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Effect of treatment by medicine or surgery on intraocular pressure and pulsatile ocular blood flow in normal-pressure glaucoma

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Abstract *Purpose:* To study the effect of trabeculectomy and monotherapy with topical betaxolol, brimonidine and latanoprost on intraocular pressure (IOP) and pulsatile ocular blood flow (POBF) in patients with normal-pressure glaucoma (NPG). *Methods:* In this retrospective study NPG patients attending the glaucoma research unit at Moorfields Eye Hospital were reviewed. Patients treated by surgery or topical medication (betaxolol, brimonidine or latanoprost) who had pre- and post-treatment IOP and POBF measurements were studied. For those patients who were having treatment to both eyes, one eye was selected at random for analysis. *Results:* A total of 147 patients were reviewed. Forty-three eyes were receiving betaxolol 0.5%, 58 eyes latanoprost 0.005%, 23 eyes brimonidine 0.2% and 23 eyes had undergone trabeculectomy surgery. There were more female than male patients in all four groups, and the groups were similar with regards age. Pre-treatment IOP and POBF values were similar among the groups (P=0.27, P=0.08 respectively). Post-treatment IOP values tended to be lower than pre-treatment values for all four groups. All groups had an increased POBF except for betaxolol, where POBF decreased. *Conclusion:* Patients treated by trabeculectomy and those receiving topical latanoprost and brimonidine had lower IOP and higher POBF following treatment. The betaxolol-treated group, despite a slight decrease in IOP, had a decreased POBF. Lowering IOP by treatment may not necessarily be associated with an increase in POBF.

Introduction

Normal-pressure glaucoma (NPG) is a subset of primary open-angle glaucoma (POAG) defined as eyes with glaucomatous cupping and visual field damage and normal intraocular pressure (IOP) [15, 28, 29, 30]. Although the pathogenesis of POAG is still unclear, IOP is considered to be a major risk factor for developing the disease [14]. Other factors, mainly of vascular origin, have been proposed for the pathogenesis [4, 28]. Systemic hypotension [7], cardiac vascular disease [4, 10], vasospasm [5, 12] and rheological alteration, such as increased viscosity and a hypercoagulable state, have been reported to occur more often in NPG patients than in normal subjects [25], suggesting that ischaemia may be partly responsible for optic nerve head damage in NPG. Angiographic studies also support the concept of reduced vascular perfusion to the optic nerve head in these patients [9, 33, 36]. Although it has been suggested that lowering IOP in NPG patients may be beneficial in slowing the disease process, some patients still show progressive damage despite reducing pressures [1, 21, 35]. Therefore, it is suggested that factors such as ocular perfusion may also play an important role in determining disease progression in NPG [2, 9].

Various methods have been developed to measure the ocular blood flow, such as scanning laser ophthalmoscopy [22, 27], Doppler ultrasound, and measurement of

pulsatile ocular blood flow (POBF). The latter is a technique based on continuous recording of IOP by means of a pneumotonometer, allowing measurement of the pressure wave (pulse amplitude) of the ocular pulsation during a cardiac cycle. This technique, described by Langham and To'may in 1987, derives blood flow measurements from the pressure/volume relationship, allowing the measurement of the pulsatile component of ocular blood flow [16, 17, 19]. (This accounts for 80–90% of total ocular blood flow.) Pulsatile blood flow is mainly determined by the choroidal circulation, with the retinal circulation contributing minimally [18]. This is relevant to studying ocular haemodynamics in NPG patients as the posterior ciliary arteries are responsible for supplying choroidal circulation and the anterior optic nerve [26]. Several studies have shown high coefficients of reliability for POBF measurement, of between 0.7 and 0.92 [23, 31, 37].

The purpose of this study was to investigate the effects of surgery and different topical medical treatments on ocular blood flow as measured by POBF tonometry in NPG patients.

Material and methods

Patients attending the NPG Clinic at Moorfields Eye Hospital who were initiated on monotherapy with either betaxolol 0.5%, brimonidine 0.2% or latanoprost 0.005% and those who had undergone trabeculectomy were studied retrospectively. The NPG diagnosis was based on: (a) mean untreated IOP <21 mmHg on diurnal phasing (no single reading exceeding 23 mmHg), (b) reproducible visual field defect typical of glaucoma, (c) glaucomatous optic nerve head cupping, (d) open drainage angles on gonioscopy and (e) no past history of elevated IOP. Patients with systemic or other ocular disease such as macular disease, diabetic retinopathy and cataract that could influence the study were excluded.

IOP and POBF measurements

If both eyes had been treated, one eye per patient was randomly selected for the study. Pre-treatment IOP values measured with the Goldmann applanation tonometer and POBF measurements with the OBF Labs., (UK) tonometer version 1.55 were taken as the baseline at a time when the patient had been taking no topical medication for at least 2 weeks. Post-treatment measurements were taken at 6 months after surgery, and 1–3 months after initiating topical medication. Although different operators measured IOP and POBF, all had gained sufficient experience with the techniques to avoid initial operator-induced variability [23].

Data were analysed using the Statistical Package for Social Sciences (SPSS for Windows, version 9.0; SPSS, Chicago, Ill., USA). Continuous variables were compared using one-way analysis of variance (ANOVA), and categorical variables were analysed using a chi-square test. If a significant difference was detected using ANOVA, *t*-tests were conducted for pairwise comparisons with appropriate Bonferroni corrections. Significant tests were constructed to compare pre-treatment IOP/POBF with post-treatment IOP/POBF. Scatter plots of the percentage change in IOP against percentage change in POBF were constructed for each treatment group. In addition to this a chi-square test was conducted to see whether the proportion of patients with reduced IOP but increases in POBF was the same in each treatment group.

Results

Pre- and post-treatment data from 147 NPG patients were analysed. Betaxolol was used in 43 eyes, latanoprost in 58, brimonidine in 23, and trabeculectomy had been performed on 23 eyes. The demographic data for age, mean deviation (MD) and corrected-pattern standard deviation (CPSD) are presented for each group in Table 1. We found no evidence of any differences in age and CPSD between the betaxolol, latanoprost, brimonidine and surgery groups. The surgery group, however, had higher mean MD than the betaxolol and latanoprost groups (P=0.04).

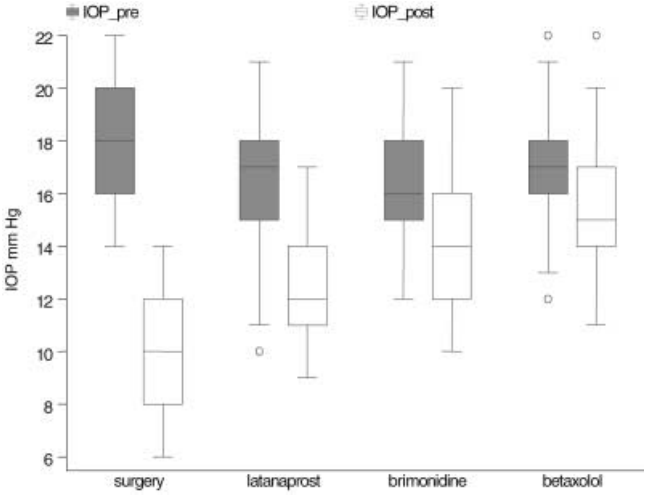

Fig. 1 Box plot of IOP pre and post treatments for each treatment group

Table 1 Demographic data of the Surgery, latanoprost, brimonodine and betaxolol group of patients

Characteristic	Surgery	Latanoprost	Brimonidine	Betaxolol	*P* value	Test
Number of eyes	23	58	23	43	–	–
Sex (M/F)	7/16	15/43	5/18	13/30	0.87	Chi-square
Age in years (SD)	66.4 (7.7)	70.5 (8.2)	71.6 (7.04)	68.7 (10.5)	0.15	ANOVA
MD[a]	–14.4 (6.5)	–9.23 (6.5)	–10.5 (7.2)	–8.9 (7.2)	0.04	ANOVA
CPSD	10.1 (2.9)	8.3 (3.8)	8.4 (3.1)	9.3 (3.7)	0.29	ANOVA

[a] Post-hoc comparisons of MD revealed statistically significant differences between surgery and each of betaxolol and latanoprost

Table 2 Pre- and post-treatment measurements of IOP and POBF for the four groups

Parameter	Surgery 1 (*n*=23)	Latanoprost 2 (*n*=58)	Brimonidine 3 (*n*=23)	Betaxolol 4 (*n*=43)	*P* value (ANOVA)	Post-hoc comparisons
IOP (mmHg)						
Before treatment	17.7 (2.5)	16.7 (2.2)	16.5 (2.5)	17.1 (2.3)	0.268	
After treatment	9.8 (2.4)	12.6 (2)	14.3 (2.6)	15.5 (2.3)	<0.001	1–2, 1–3, 1–4, 2–3, 2–4
Difference	7.9 (3.8)	4.1 (2.5)	2.2 (2.3)	1.6 (2.1)		
Mean change (%)	43.3 (18.2)	23.8 (13.5)	12.7 (12.8)	8.6 (12.1)	<0.001	1–2, 1–3, 1–4, 2–3, 2–4
POBF (µl/min)						
Before treatment	612.3 (166.6)	628.9 (224.3)	662.9 (200.7)	724.1 (193.5)	0.08	
After treatment	752.3 (236.4)	880.4 (305.9)	794.8 (269.1)	631 (180.9)	<0.001	2–4, 3–4
Difference	–140.0 (148.1)	–251.6 (154.9)	–132.0 (158.3)	93 (105.3)		
Mean change (%)	–24.2 (27.8)	–43.5 (25.1)	–22.7 (31.5)	11.95 (15.8)	<0.001	1–2, 1–4, 2–3, 2–4, 3–4

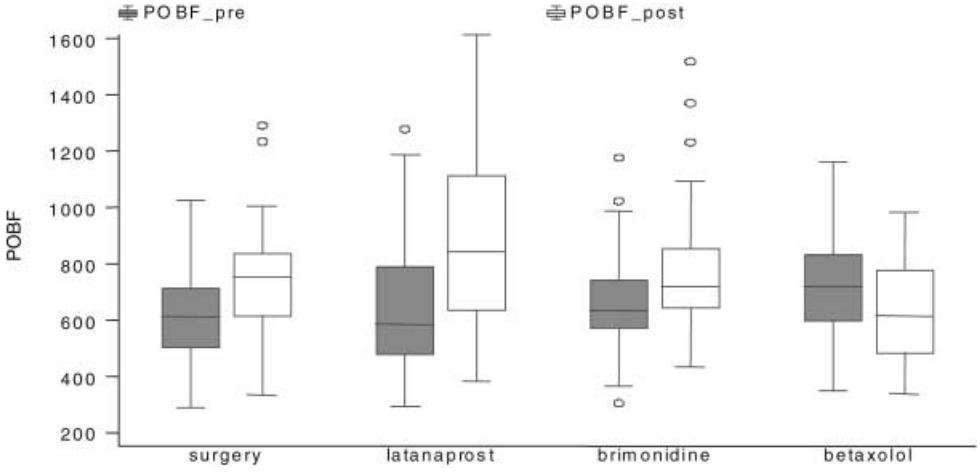

Fig. 2 Box plot of POBF pre and post treatments for each treatment group

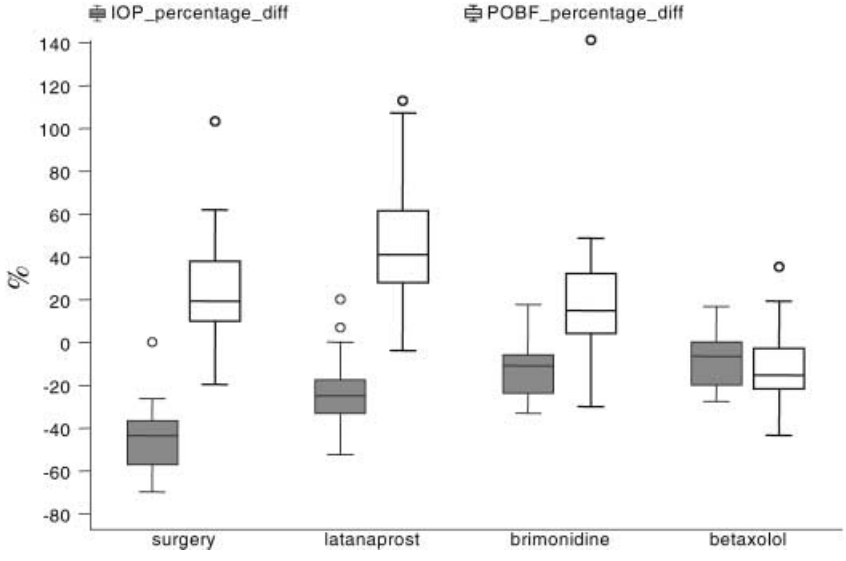

Fig. 3 Box plot of percentage change in IOP and POBF for each treatment group

The IOP and POBF measurements, before and after treatment, are displayed in Table 2. Prior to treatment, IOP and POBF were similar in the four treatment groups, as shown in Figs. 1 and 2, although POBF tended to be slightly higher in the group which was later treated with betaxolol. In each group, IOP was reduced with treatment, but greater reductions were seen in the surgically treated group than the medically treated groups

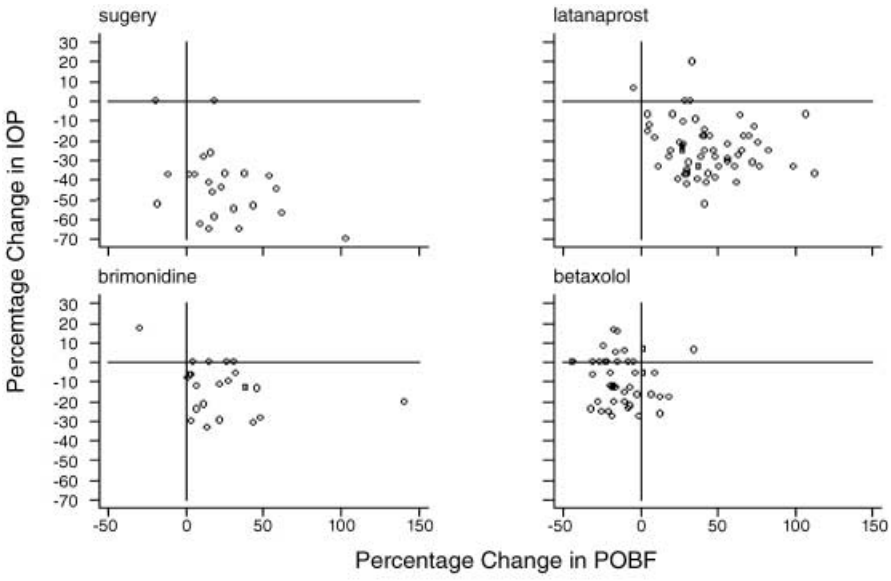

Fig. 4 Scatter plot of percentage change IOP against POBF for each treatment group

(P<0.001) and patients treated with latanoprost had greater reductions in IOP than patients treated with brimonidine and betaxolol (P<0.001): 43% IOP reduction in the surgery group, 24% with latanoprost, 13% with brimonidine and 9% in the betaxolol group. The difference in IOP/POBF between pre- and post-treatment valueswas statistically significant for each group {P<0.001}

Prior to treatment, POBFs were similar between the groups, although slightly higher in the group which was to be treated with betaxolol. Whilst in the groups treated with surgery, latanoprost and brimonidine there was an increase in POBF, the reverse was seen in the group treated with betaxolol; the difference was statistically significant (P<0.001). The greatest increase in POBF was seen in the group treated with latanoprost, and this increase was statistically significantly greater than that observed in the other three groups (P<0.001): 24% increase in the surgery group, 44% with latanoprost, 23% with brimonidine and 12% decrease in the betaxolol group (Fig. 3).

Figure 4 shows that there is a tendency for POBF to increase with a decrease in IOP. Despite this overall trend, many patients in the betaxolol-treated group showed a decreased POBF despite a decrease in IOP, compared with none in the latanoprost or brimonidine groups and just 2/19 patients treated surgically. This difference was statistically significant (P<0.001).

Discussion

This study shows that lowering of the mean IOP may not necessarily be associated with a corresponding increase in POBF. Trabeculectomy achieved a mean IOP reduction of 43% associated with POBF increasing by 24%; latanoprost reduced IOP by 24% and increased the POBF by 44%; brimonidine reduced IOP by 13% and increased POBF by 23%; and betaxolol reduced IOP by 9% and reduced POBF by 12%.

Our clinic policy was to restrict treatment to eyes with visual field progression in NPG. They were usually started on topical medication first as monotherapy, then additional drops were added if the desired IOP was not achieved. Surgery was usually offered when medical treatment failed to maintain IOP at the desired level. Most patients were on medical therapy prior to surgery which was stopped after surgery. As POBF measurements were taken 6 months after surgery, any effect of medical therapy would have ceased. The results in this study may therefore reflect inherent biases from this practice. As this was a retrospective study, further bias arising from case selection could not be excluded. All patients in this study were managed on monotherapy.

Latanoprost, although not as effective as surgery in reducing IOP, had a greater effect on POBF; this may reflect a local increase to flow in the microvascular circulation of the optic nerve head [32]. Our findings of increased POBF with latanoprost are in line with previous studies. Vertrugno et al. [34] reported a decrease in IOP by 47% and increased choroidal perfusion of 55% after first instillation of latanoprost. Similar results were reported by McKibbin and Menage [20], who found a reduction in IOP accompanied by an increase in POBF of around 140 µl/min. Furthermore, the significant reduction in IOP and increase in POBF after surgical treatment in our sample is similar to the results of James [13], who found a decrease of 48% in IOP and an increase of 29% in POBF in glaucoma patients.

The beta-blocker effect on POBF was studied by Morsman et al. [24], who compared the effects of three

types of topical beta-adrenoceptor agents (timolol, levobunolol and betaxolol) on POBF and IOP. Betaxolol produced the least reduction in IOP but decreased POBF in a way similar to timolol, while levobunolol reduced IOP and increased POBF.

Although betaxolol is a selective beta1-receptor drug, it is recognized to have some beta2-receptor effect. We speculate that the negative effect of betaxolol on POBF may be due to an effect on cardiac output, for by inducing slower heart rate and reduction in myocardial contraction, the arterial flow to the upper body may be reduced, especially at night [11]. Previous reports have also suggested an increased vasoconstriction of the ocular vessels due to blockage of beta-receptors existing in the choroid, optic nerve head and retina [3, 6]. Furthermore, the stimulation of alpha vascular receptors is not inhibited by the beta-blockers [7].

The relevance of POBF to the preservation of vision in glaucoma is not fully understood. Optic nerve blood flow is presumably dependent on both pulsatile and nonpulsatile components and this may vary regionally through the tissue and affect susceptibility to ischaemia in its different parts. Although retinal blood flow is a small component of total ocular blood flow, it may still be important in the perfusion of retinal ganglion cells; treatment that increases choroidal, retinal and optic nerve blood flow, while lowering IOP, is therefore desirable [34]. Although IOP is important in NPG, studies suggest that other factors, such as poor ocular perfusion, may also be important in mediating ongoing optic nerve head damage.

In summary, we found that all forms of treatment were associated with decreases in IOP but that changes were most marked in our NPG patients treated with surgery and in those treated with latanoprost. Increases in POBF were seen in our NPG patients treated with surgery, latanoprost and brimonidine, but in patients treated with betaxolol we observed a small reduction in POBF.

References

1. Bhandari A, Crabb DP, Poinoosawmy D, Fitzke FW, Hitchings RA, Noureddin BN (1997) Effect of surgery on visual field progression in normal-tension glaucoma. Ophthalmology 104:1131–1137
2. Butt Z, McKillop G, O'Brien C, Allan P, Aspinall P (1995) Measurement of ocular blood flow velocity using colour Doppler imaging in low tension glaucoma. Eye 9:29–33
3. Dawidek GM, Robinson MI (1993) Beta-adrenergic receptors in human anterior optic nerve: an autoradiographic study. Eye 7:122–126
4. Drance SM, Sweeney VP, Morgan RW, Feldman F (1973) Studies of factors involved in the production of low tension glaucoma. Arch Ophthalmol 89:457–465
5. Drance SM, Douglas GR, Wijsman K, Schulzer M, Britton RJ (1988) Response of blood flow to warm and cold in normal and low-tension glaucoma patients. Am J Ophthalmol 105:35–39
6. Elena PP, Denis P, Kosina-Boix M, Saraux H, Lapalus P (1990) Beta adrenergic binding sites in the human eye: an autoradiographic study. J Ocul Pharmacol 6:143–149
7. Graham SL, Drance SM, Wijsman K, Douglas GR, Mikelberg FS (1995) Ambulatory blood pressure monitoring in glaucoma. The nocturnal dip. Ophthalmology 102:61–69
8. Grajewski AL, Ferrari-Dileo G, Feuer WJ, Anderson DR (1991) Beta-adrenergic responsiveness of choroidal vasculature. Ophthalmology 98:989–995
9. Harris A, Sergott RC, Spaeth GL, Katz JL, Shoemaker JA, Martin BJ (1994) Color Doppler analysis of ocular vessel blood velocity in normal-tension glaucoma. Am J Ophthalmol 118:642–649
10. Hayreh SS, Zimmerman MB, Podhajsky P, Alward WL (1994) Nocturnal arterial hypotension and its role in optic nerve head and ocular ischemic disorders. Am J Ophthalmol 117:603–624
11. Hayreh SS, Podhajsky P, Zimmerman MB (1999) Beta-blocker eyedrops and nocturnal arterial hypotension. Am J Ophthalmol 128:301–309
12. Hollo G, Lakatos P, Farkas K (1998) Cold pressor test and plasma endothelin-1 concentration in primary open-angle and capsular glaucoma. J Glaucoma 7:105–110
13. James CB (1994) Effect of trabeculectomy on pulsatile ocular blood flow. Br J Ophthalmol 78:818–822
14. Jay JL, Murdoch JR (1993) The rate of visual field loss in untreated primary open angle glaucoma. Br J Ophthalmol 77:176–178
15. Klein BE, Klein R, Sponsel WE, Franke T, Cantor LB, Martone J, Menage MJ (1992) Prevalence of glaucoma. The Beaver Dam Eye Study. Ophthalmology 99:1499–1504
16. Krakau CE (1992) Calculation of the pulsatile ocular blood flow. Invest Ophthalmol Vis Sci 33:2754–2756
17. Langham ME, To'may K (1987) A clinical procedure for measring the ocular pulse pressure relationship and the ophthalmic arterial pressure. Exp Eye Res 27:17–25
18. Langham ME, Farrell MA, O'Brien V, Silver DM, Schilder P (1989a) In: Lambrou GN, Greve EL (eds) Ocular blood flow in glaucoma. pp 93–99
19. Langham ME, Farrell RA, O'Brien V, Silver DM, Schilder P (1989b) Blood flow in the human eye. Acta Ophthalmol Suppl 191:9–13
20. McKibbin M, Menage MJ (1999) The effect of once-daily latanoprost on intraocular pressure and pulsatile ocular blood flow in normal tension glaucoma. Eye 13:31–34
21. Membrey WL, Poinoosawmy DP, Bunce C, Fitzke FW, Hitchings RA (2000) Comparison of visual field progression in patients with normal pressure glaucoma between eyes with and without visual field loss that threatens fixation. Br J Ophthalmol 84:1154–1158
22. Michelson G, Groh MJM (1994) Methods for investigation of circulatory changes in glaucoma. Curr Opin Ophthalmol 5:46–57
23. Morgan A, Hosking S (2001) Ocular blood flow tonometer reproducibility: the effect of operator experience and mode of application. Ophthalmic Physiol Opt 21:401–406

24. Morsman CD, Bosem ME, Lusky M, Weinreb RN (1995) The effect of topical beta-adrenoceptor blocking agents on pulsatile ocular blood flow. Eye 9:344–347
25. O'Brien C, Butt Z, Ludlam C, Detkova P (1997) Activation of the coagulation cascade in untreated primary open-angle glaucoma. Ophthalmology 104:725–729; discussion 729–730
26. Onda E, Cioffi GA, Bacon DR, Van Buskirk EM (1995) Microvasculature of the human optic nerve. Am J Ophthalmol 120:92–102
27. Riva CE, Harino S, Petrig BL, Shonat RD (1992) Laser Doppler flowmetry in the optic nerve. Exp Eye Res 55:499–506
28. Schulzer M, Drance SM, Carter CJ, Brooks DE, Douglas GR, Lau W (1990) Biostatistical evidence for two distinct chronic open angle glaucoma populations. Br J Ophthalmol 74:196–200
29. Shiose Y, Kitazawa Y, Tsukahara S, Akamatsu T, Mizokami K, Futa R, Katsushima H, Kosaki H (1991) Epidemiology of glaucoma in Japan – a nationwide glaucoma survey. Jpn J Ophthalmol 35:133–155
30. Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt J, Singh K (1991) Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. Arch Ophthalmol 109:1090–1095
31. Spraul CW Lang, GE Ronzani, M Hogel J, Lang GK (1998) Reproducibility of measurements with a new slit lamp-mounted ocular blood flow tonograph. Graefes Arch Clin Exp Ophthalmol 236:274–279
32. Stjernschantz J, Selen G, Astin M, Resul B (2000) Microvascular effects of selective prostaglandin analogues in the eye with special reference to latanoprost and glaucoma treatment. Prog Retin Eye Res 19:459–496
33. Tuulonen A, Nagin P, Schwartz B, Wu DC (1987) Increase of pallor and fluorescein-filling defects of the optic disc in the follow-up of ocular hypertensives measured by computerized image analysis. Ophthalmology 94:558–563
34. Vetrugno M, Cantatore F, Gigante G, Cardia L (1998) Latanoprost 0.005% in POAG: effects on IOP and ocular blood flow. Acta Ophthalmol Scand Suppl 227:40–41
35. Werner EB, Drance SM (1977) Progression of glaucomatous field defects despite successful filtration. Can J Ophthalmol 12:275–280
36. Wolf S, Arend O, Sponsel WE, Schulte, K Cantor LB, Reim M (1993) Retinal hemodynamics using scanning laser ophthalmoscopy and hemorheology in chronic open-angle glaucoma. Ophthalmology 100:1561–1566
37. Yang YC, Hulbert MF. Batterbury M, Clearkin LG (1997) Pulsatile ocular blood flow measurements in healthy eyes: reproducibility and reference values. J Glaucoma 6:175–179