to the glaucoma outpatient clinic of Gulhane Military Medical Faculty Hospital between January 1, 2006 and June 30, 2007 were included in the study. A local ethical committee approval was obtained for this cross-sectional study. The study was performed according to the tenets of the Declaration of Helsinki. Informed consent was obtained from each subject.

Patients

Sixty-two eyes of 31 asymmetric POAG patients included. Mean age was 69.8±8.8 years. Female/male ratio was 17/14. Eyes those having IOP greater or equal to 21 mmHg (without medication), glaucomatous visual field defects confirmed by at least two reliable and reproducible visual field examination, increased cupping (vertical cup-disc ratio of ≥0.4), diffuse or focal neural rim thinning, nerve fiber layer defects, and hemorrhage were included in the glaucoma group. Asymmetricity was accepted if there was a difference of ≥6dB in MD of visual field. Visual fields were tested by Humphrey Field Analyzer II 750 (Carl Zeiss Ophthalmic System, Humphrey Division, Dublin, California USA) by using central 24/2 SITA Fast program. Patients with poor visual field reliability (fixation loss exceeding 15%, false positive or false negative exceeding 30%) were not included. Patients using topical or systemic β- blockers, alpha adrenergic agonists, diabetes, systemic arterial hypertension, hematologic disease including anemia, cancer, eye disease including cataract with a lower visual acuity than 9/10, previous ocular surgery and ocular trauma in any eye were excluded.

Measurements

IOP measurements were performed by Pascal DCT under topical anesthesia (proparacine HCL, 0.5%). Pascal DCT is designed to measure IOP largely independent of the corneal properties (12). Pascal DCT was mounted on a base plate designed to clip easily into position on the slit lamp. It is equipped with a digital LCD screen that displays the IOP, ocular pulse amplitude (OPA) and the quality score (Q) of the measurements [range 1 (excellent) to 5 (poor)]. Only Q1 and Q2 values were eligible for including in the statistical analyses. The patients stayed one day and one night at the hospital. The OPA value, expressed in mmHg, was automatically calculated after registering ten seconds of the ocular pulse wave. IOPs and OPAs of both eyes were measured in 10 sessions in a 24-hour period (2 hour intervals between 7am-11pm, and 3-hour intervals between 11pm-7am hours) in the same hours for all patients. Mean and standard deviation (SD) values for IOPs and OPAs were calculated for each patient. The variability of IOP and OPA for each patient were assessed by a normalized index that is coefficient of variation (CV). The CV is the ratio of SD to mean (SD/mean).

Color Doppler Ultrasonography of the internal carotid artery and ophthalmic artery were performed by an experienced sonographer (BB) who was unaware of the subjects' clinical status. A color Doppler imaging system (General Electronics LOGIQ9, Wauwatosa/ Wisconsin) was used with a 12-MHz lineer phase-array transducer. The sonography was performed as previosly described (13). During the sonography of ophthalmic artery, the patients were in the supine position, with the head tilted at a 30-degree angle. The transducer was applied gently to the closed eyelid with a coupling gel. Care was taken to avoid applying any pressure to the eye. The ophthamic artery was traced nasal to the optic nerve after their crossing, and measurements were performed immediately 10 to 15 mm posterior to the globe.

During the internal carotid artery scans, patients were recumbent in position with the head turned slightly away from the side under investigation. The peak systolic velocity (PSV) defined as the highest blood velocity during the systolic phase of the cardiac cycle; the end diastolic velocity (EDV) defined as the velocity during the diastolic phase of the cardiac cycle; the mean velocity defined as the mean blood flow during a cardiac phase. Resistivity index (RI) and pulsatility indexes (PI) are defined as (PSV-EDV)/PSV and (PSV-EDV)/mean velocity, respectively. These indexes are influenced by the resistance to the blood flow. In order to measure volume blood flow, the time averaged velocity over 4 cardiac cycles was used together with the vessel diameter by the internal software. The volume blood flow is defined in terms of ml/min (13). These vascular parameters were calculated for both ophthalmic artery and internal carotid artery. **Figure 1** shows a representative sonography of ophthalmic artery from a patient. Central corneal thickness (CCT) was measured with an Ultrasonic Pachymeter (Humphrey Instruments/Smithkline Company, California).

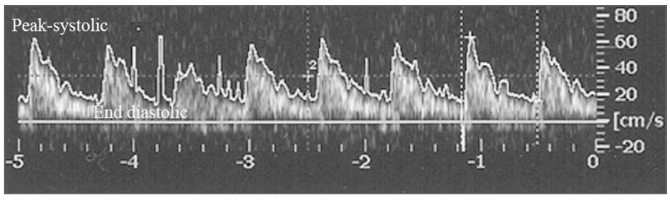

Figure 1. Representative sonography of ophthalmic artery
77x22mm (300 x 300 DPI)

Statistical Anaylsis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). For the normality check, the Shapiro-Wilk test was used. Data are given as mean±standard deviation for and frequency (percentage) for categorical variables. Normally distributed variables were analyzed with the independent samples t test. Non-normally distributed variables were analyzed with the Mann Whitney U test. The correlations between the hemodynamic variables, OPA and IOP were evaluated by Pearson test. Coefficient of variability of diurnal IOP and OPA was calculated as the ratio of standard deviation to mean values (SD/mean).

RESULTS

Mean MD values in the better-MD and worse-MD eyes were -3.8±4.8 and -17.3±7.9, respectively (p<0.0001). Mean PSD values in the better-MD and worse-MD eyes were 2.9±2.6 and 8.6±3.1, respectively (p<0.0001). Mean diurnal OPA, mean diurnal IOP, standard deviation of diurnal OPA and IOP and coefficient of variability of diurnal OPA and IOP were all statistically insignificant (**Table 1**). In addition, each diurnal IOP and OPA measurements (11 diurnal measurements) did not differ between better- and worse-MD eyes (**Figure 2A, 2B**).

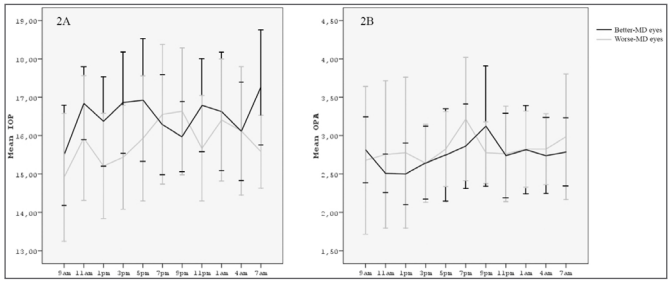

Figure 2. Diurnal OPA and IOP differences between the groups 180x73mm (300 x 300 DPI)

Table 1. Mean IOP and OPA results

	Eye		p
	Better-MD	Worse-MD	
Mean IOP	16.51±1.81	15.86±2.57	0.387
Mean OPA	2.75±69.00	2.82±87.00	0.820
SD of diurnal IOP	1.86±0.73	1.92±0.98	0.831
SD of diurnal OPA	0.52±0.20	0.69±0.48	0.271
IOP coefficient of variation	0.12±0.04	0.12±0.06	0.791
OPA coefficient of variation	0.19±0.05	0.23±0.11	0.228

IOP; intraocular pressure, OPA; ocular pulse amplitude, MD; Mean Deviation, Data are given as mean±standard deviation.

The differences in ICA and OA PSV, EDV, PSV/EDV, flow volume, PI and RI between the better and worse-MD eyes were insignificant (**Table 2, Table 3**)

Table 2. Internal carotid artery color Doppler Ultrasonography results

	Eye		
	Better-MD	Worse-MD	p
Peaksystolic velocity	63.21±15.61	60.73±15.02	0.526
End diastolic velocity	22.42±8.34	22.99±7.57	0.779
Peaksystolic/End diastolic velocity	3.07±1.37	2.94±0.69	0.624
Volumetric flow	403.19±130.42	374.27±107.35	0.344
Pulsatility index	1.13±0.32	1.15±0.40	0.819
Resistivitiy index	0.64±0.10	0.86±1.31	0.348

MD; Mean Deviation, Data are given as mean±standard deviation.

Table 3. Ophthalmic artery color Doppler Ultrasonography results

	Eye		
	Better-MD	Worse-MD	p
Peaksystolic velocity	60.87±15.15	63.09±16.4	0.564
End diastolic velocity	23.05±7.92	23.01±8.93	0.982
Peaksystolic/End diastolic velocity	2.89±0.67	2.99±1.33	0.624
Volumetric flow	372.50±122.50	415.18±145.95	0.195
Pulsatility index	1.13±0.38	1.10±0.31	0.657
Resistivitiy index	0.83±1.24	0.63±0.10	0.335

MD; Mean Deviation, Data are given as mean±standard deviation.

Mean IOP/mean OPA values were insignificantly correlated to age of the patients (r=-0.37/0.16, p=0.132/0.608). MD/PSD values were insignificantly correlated to each diurnal IOP and OPA values, minimum, maximum and mean IOP and OPA values, all measured (PSV, EDV, PSV/EDV, PI, RI) ophthalmic artery and internal carotid artery hemodynamic variables.

DISCUSSION

OPA has been proposed to be an indicator of the choroidal perfusion and reflects the ocular blood flow corresponding with the heart pulse as a function of time. Pulsatile blood flow is mainly determined by the choroidal circulation and the contribution of the retinal circulation is almost negligible. According to the working principles of DCT, matching up the concave pressure sensor with the cornea is claimed to provide direct measurements independent of corneal properties (6, 8). However, this is controversial (14). OPA implies the pulse wave originating from the difference between the mean systolic and mean diastolic blood pressure. The effect of CCT and OPA recordings was studied in many articles and all of them concluded that OPA is not influenced by CCT (1, 7, 14). In this study, the correlation between the CCT and OPA was not statistically significant. This finding supports the literature.

Ocular perfusion pressure depends largely on both arterial blood pressure and intraocular pressure. That is, an arterial circulatory problem to the eye caused by any

of the carotid artery or ophthalmic artery disease, is of no doubt to cause reduced blood flow to the optic nerve, choroid and retina.

Also there is another known risk factor for glaucoma is hypertension (HTN). According to the study of Topouzis et al. both treated HTN and high systolic or diastolic BP are risk factors for POAG (27). In addition, glaucoma severity was determined to be higher in patients with HTN than in glaucomatous patients presenting with normal blood pressure (28).

The first ophthalmodynamometric studies that explored a relationship between carotid artery disease and glaucoma were performed by Drance et al. (15, 16) Later, O'Brien et al. reported advanced visual field loss on the side with greater resistance to blood flow in the internal carotid arteries (13). In contrast to these findings, Jampol and Miller reported five ocular hypertensive patients who did not develop chronic glaucoma after a duration between 3-12 years (17). In this study, we did not find any significant difference in the internal carotid artery flow parameters between the better-MD and worse-MD eyes of the glaucoma patients. We think that insignificant differences in blood flow parameters between the better and worse eyes does not mean 'insignificant effect' of the internal carotid artery. To explore this issue, longitudinal studies investigating the emergence of glaucoma in patients with both advanced and initial stenotic lesions in the internal carotid arteries are warranted. A reduction of the blood flow to the eye may cause hypoxia and further cell death and therefore may initiate diseases such as glaucoma (1, 8). In accordance with that assumption, most of the studies have led to the consensus about the role of ocular blood flow in the pathogenesis of glaucoma (2-5, 7-9, 18-21). Several studies reported lower OPA values in normotensive glaucoma compared with healthy subjects (7, 14, 20). However, reports conflicts for POAG. Romppaien et al. and Punjabi et al., in their large studies, found significantly higher OPA values in ocular hypertensives than normotensive glaucoma patients and normal controls (22, 23). Romppaien et al. also reported significantly lower OPA values after trabeculectomy than normal healthy controls. Stalmans et al. also found lower OPA values in POAG and NTG patients compared with healthy controls (14). Kac et al. reported significantly lower OPA values in the better eyes group than those obtained in the worse eyes group (1). However, the investigators found that the significance disappeared after correcting OPA values by IOP. In contrast to that finding, Vulsteke et al. (24) reported significant correlation between OPA and MD even after correction the OPA value for IOP. Because the latter study has a longitudinal design, its scientific value seems to be more than Kac et al.'s study.

Because the patients went on using anti-glaucoma medication during this study, the insignificant correlation between IOP and visual field loss is not surprising. However, insignificant OPA difference between the better-MD eyes and worse-MD eyes tells us important clues about POAG. With the addition of ocular hypotensive agents, IOP lowers. Then, what happens to OPA levels? If OPA would be a primary determiner in the emergence of glaucoma independent from the changes in IOP, we still would have found significant correlations between the OPA and other studied variables! But, we did not find significant correlations. This is a significant finding and tells us that OPA change in glaucoma is probably a secondary change due to IOP rather than a primary determiner in glaucoma. This is the most important finding in this study.

In the previous publications, pulsatile ocular blood flow was measured with a different device, 'Langham pulsatile ocular blood flow'. One study using that device also found lower pulse amplitudes in chronic open-angle glaucoma patients (25). Using a similar device, Zhang et al. (21) reported significantly lower pulsatile ocular blood flow in patients with POAG with respect to normal controls. The authors reported insignificant correlation between pulsatile ocular blood flow and visual field changes. However, the sensitivity and specificity of pulsatile ocular blood flow (less than 10.75 microl/s being abnormal) in diagnosing POAG was too low to be used as a diagnostic test for POAG (0.422 and 0.623, respectively).

In this study, the eyes that we included are all glaucoma eyes despite asymmetric involvement. However, we found no significant difference in both internal carotid artery and ophthalmic artery hemodynamic parameters. We know from Ocular Hypertensive Treatment study that each additional 1 mmHg increase in IOP asymmetry between the eyes is associated with a significant 21% increase in the risk of converting to POAG (26). As Romppaien et al. reported (22), ocular pulsatile blood flow are increased in ocular hypertensives, but lowered in POAG and NTG patients (1, 14, 21, 25). In addition, lowering of IOP by trabeculectomy lowers ocular pulse blood flow even under the values of healthy controls. What do these findings tell us in the light of above-explained literature findings?

IOP increase is an unobjectionable risk factor for glaucoma. The higher OPA value in the ocular hypertensive patients is probably an adaptive change to supply enough blood flow to ocular structures. This is plausible to protect the ocular homeostasis. Probably when IOP reaches to a trigger point, the balance between IOP and ocular blood supply breaks down and the pulsatile ocular blood flow or OPA values are lowered. It is probably for this reason that we did not find any significant difference

between the better-MD eyes and worse-MD eyes. That is, irrespective of MD values, all the eyes had destroyed ocular homeostasis. After IOP control, we predict that the OPA values should return to normal values. However this not the case as Romppaien et al. reported. The OPA values are lowered even beyond the normal values. That finding is also in favor of the destroyed ocular homeostasis after glaucoma trigger point.

To the best of our knowledge this is the first study reporting diurnal OPA values in asymmetric controlled glaucoma patients. This is maybe the most important and valuable aspect of this study.

CONCLUSION

This study in the light of the reports in the literature suggests that ocular balance and homeostatis may be destroyed after a critical trigger point in the glaucoma initiation despite ongoing therapy. After that point, the relation of IOP to pulsatile ocular blood flow cannot dependent to normal hemodynamic changes.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was performed with informed consent and following all the guidelines for experimental investigations required by the Institutional Review Board or Ethics Committee of which all authors are affiliated (6 June 2007, 1491-444-07).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Kac MJ, Solari HP, Velarde GC, Brazuna R, Cardoso GP, Ventura MP. Ocular pulse amplitude in patients with asymmetric primary open-angle glaucoma. Curr Eye Res 2011; 36: 727-32.
2. Agarwal HC, Gupta V, Sihota R, Singh K. Pulsatile ocular blood flow among normal subjects and patients with high tension glaucoma. Indian J Ophthalmol 2003; 51: 133-8.
3. Cioffi GA, Alm A. Measurement of ocular blood flow. J Glaucoma 2001; 10: S62-4.
4. Emre M, Orgul S, Gugleta K, Flammer J. Ocular blood flow alteration in glaucoma is related to systemic vascular dysregulation. Br J Ophthalmol 2004; 88: 662-6.
5. Fontana L, Poinoosawmy D, Bunce CV, O'Brien C, Hitchings RA. Pulsatile ocular blood flow investigation in asymmetric normal tension glaucoma and normal subjects. Br J Ophthalmol 1998; 82: 731-6.
6. Kanngiesser HE, Kniestedt C, Robert YC. Dynamic contour tonometry: presentation of a new tonometer. J Glaucoma 2005; 14: 344-50.
7. Schwenn O, Troost R, Vogel A, Grus F, Beck S, Pfeiffer N. Ocular pulse amplitude in patients with open angle glaucoma, normal tension glaucoma, and ocular hypertension. Br J Ophthalmol 2002; 86: 981-4.
8. Hoffmann EM, Grus FH, Pfeiffer N. Intraocular pressure and ocular pulse amplitude using dynamic contour tonometry and contact lens tonometry. BMC Ophthalmol 2004; 4: 4.
9. Flammer J, Orgul S, Costa VP, et al. The impact of ocular blood flow in glaucoma. Progress in retinal and eye research 2002; 21: 359-93.
10. Flammer J, Orgul S. Optic nerve blood-flow abnormalities in glaucoma. Prog Retin Eye Res 1998; 17: 267-89.
11. Plange N, Bienert M, Remky A, Arend KO. Optic disc fluorescein leakage and intraocular pressure in primary open-angle glaucoma. Current eye research 2012; 37: 508-12.
12. Knecht PB, Bosch MM, Menke MN, Bachmann LM, Funk J, Kaufmann C. Dynamic contour tonometry: handheld versus slit-lamp-mounted. Ophthalmology 2009; 116: 1450-4.
13. O'Brien C, Saxton V, Crick RP, Meire H. Doppler carotid artery studies in asymmetric glaucoma. Eye (Lond) 1992; 6: 273-6.
14. Stalmans I, Harris A, Vanbellinghen V, Zeyen T, Siesky B. Ocular pulse amplitude in normal tension and primary open angle glaucoma. J Glaucoma 2008; 17: 403-7.
15. Drance SM, Wheeler C, Pattullo M. Uniocular open-angle glaucoma. Am J Ophthalmol 1968; 65: 891-902.
16. Feldman F, Sweeney VP, Drance SM. Cerebro-vascular studies in chronic simple glaucoma. Can J Ophthalmol 1969; 4: 358-64.
17. Jampol LM, Miller NR. Carotid artery disease and glaucoma. Br J Ophthalmol 1978; 62: 324-6.
18. Flammer J. Psychophysical mechanisms and treatment of vasospastic disorders in normal-tension glaucoma. Bulletin de la Societe belge d'ophtalmologie 1992; 244: 129-34.
19. Goff MJ, Kerrison JB. Bilateral simultaneous anterior ischemic optic neuropathy in a young, healthy man. Arch Ophthalmol 2003; 121: 1652-3.
20. Schmidt KG, von Ruckmann A, Pillunat LE. Topical carbonic anhydrase inhibition increases ocular pulse amplitude in high tension primary open angle glaucoma. Br J Ophthalmol 1998; 82: 758-62.
21. Zhang MZ, Fu ZF, Liu XR, Zheng C. [A comparison study of pulsitile ocular blood flow in normal eyes and primary open angle glaucoma]. Zhonghua Yan Ke Za Zhi 2004; 40: 250-3.
22. Romppainen T, Kniestedt C, Bachmann LM, Sturmer J. [Ocular pulse amplitude: a new biometrical parameter for the diagnose of glaucoma?]. Ophthalmologe 2007; 104: 230-5.
23. Punjabi OS, Ho HK, Kniestedt C, Bostrom AG, Stamper RL, Lin SC. Intraocular pressure and ocular pulse amplitude comparisons in different types of glaucoma using dynamic contour tonometry. Curr Eye Res 2006; 31: 851-62.
24. Vulsteke C, Stalmans I, Fieuws S, Zeyen T. Correlation between ocular pulse amplitude measured by dynamic contour tonometer and visual field defects. Graefes Arch Clin Exp Ophthalmol 2008; 246: 559-65.
25. Trew DR, Smith SE. Postural studies in pulsatile ocular blood flow: II. Chronic open angle glaucoma. Br J Ophthalmol 1991; 75: 71-5.

26. Levine RA, Demirel S, Fan J, et al. Asymmetries and visual field summaries as predictors of glaucoma in the ocular hypertension treatment study. Invest Ophthalmol Vis Sci 2006; 47: 3896-903.
27. Topouzis F, Wilson MR, Harris A, et al. Risk factors for primary open-angle glaucoma and pseudoexfoliative glaucoma in the Thessaloniki eye study. Am J Ophthalmol 2011; 152: 219-28.
28. Khatri A, Shrestha JK, Thapa M, Khatri BK, Kharel M. Severity of primary open-angle glaucoma in patients with hypertension and diabetes. Diabetes Metab Syndr Obes 2018; 11: 209-15.