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Effects of betaxolol and latanoprost on ocular blood flow and visual fields in patients with primary open-angle glaucoma

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PURPOSE. *To evaluate the effects of betaxolol and latanoprost on ocular blood flow and visual fields in patients with primary open-angle glaucoma (POAG) by means of an observer-masked, prospective clinical study.*

METHODS. *Thirty-two patients with newly diagnosed POAG were included in the study. The patients were randomized into two groups. The first group was treated with betaxolol 0.50% twice daily and the second group with latanoprost 0.005% once daily. Baseline and post-treatment examinations on the first and third months of treatment included intraocular pressure (IOP) measurement, automated visual field testing, and ocular blood flow assessment. For evaluation of visual fields, mean defect and pattern standard deviation indices were used. Ocular blood flow was assessed by means of color Doppler imaging of the central retinal artery (CRA) and the temporal short posterior ciliary artery (PCA). For each vessel, peak systolic (PSV) and end-diastolic (EDV) blood flow velocities were measured and resistivity index (RI) calculated.*

RESULTS. *After exclusion of one noncompliant patient, the study was completed with 31 eyes of 31 patients. Both drugs significantly reduced IOP ($p<0.05$). The mean IOP lowering effect of latanoprost was significantly higher than that of betaxolol ($p=0.03$). Visual field indices exhibited no significant changes in either group ($p>0.05$). There were no significant changes in PSV or EDV measurements of CRA or PCA in either group ($p>0.05$). RI decreased in both CRA and PCA with both drugs. The mean changes between baseline and 3 month blood flow measurements were not significantly different between betaxolol and latanoprost ($p>0.05$).*

CONCLUSIONS. *Over a treatment period of 3 months, both betaxolol and latanoprost tended to improve ocular blood flow without one of them being superior to the other. The results suggest that the direct (non IOP-dependent) influence on ocular circulation is better for betaxolol than for latanoprost. In addition, neither drug caused significant generalized improvements in visual fields during this period. (Eur J Ophthalmol 2004; 14:211-9)*

KEY WORDS. *Betaxolol, Blood flow, Color Doppler imaging, Latanoprost, Primary open-angle glaucoma, Visual fields*

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INTRODUCTION

Primary open-angle glaucoma (POAG) is an optic neuropathy accompanied by characteristic visual field losses. The exact pathophysiology of glaucoma is unknown. Elevated intraocular pressure (IOP) is the best known and regarded as the most important causative factor, although there is growing interest and evidence in other risk factors and their potential association with glaucoma (1-4).

The current treatment strategy in the management of POAG is lowering of IOP by either ocular hypotensive medications or surgery. However, clinical research and observations suggest that decreased optic nerve head perfusion is one of the suspected factors involved in the pathogenesis of the disease (3, 5, 6). Thus, it can be speculated that ocular hypotensive medications may have additional beneficial effects if they improve ocular hemodynamics besides decreasing IOP. In addition, any reduction in ocular blood flow due to topical ocular hypotensive drugs should be avoided.

Beta blockers have been the drug of choice for the treatment of glaucoma for the past two decades, but newer and more potent agents have become available, such as the prostaglandin derivatives. Studies on both betaxolol, a $ß_1$ selective blocker (7-13), and latanoprost, a prostaglandin analogue (14-21), suggest that they may have influences on ocular blood flow besides their ocular hypotensive effects. Ocular hypotensive drugs that possess multiple beneficial effects in halting the progression of the disease might prove to be the drugs of choice in the management of POAG.

The aim of this observer-masked, prospective clinical study was to investigate the effects of betaxolol and latanoprost on ocular blood flow and visual fields in patients with POAG.

METHODS

Thirty-two patients who were diagnosed with POAG, with no previous history of medical or surgical treatment for glaucoma or cataract, were enrolled in the study. Diagnosis of POAG was established by IOP measurement, gonioscopic examination, typical automated visual field defects, and funduscopic findings.

The patients were randomized into two groups. The first group was treated with topical betaxolol 0.50% eye drops twice daily and the second group with topical latanoprost 0.005% drops once daily. Baseline and post-treatment examinations on the first and third months of treatment included IOP measurement, automated visual field testing, and color Doppler imaging (CDI).

All IOP measurements were done with Goldmann applanation tonometer by one of us (H.D.), who was masked to the type of treatment. The visual fields were derived using SITA-Standard 30-2 algorithm of the Humphrey Field Analyzer (Humphrey-Zeiss, Jena, Germany). Before the commencement of the study, automated visual field testing was explained to all participating patients. To determine the baseline perimetry, two visual field examinations were performed, and the second test was used for analysis. Reliability indices for perimetric testing were within the manufacturer's standards required for a reliable test. Mean deviation (MD) and pattern standard deviation (PSD) indices as calculated by the Humphrey Field Analyzer were used for evaluation of the test results.

CDI was carried using the 7.5 mHz electronic linear transducer of Hewlett-Packard Image-Point instrument (Model L7535, CA). For cardiac stability, blood flow velocities were measured after 5 minutes of resting in supine position. Methylcellulose gel was applied onto closed eyelids and patients were instructed not to move their eyes and to look forward; care was given to avoid pressure on the eye during the examination. At each examination, peak systolic velocity (PSV) and end-diastolic velocity (EDV) were measured for central retinal artery (CRA) and the temporal short posterior ciliary artery (PCA). The resistivity index (RI) was calculated automatically from the instrument, by using Pourcelot's formula: (PSV–EDV)/PSV. At each examination period, blood flow velocity was measured three times for each patient and each vessel and the results averaged to obtain a single value. All the CDI procedures were performed by an experienced operator (S.T.) who was masked to the type of treatment.

During Doppler examination, the operator attempted to align the beam parallel to the vessel under observation. Since the angle between the transducer and the CRA was usually less than 20° and close to 0, no angle correction was applied for CRA (22). However, angle correction was applied for PCA since the anatomic pathway of the PCA is tortuous (23).

After the completion of the study, baseline and both

posttreatment periods' IOP, visual field index, and CDI values were statistically compared by using Friedman test. If a significance was found, Wilcoxon signed rank test was performed to find between which study periods this significance occurred. We also compared the mean changes between baseline and third month values of blood flow data by using Mann-Whitney U test. Only the data from right eyes of patients were included for statistical comparison. A p value of <0.05 was regarded as statistically significant.

RESULTS

One patient from the latanoprost group was excluded from the study because of noncompliance, and the study was completed with 31 patients, 16 in betaxolol, 15 in latanoprost group. There were 10 women and 6 men in the betaxolol group, and 9 women and 6 men in the latanoprost group. The mean age of patients in the betaxolol group was 49.6 ± 8.1, and the mean age in the latanoprost group was 54.3 ± 10.9. The groups were similar with regards to age (p=0.20).

The mean baseline and post-treatment IOP measurements in betaxolol and latanoprost groups are shown in Table I. The mean basal IOP measurements of the two treatment groups were not significantly different from each other (p=0.18). With treatment, mean IOP measurements decreased significantly in both groups (p=0.001, Friedman test, Tab. I). The mean IOP decrease in betaxolol and latanoprost groups were 3.3±2.3 mmHg and 5.2±3.5 mmHg, respectively. The mean IOP lowering effect of latanoprost was significantly higher than that of betaxolol (p=0.03).

The results of visual field indices in the betaxolol group are shown in Table II. The MD increased and the PSD decreased from basal values with treatment. However, these improvements in MD and PSD were not statistically significant (p>0.05, Friedman test, Tab. II).

The results of visual field indices in the latanoprost group are presented in Table III. The MD increased and the PSD decreased from basal values with treatment. All of these changes were statistically insignificant (p>0.05, Friedman test, Tab. III).

TABLE I - MEAN BASELINE AND POST-TREATMENT IOP MEASUREMENTS

Group	Baseline	Post-treatment 1 month	Post-treatment 3 months	p value
Betaxolol	23.1±2.0	21.0±2.2	20.1±2.4	0.001
Latanoprost	24.4±3.0	20.9±3.3	19.9±3.2	0.001

Values are mmHg; IOP = Intraocular pressure

TABLE II - MEAN BASELINE AND POST-TREATMENT VISUAL FIELD INDICES OF BETAXOLOL GROUP

Indices	Baseline	Post-treatment 1 month	Post-treatment 3 months	p value
MD (dB)	-1.98±2.40	-1.09±2.22	-1.53±2.27	0.15
PSD (dB)	2.40±1.42	2.08±1.24	2.35±2.00	0.14

MD = Mean deviation; PSD = Pattern standard deviation

TABLE III - MEAN BASELINE AND POST-TREATMENT VISUAL FIELD INDICES OF LATANOPROST GROUP

Indices	Baseline	Post-treatment 1 month	Post-treatment 3 months	p value
MD (dB)	-1.13±3.51	-1.43±1.96	-1.15±2.18	0.31
PSD (dB)	2.90±1.69	2.65±1.85	2.42±1.44	0.34

MD = Mean deviation; PSD = Pattern standard deviation

The results of CDI measurements for the betaxolol group are shown in Table IV. In the CRA, mean PSV and EDV increased, RI decreased with treatment ($p>0.05$, Friedman test, Tab. IV). In the PCA, mean PSV and RI decreased, EDV increased ($p>0.05$, Friedman test, Tab. IV).

The results of CDI measurements for the latanoprost group are displayed in Table V. With latanoprost treatment, mean PSV, EDV, and RI decreased in the CRA, without reaching statistical significance ($p>0.05$, Friedman test, Tab. V). In the PCA, mean PSV decreased and EDV increased ($p>0.05$, Friedman test, Tab. V). Latanoprost treatment decreased RI of PCA ($p=0.01$, Friedman test, Tab. V). Wilcoxon signed rank test revealed that this significance occurred between the first and third months ($p=0.04$). Comparison of baseline and first month RI values was not significant ($p>0.05$, Wilcoxon signed rank test).

When we compared the mean changes between baseline and 3-month blood flow measurements, we found no significant differences between betaxolol and latanoprost ($p>0.05$, Mann-Whitney U test, Tab. VI).

DISCUSSION

CDI is an ultrasound technique that combines B-scan gray scale imaging of tissue structures, color representation of blood flow based on Doppler shift, and pulsed Doppler measurements of blood flow measurements. This noninvasive technique, well established in many different fields of medicine, enables the examiner to measure the blood flow velocity of small vessels quantitatively (24-26). In ophthalmology, CDI has been used to evaluate CRA and central retinal vein occlusions, intraocular and intraorbital tumors, orbital varices, ocular ischemic syndrome, diabetic retinopathy, glaucoma, some common surgical procedures like trabeculectomy, and to test the effects of topically applied drugs (5).

CDI is vessel specific and is the only technique that allows assessment of the retrobulbar vessels, namely, the ophthalmic artery, the CRA, and the PCA. CDI has provided important insight into the hemodynamics of retrobulbar vessels in patients with glaucoma (6, 27-29). In patients with glaucoma associated with ei-

TABLE IV - BLOOD FLOW VELOCITY (cm/sec) MEASUREMENTS AND RESISTIVITY INDICES IN BETAXOLOL GROUP

Variable	Central retinal artery				Posterior ciliary artery			
	Baseline	PT 1	PT3	p value	Baseline	PT1	PT3	p value
PSV	9.14±3.3	8.97±3.12	9.76±3.19	0.65	22.65±9.43	17.91±7.57	22.14±11.00	0.23
EDV	2.50±1.18	3.18±1.53	3.74±1.30	0.18	6.70±3.48	8.17±5.34	10.03±4.71	0.10
RI	0.72±0.09	0.69±0.06	0.68±0.05	0.10	0.68±0.10	0.65±0.06	0.63±0.07	0.11

Values are mean±SD.
PT1 = Post-treatment 1 month; PT3 = Post-treatment 3 months; PSV = Peak systolic blood flow velocity; EDV = End-diastolic blood flow velocity; RI = Resistivity index

TABLE V - MEAN BLOOD FLOW VELOCITY (Cm/sec) MEASUREMENTS AND RESISTIVITY INDICES IN LATANOPROST GROUP

Variable	Central retinal artery				Posterior ciliary artery			
	Baseline	PT 1	PT2	p value	Baseline	PT1	PT2	p value
PSV	11.9±6.0	9.97±2.3	10.66±3.9	0.94	23.15±10.79	22.29±10.50	21.58±11.02	0.42
EDV	3.66±2.39	2.8±1.06	3.27±1.54	0.82	7.77±4.80	8.69±5.34	10.44±7.26	0.63
RI	0.73±0.67	0.71±0.07	0.68±0.05	0.16	0.67±0.08	0.68±0.18	0.63±0.06	0.01*

Values are mean±SD.
*Statistically significant, Friedman test. Comparisons are significant for baseline and PT2 ($p<0.05$, Wilcoxon signed rank test), and for PT1 and PT2 ($p<0.05$, Wilcoxon signed rank test).
PT1 = Post-treatment 1 month; PT3 = Post-treatment 3 months; PSV = Peak systolic blood flow velocity; EDV = End-diastolic blood flow velocity; RI = Resistivity index

ther high or normal pressures, there appears to be a decreased EDV and an associated elevation of the RI in CRA and short PCA. A decrease in EDV is a sensitive indicator of increased downstream impedance, which also leads to raised RI. This increase in downstream resistance has ben attributed to various factors such as raised IOP, vasoconstriction, or vasospasm (3).

Inaccuracies in quantitative CDI measurements can arise from errors in interpreting Doppler-shifted frequency spectrum and in measuring the Doppler angle (25). RI is accepted as the most appropriate parameter for evaluating blood flow in the retrobulbar vessels. PSV and EDV are dependent on Doppler angle; therefore they are both regarded, to a degree, as operator dependent. However, the RI is not angle-dependent and is regarded as a good method to quantify the vascular resistance of circulation, particularly in the cephalic region (3).

While our velocity measurements in the CRA correspond with the literature, our measurements in the PCA are higher than reported in the literature (25, 30). This might have arisen from possible errors of CDI operator when applying angle correction owing to tortuous pathway of the PCA. In our study, since only one operator performed all the measurements and applied angle correction for calculating PSV and EDV, the RI values we report in both CRA and PCA correspond with the literature (25, 30).

The relationship between ocular blood flow and visual function has been a topic of interest for many years. Studies published around the 1970s to 1980s have found correlations between the extent of visual field loss and ocular circulation times using fluorescein angiography and shown that the number of fluorescein filling defects of the optic disc correlated with the degree of visual field loss (31-33). Quantitative measures to evaluate blood flow such as CDI have indicated the correlation of EDV of the CRA with MD in chronic open-angle glaucoma patients. Furthermore, reduced short PCA velocities were reported to correlate with corresponding visual hemifield defects (28). Based on these and other findings, there have been attempts to modulate blood flow with the hope of improvements in visual field (8, 27, 34-36).

ß adrenoceptor stimulation causes vasodilatation in most vessels. It is argued that nonselective ß blockers can decrease blood flow of the optic nerve by blocking $ß_2$ vasodilatatory receptors. Theoretically, a $ß_1$ selective blocker like betaxolol provides the advantage of improved blood flow by selectively not blocking $ß_1$ receptors (10, 27). Harris et al (29) have demonstrated ocular vasorelaxant effects of betaxolol independent of IOP in glaucoma patients.

ß blockers with significant calcium channel blocking activity, such as betaxolol, can act as a vasodilator in glaucoma patients, depending on the concentration of the drug, its systemic absorption, and its possible diffusion and accumulation in the eye after long-term application (10). Betaxolol was reported to have a better effect on preservation of visual fields than the nonselective ß blocker timolol (27, 34, 36), suggesting a possible calcium channel antagonistic effect (37).

In the present study, betaxolol treatment improved hemodynamics by increasing EDV and decreasing RI in both CRA and PCA. In another CDI study, Turaçlı

TABLE VI - MEAN CHANGES BETWEEN BASELINE AND THIRD MONTH BLOOD FLOW MEASUREMENTS

Measurement	Betaxolol	Latanoprost	p value
CRA PSV	-0.61±4.24	1.19±6.60	0.3
CRA EDV	-0.56±1.27	0.38±2.95	0.2
CRA RI	0.037±0.069	0.04±0.09	0.6
PCA PSV	0.50±12.54	1.56±9.19	0.7
PCA EDV	-3.33±5.01	-2.66±8.12	0.3
PCA RI	0.063±0.084	0.042±0.10	0.5

Values are mean±SD.
CRA = Central retinal artery; PSV = Peak systolic blood flow velocity; EDV = End-diastolic blood flow velocity; RI = Resistivity index; PCA = Posterior ciliary artery

et al (7) had previously reported no significant changes in ocular hemodynamics of patients with normotension glaucoma after short-term (4 months) treatment with betaxolol. The same authors reported the long-term (1 year) results of the same study declaring that long-term treatment with betaxolol improved ocular hemodynamics by lowering the RI of the ophthalmic artery (27).

In the present study the visual field indices of our patients tended to improve with betaxolol use without reaching statistical significance. There are some reports in the literature about the beneficial effects of betaxolol on the visual fields (38-40). Drance (38) reported that betaxolol appeared to have a positive influence on the blue-yellow sensitivity of the upper nasal and upper temporal field visual fields compared to timolol. Similarly, Araie et al (39) assessed the effects of topical betaxolol on the visual fields and reported that while the classical visual field indices – MD and corrected pattern standard deviation – showed no significant differences, there was a significant trend in improvement in the inferior arcuate subfield. The possible difference between the above mentioned authors' results and ours can be explained by their longer study periods, and assessment of local sensitivity changes, rather than generalized changes.

Rainer et al (40) assessed the visual fields 3 months after changing from timolol to betaxolol and found slight improvement from baseline, which was not significant versus timolol. Their study was different from ours in that they included patients using other antiglaucoma drugs during the study, which could possibly affect the results. We included only newly diagnosed POAG patients who have not used any antiglaucoma drugs before.

Another study comparing the effect of betaxolol and timolol on visual fields by Messmer et al (36) reported that during the 6 months of treatment, the betaxolol group showed more pronounced improvement on the visual fields, based on decrease of MD. Our 3-month study also revealed slight improvements in MD and PSD. Based on the above mentioned findings and our findings, the significantly beneficial effects of betaxolol on visual fields do not become readily evident on short term (3 months).

Latanoprost, a prostaglandin $F_{2\alpha}$ related compound, has been proved to be a potent ocular hypotensive agent. Hoste (41) argued that prostaglandin $F_{2\alpha}$ is known to possess vasoconstrictor properties in human coronary and cerebral arteries and questioned whether latanoprost could possibly cause vasoconstriction at the vessels of the posterior pole of the eye. In response, Rulo and Hoyng (42) proposed that the concentration of latanoprost reaching the posterior pole of the eye was 1000 times lower than the lowest concentration of prostaglandin $F_{2\alpha}$ known to induce vasoconstriction.

Other studies have suggested that prostaglandin $F_{2\alpha}$ may act either as vasoconstrictor or vasodilatator, depending on the concentration of the drug, the characteristics of the vascular bed, and the animal species (43-47). In a recent study, Brogiolo et al (47) demonstrated a significant and concentration dependent vasoconstrictor effect of latanoprost in isolated porcine ciliary arteries.

The effects of latanoprost on ocular blood flow have been investigated in various recent scientific studies (14-21). In studies using the laser speckle method, topical latanoprost significantly increased optic nerve head blood velocity in rabbits, monkeys, and normal humans, which was independent of its IOP lowering effect (15, 16). Studies in which pulsatile ocular blood flow (POBF) were measured have reported that topical latanoprost increased POBF after 8 hours, 1 week, 3 to 4 weeks, and 6 months of dosing, in healthy volunteers and glaucoma patients, attributed to its ocular hypotensive effect or not (14, 17-21).

In a CDI study, Nicolela et al (48) demonstrated no substantial hemodynamic changes in the retrobulbar vessels attributable to a 1-week course of topical latanoprost administration. Similarly, Tamaki et al (15) found no significant changes attributable to one drop of latanoprost in PSV, EDV, and RI of the CRA in healthy volunteers. To our knowledge, there are no other CDI studies evaluating the ocular blood flow effects of latanoprost administered over 3 months in glaucoma patients.

In the present CDI study, latanoprost treatment decreased RI of both the CRA and the PCA, indicating possible improvement in ocular hemodynamics. In the PCA, comparison of baseline and first month RI values was not significant. These data suggest that improvement in hemodynamics occurred after the first month.

The results of our study indicated that RI improved with both betaxolol and latanoprost. Further statistical analysis comparing the mean changes (baseline-third month) of RI values revealed no significant difference between betaxolol and latanoprost (Tab. VI). Hence, it can be speculated that both drugs improve hemodynamics, without one of them being superior to the other.

The positive effects of an ocular hypotensive drug on ocular hemodynamics may be related to the reduction of IOP, as well as local penetration and direct vasoactive effects on the small orbital vessels. Recent evidence suggests that drug penetration from the tear fluid takes place by direct diffusion across the conjunctiva into the sclera and orbit when the head is supine (49). Significant periocular accumulation of betaxolol in patients under long-term therapy has been demonstrated, which could possibly provide more immediate access to the posterior segment of the eye (50). ?shii et al (16) demonstrated an increase in blood velocity due to latanoprost, independent of IOP reduction, suggesting local penetration of the drug and production of endogenous prostaglandins.

Lowering IOP can improve retrobulbar hemodynamics. Trible et al (51) performed CDI on both eyes of patients undergoing trabeculectomy and demonstrated significant improvements in hemodynamics in nearly all postoperative cases. In the present study, both betaxolol and latanoprost decreased IOP significantly. Thus IOP-lowering treatment in itself induces an improvement of circulation measured with the CDI. Although latanoprost reduced IOP much further than betaxolol, the influence on CDI of the two treatment modalities was not different. This suggests that the direct (non IOP-dependent) influence on ocular circulation is better for betaxolol than for latanoprost. Our results confirm previous findings that betaxolol causes vasodilatation in the eye.

In conclusion, the results of this study indicated that over a treatment period of 3 months, both betaxolol and latanoprost tended to improve ocular hemodynamics by reducing the RI. In addition, neither betaxolol nor latanoprost caused significant generalized improvements in the visual fields during this period. Evaluation of the same patients after longer periods will provide information on whether any visual field improvements will accompany the changes in hemodynamics.

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REFERENCES

1. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. Am J Ophthalmol 2000; 130: 429-40.
2. Heijl A, Leske CL, Bengtsson B, Hyman L, Bengtsson B, Hussein M, for the Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression. Arch Ophthalmol 2002; 120: 1268-79.
3. Rankin SJA. Color Doppler imaging of the retrobulbar circulation in glaucoma. Surv Ophthalmol 1999; 43 (Suppl): S176-82.
4. Soltau JB, Zimmerman TJ. Changing paradigms in the medical treatment of glaucoma. Surv Ophthalmol 2002; 47 (Suppl): S2-5.
5. Flammer J, Orgül S, Costa VP, et al. The impact of ocular blood flow in glaucoma. Prog Retin Eye Res 2002; 21: 359-93.
6. Nicolela MT, Drance SM, Rankin SJ. Color Doppler imaging in patients with asymmetric glaucoma and unilateral visual field loss. Am J Ophthalmol 1996; 121: 502-10.
7. Turaçlı ME, Özden RG, Bardak Y, Yazıcıoğlu KM. Normal tansiyonlu glokomda betaksololün görme alanı ve okuler kan akımı üzerindeki erken dönem etkisi. T Klin Oftalmoloji 1995; 4: 345-9.

8. Harris A, Spaeth GL, Sergott RC, Katz JL, Cantor LB, Martin BJ. Retrobulbar arterial hemodynamic effects of betaxolol and timolol in normal-tension glaucoma. Am J Ophthalmol 1995; 120: 168-75.
9. Boles Carenini AB, Sibour G, Boles Carenini B. Differences in the long term effect of timolol and betaxolol on the pulsatile ocular blood flow. Surv Ophthalmol 1994; 38 (Suppl): S118-24.
10. Hoste AM. *In vitro* studies of the effects of ß-adrenergic drugs on retinal and posterior ciliary microarteries. Surv Ophthalmol 1999; (Suppl): S183-90.
11. Hester RK, Chen Z, Becker EJ, McLaughlin M, DeSantis L. The direct vascular relaxing action of betaxolol, carteolol and timolol in porcine long posterior ciliary artery. Surv Ophthalmol 1994; 38: (Suppl): S125-34.
12. Gupta A, Chen HC, Rassam SMB, Kohner EM. Effect of betaxolol on the retinal circulation in eyes with ocular hypertension study. Eye 1994; 8: 668-71.
13. Hesse RJ. Color Doppler ultrasound measurement of beta-blocker response in normal tension glaucoma. Neuro-Ophthalmol 1995; 15: 259-63.
14. Georgopoulos GT, Diestelhorst M, Fisher R, Ruokonen P, Krieglstein GK. The short-term effect of latanoprost on intraocular pressure and pulsatile ocular blood flow. Acta Ophthalmol Scand 2002; 80: 54-8.
15. Tamaki Y, Nagahara M, Araie M, Tomita K, Sandoh S, Tomidokoro A. Topical latanoprost and optic nerve head and retinal circulation in humans. J Ocul Pharmacol Ther 2001; 17: 403-11.
16. Ishii K, Tomidokoro A, Nagahara M, et al. Effects of topical latanoprost on optic nerve head circulation in rabbits, monkeys, and humans. Invest Ophthalmol Vis Sci 2001; 42: 2957-63.
17. Geyer O, Man O, Weintraub M, Silver DM. Acute effects of latanoprost on pulsatile ocular blood flow in normal eyes. Am J Ophthalmol 2001; 131: 198-202.
18. Sponsel WE, Mensah J, Kiel JW, et al. Effects of latanoprost and timolol-XE on hydrodynamics in the normal eye. Am J Ophthalmol 2000; 130: 151-9.
19. McKibbin M, Menage MJ. The effect of once-daily latanoprost on intraocular pressure and pulsatile ocular blood flow in normal tension glaucoma. Eye 1999; 13: 31-4.
20. Vetrugno M, Cantatore F, Gigante G, Cardia L. Latanoprost 0.005% in POAG: effects on IOP and ocular blood flow. Acta Ophthalmol Scand 1998; 227 (Suppl): S40-1.
21. Liu CJ, Ko YC, Chou JC, Hsu WM, Liu JH. Effect of latanoprost 0.005% and brimonidine tartrate 0.2% on pulsatile ocular blood flow in normal tension glaucoma. Br J Ophthalmol 2002; 86: 1236-9.
22. Aburn NS, Sergott RC. Orbital colour Doppler imaging. Eye 1993; 7: 639-47.
23. Greeenfield DS, Heggerick PA, Hedges III TR. Color Doppler imaging of normal orbital vasculature. Ophthalmology 1995; 102: 1598-605.
24. Guthoff RF, Berger RW, Winkler P, Helmke K, Chumbley LC. Doppler ultrasonography of the ophthalmic and central retinal vessels. Arch Ophthalmol 1991; 109: 532-6.
25. Lieb WE, Cohen SM, Merton AD, Shields JA , Mitchell DG, Goldberg BB. Color Doppler imaging of the eye and orbit. Technique and normal vascular anatomy. Arch Ophthalmol 1991; 109: 527-31.
26. Williamson TH, Haris JA. Color Doppler ultrasound imaging of the eye and orbit. Surv Ophthalmol 1996; 40: 255-67.
27. Turaçlı ME, Özden RG, Gürses MA. The effect of betaxolol on ocular blood flow and visual fields in patients with normotension glaucoma. Eur J Ophthalmol 1998; 8: 62-6.
28. Rankin SJ, Drance SM, Buckley AR, Walman BE. Visual field correlations with color Doppler studies in open angle glaucoma. J Glaucoma 1996; 5: 15-21.
29. Harris A, Williamson TH, Martin B. Test/retest reproducibility of color Doppler imaging assessment of blood flow velocity in orbital vessels. J Glaucoma 1995; 4: 281-6.
30. Kaiser HJ, Schötzau A, Flammer J. Blood-flow velocities in the extraocular vessels in normal volunteers. Am J Ophthalmol 1996; 122: 364-70.
31. Talusan ED, Schwartz B, Wilcox LM. Fluorescein angiography of the optic disc. Arch Ophthalmol 1980; 98: 1579-87.
32. Hitchings RA, Spaeth GL. Fluorescein angiography in chronic simple and low-tension glaucoma. Br J Ophthalmol 1977; 61: 126-32.
33. Spaeth GL. Fluorescein angiography: its contributions towards understanding the mechanisms of visual loss in glaucoma. Trans Am Ophthalmol Soc 1975; 73: 491-553.
34. Kaiser HJ, Flammer J, Stumpfig D, Hendrickson P. Long-term visual field follow-up of glaucoma patients treated with beta-blockers. Surv Ophthalmol 1994; 38 (Suppl): S156-9.
35. Montanari P, Marangoni P, Oldani A, Ratiglia R, Raiteri M, Berardinelli L. Color Doppler imaging study in patients with primary open-angle glaucoma treated with timolol 0.5% and carteolol 2%. Eur J Ophthalmol 2001; 11: 240-4.
36. Messmer C, Flammer J, Stumpfig D. Influence of betaxolol and timolol on the visual fields of patients with glaucoma. Am J Ophthalmol 1991; 112: 678-81.
37. Hoste AM, Sys SU. The relaxant action of betaxolol on isolated bovine retinal microarteries. Curr Eye Res 1994; 13: 483-7.

38. Drance SM. A comparison of the effects of betaxolol, timolol and pilocarpine on visual function in patients with open-angle glaucoma. J Glaucoma 1998; 7: 247-52.
39. Araie M, Azuma I, Kitazawa Y. Influence of topical betaxolol and timolol on visual fields in Japanese open-angle glaucoma patients. Jpn J Ophthalmol 2002; 47: 199-207.
40. Rainer G, Dorner GT, Garhofer G, Vass C, Pfleger T, Schmetterer L. Changing antiglaucoma therapy from timolol to betaxolol: effect on ocular blood flow. Ophthalmologica 2003; 217: 288-93.
41. Hoste AM. Reduction of IOP with latanoprost. Ophthalmology 1997; 104: 895-7.
42. Rulo AH, Hoyng PFJ. Authors reply to letter of A. Hoste. Ophthalmology 1997; 104: 896-7.
43. Kimura T, Yoshida Y, Toda N. Mechanisms of relaxation induced by prostaglandins in isolated canine uterine arteries. Am J Obstet Gynecol 1992; 167: 1409-16.
44. Maigaard S, Forman A, Andersonn KE. Relaxant and contractile effects of some amines and prostanoids in myometrial and vascular smooth muscle within the human uteroplacental unit. Acta Physiol Scand 1986; 128: 33-40.
45. Astin M. Effect of prostaglandin E2, $F2_{\alpha}$, and latanoprost acid on isolated ocular blood vessels *in vitro*. J Ocul Pharmacol Ther 1998; 14: 119-28.
46. Stjernschantz J, Selen G, Astin M, Karlsson M, Resul B. Effect of latanoprost on regional blood flow and capillary permeability in the monkey eye. Arch Ophthalmol 1999; 117: 1363-7.
47. Brogiolo G, Flammer J, Haefliger IO. Latanoprost is a vasoconstrictor in isolated porcine ciliary arteries. Klin Monatsbl Augenheilkd 2001; 218: 373-5.
48. Nicolela MT, Buckley AR, Walman BE, Drance SM. A comparative study of the effects of timolol and latanoprost on blood flow velocity of the retrobulbar vessels. Am J Ophthalmol 1996; 122: 784-9.
49. Maurice DM. Drug delivery to the posterior segment from the drops. Surv Ophthalmol 1999; 47 (Suppl): S41-58.
50. Sponsel WE, Terry S, Khuu HD, Lam KW, Frenzel H. Periocular accumulation of timolol and betaxolol in glaucoma patients under long-term therapy. Surv Ophthalmol 1999; 43 (Suppl): S210-3.
51. Trible JR, Sergott RC, Spaeth GL. Trabeculectomy is associated with retrobulbar hemodynamic changes: a color Doppler analysis. Ophthalmology 1994; 101: 340-51.