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Optic Nerve Head Blood Flow in Glaucoma

Tetsuya Sugiyama, Maho Shibata, Shota Kojima and Tsunehiko Ikeda
*Osaka Medical College
Japan*

1. Introduction

These days it is commonly accepted that multiple factors are involved in the etiology of glaucoma. Although many studies have demonstrated that the major risk factor for glaucoma is an increase in intraocular pressure (IOP), some studies, including epidemiologic studies, have suggested an association between glaucoma, especially primary open-angle glaucoma (POAG) and normal-tension glaucoma (NTG), and vascular factors. In this chapter, previous studies regarding the implications of optic nerve head (ONH) blood flow in glaucoma will be reviewed, and then our recent studies will be presented.

Some population-based prevalence surveys demonstrated that lower perfusion pressure (blood pressure - intraocular pressure), especially diastolic perfusion pressure, was strongly associated with an increased prevalence of POAG or NTG in the US, Europe and Asia (Tielsch et al, 1995; Bonomi et al, 2000; Leske et al, 2002; Hulseman et al, 2007). These reports suggest that POAG including NTG is associated with alterations in factors related to ocular blood flow. There is also sufficient evidence that optic disc hemorrhage is an important risk factor for glaucoma progression (Daugeliene et al, 1999; Leske et al, 2003; Bengtsson et al, 2008; Prata et al, 2010). Additionally, increasing peripapillary atrophy, which might be related with hypoperfusion to the ONH, was reportedly associated with progressive glaucoma (Araie et al, 1994; Uchida et al, 1998; Daugeliene et al, 1999), and it has been reported that non-use of calcium channel blockers was significantly associated with the progression of visual field loss in NTG (Daugeliene et al, 1999).

Clinically usable methods for the measurement of ONH blood flow include fluorescein fundus angiography, scanning laser Doppler flowmetry, and laser speckle flowgraphy. Fluorescein fundus angiography has multiple limitations in quantitatively evaluating ONH blood flow (Hayreh, 1997). Above all, once the dense capillary network in the surface nerve fiber layer of the ONH fills completely with fluorescein-stained blood, underlying ciliary vessels are masked so that no information can be obtained about the circulation in the deeper capillaries. Laser Doppler flowmetry is predominantly sensitive to blood flow changes in the superficial layers of the ONH and gives very little information about the prelaminar and deeper regions of the ONH (Petrig et al, 1999). Laser speckle flowgraphy (LSFG) can detect capillary blood flow in the ONH, probably around the laminar region, and is suitable for monitoring the time-course of its change (Sugiyama et al, 2010). LSFG was developed to facilitate the non-contact analysis of ocular blood flow utilizing the laser speckle phenomenon (Tamaki et al, 1995). Originally, normalized blur and square blur rate had been used as indexes of blood velocity, but later they were experimentally shown to be well correlated with blood flow rate. In the recent version of LSFG, a new parameter, mean blur rate (MBR), which is

theoretically proportional to the square blur rate, is also commonly used as an index of blood flow rate (Konishi, 2002). There have been many reports demonstrating the effects of various treatments on the ONH blood flow in humans using LSF (Sugiyama et al, 2010).

Some investigators have reported that ONH blood flow is autoregulated in normal eyes, but not in patients with POAG. Several reports have suggested a larger diurnal fluctuation of parameters for ocular blood flow including ONH blood flow in patients with POAG or NTG (Claridge & Smith, 1994; Chung et al, 1999; Okuno T et al, 2004; Pemp et al, 2009). There has also been some evidence that endothelin (ET)-1 and nitric oxide may play roles in the dysregulation of ocular blood flow in glaucoma (Yorio et al, 2002; Flammer et al, 2007; Polak et al, 2007; Nicolela, 2008; Venkataraman et al, 2010).

There have been some studies on the effects of anti-glaucoma medication on ONH blood flow. The effects of prostaglandin (PG) derivatives, beta-blockers, and carbonic anhydrase inhibitors (CAIs) on ONH blood flow are summarized below. Regarding latanoprost, a representative PG derivative, some reports showed that it increased ONH blood flow, but others reported that it had no significant effect on ONH blood flow in healthy subjects or in glaucoma patients (Seong et al, 1999; Ishii et al, 2001; Gherghel et al, 2008; Sugiyama et al, 2009). Unoprostone, another PG derivative, reportedly increased ONH blood flow in healthy subjects (Tamaki et al, 2001; Makimoto et al, 2002). There has been no report regarding the effects of travoprost, bimatoprost or tafluprost on ONH blood flow in humans as far as we know. It is reported that timolol either had no significant effect on or decreased ONH blood flow in humans (Yoshida et al, 1991; Tamaki et al, 1997a, 1997b; Netland et al, 1999; Haefliger et al, 1999; Lübeck et al, 2001). In contrast, carteolol, betaxolol and nipradilol reportedly increased ONH blood flow in humans (Tamaki et al, 1997a, 1997b; Tamaki et al, 1999; Mizuno et al, 2002). It was reported that dorzolamide, a topical CAI, had no significant effect on ONH blood flow in healthy subjects but increased ONH blood flow in glaucoma patients (Pillunat et al, 1999; Fuchsjäger-Mayrl et al, 2005; Rolle et al, 2008). To the best of our knowledge, there have been few reports on the effect of brinzolamide, another topical CAI, on ONH blood flow in humans (Iester et al, 2004).

2. Clinical studies of ONH blood flow in glaucoma

2.1 Association of ONH blood flow with stages of glaucoma (Clinical study 1)

The correlation between the stages of the visual field defect and the impairment of ONH blood flow was investigated in a retrospective study involving glaucoma patients. The subjects included 18 eyes of 13 patients with preperimetric glaucoma, 54 eyes of 31 patients with POAG and 39 eyes of 21 age-matched normal control subjects. POAG was defined as showing the following criteria in two consecutive examinations by Humphrey Field Analyzer (HFA, Carl Zeiss Meditec, Dublin, CA) using Program 30-2, SITA standard strategy: 1) Outside normal limits by the glaucoma hemi-field test; 2) Pattern standard deviation with P values $< 5\%$; 3) Cluster of 3 or more points in the pattern deviation plot in the abnormal hemifield with P values $< 5\%$ and one of which has a P value $< 1\%$. POAG patients were divided into the initial, middle or advanced stage as classified by Anderson & Pattela (1999). Preperimetric glaucoma is defined as showing no abnormality in the HFA examination in spite of having glaucomatous optic neuropathy detected by the examination of the ocular fundus. The exclusion criteria for all patients were: best corrected visual acuity less than 10/20, myopia more than -6D, age less than 40 years old, history of ocular disease other than glaucoma and mild cataract, history of serious systemic disease such as hypertension or diabetes, and poor fixation for the measurement of the blood flow or visual field.

MBR value, an index of ONH blood flow, was measured on the same day or within 3 months after the HFA examination was done. In this study, 8 divisions of sectoral tissue blood flow in the ONH rim were analyzed using LSFSG Analyzer (ver. 3) and Layer Viewer (Softcare, Fukuoka, Japan). The edge of ONH cupping was determined using Heidelberg Retina Tomograph 2 (Heidelberg Engineering, Heidelberg, Germany). The ratio of the MBR value of each sector was calculated and compared between groups.

As a result, less blood flow was observed at the superior and inferior sectors of the ONH rim in patients with preperimetric glaucoma compared to normal control subjects (Fig. 1). In contrast, the blood flow became reduced at the temporal sectors as POAG progressed in comparison to patients with preperimetric glaucoma (Fig. 2).

2.2 ONH blood flow and progression of glaucoma (Clinical study 2)

In order to verify the correlation between ONH blood flow and the progression of the visual field defect, a 3-year prospective study was performed in 12 patients with NTG. The inclusion criteria were: 1) Both eyes had a glaucomatous visual field defect with HFA mean deviation (MD) of -20 dB or more and IOP of 20 mmHg or less before treatment for glaucoma; and 2) The difference between the MD values of both eyes was 5 dB or less at the beginning of this study. The exclusion criteria were the same as in Clinical Study 1. During the study, all of the patients were treated with anti-glaucoma eye drops in both eyes in the same manner. HFA was examined every 6 months to calculate the MD slope. At the same time, the MBR value was measured at each temporal sector using LSFSG. The difference of the MD slopes obtained from the right and left eyes, defined as Δ MDS, and the ratio of the MBR values or IOPs obtained from the right eye to those from the left eye, defined as relative MBR or relative IOP, were calculated and averaged throughout the study.

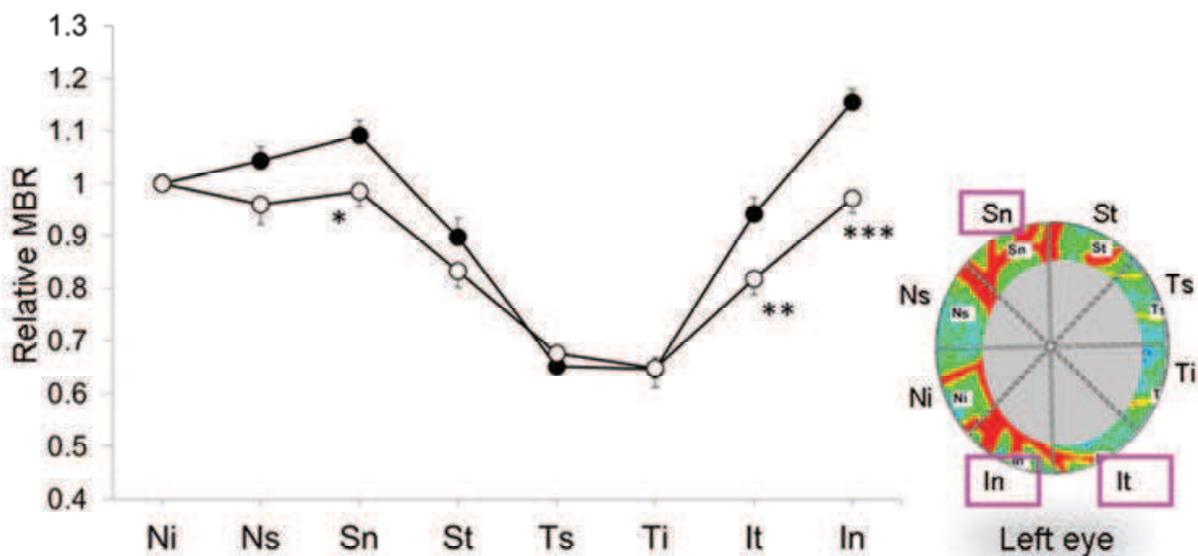


Fig. 1. Ratios of the MBR (mean blue rate) values of each sector of the ONH (optic nerve head) rim in patients with preperimetric glaucoma (open circles, $n=18$) and normal control subjects (closed circles, $n=39$). Data are expressed as mean \pm SEM. Asterisks indicate significant differences between the two groups (unpaired t-test, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

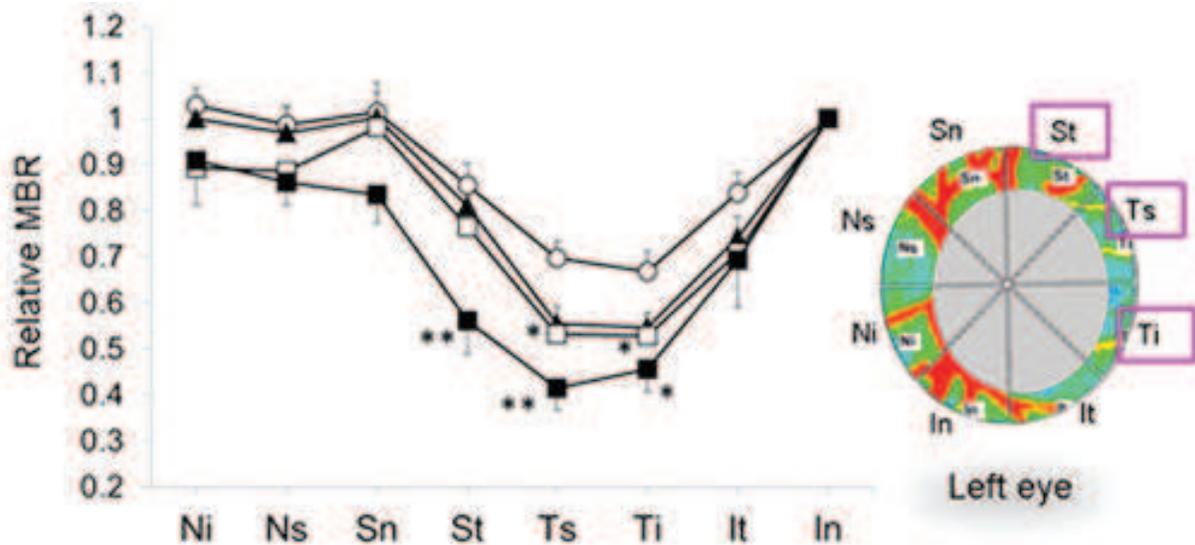


Fig. 2. Ratios of the MBR values of each sector of the ONH rim in patients with preperimetric glaucoma (open circles, $n=18$), initial POAG (closed triangles, $n=26$), middle POAG (open squares, $n=21$), and advanced POAG (closed squares, $n=7$). Data are expressed as mean \pm SEM. Asterisks indicate significant differences when compared with the preperimetric glaucoma group (unpaired t-test, * $p < 0.05$, ** $p < 0.01$).

The mean \pm SD of their ages at the start of this study was 63.7 ± 10.6 years, male-to-female ratio was 4:8. Both the MD (dB) and MBR values were not different between both eyes at the initial level (right eyes: -4.48 ± 6.24 and 9.16 ± 3.35 , left eyes: -5.32 ± 5.93 and 10.67 ± 4.16 , respectively). In addition, throughout the study the mean IOP (mmHg) was not different between both eyes (right eyes: 12.1 ± 1.8 , left eyes: 12.1 ± 1.9). There was a significant correlation between relative MBR and Δ MDS (Fig. 3). However, there was no correlation between relative IOP and Δ MDS (Fig. 4).

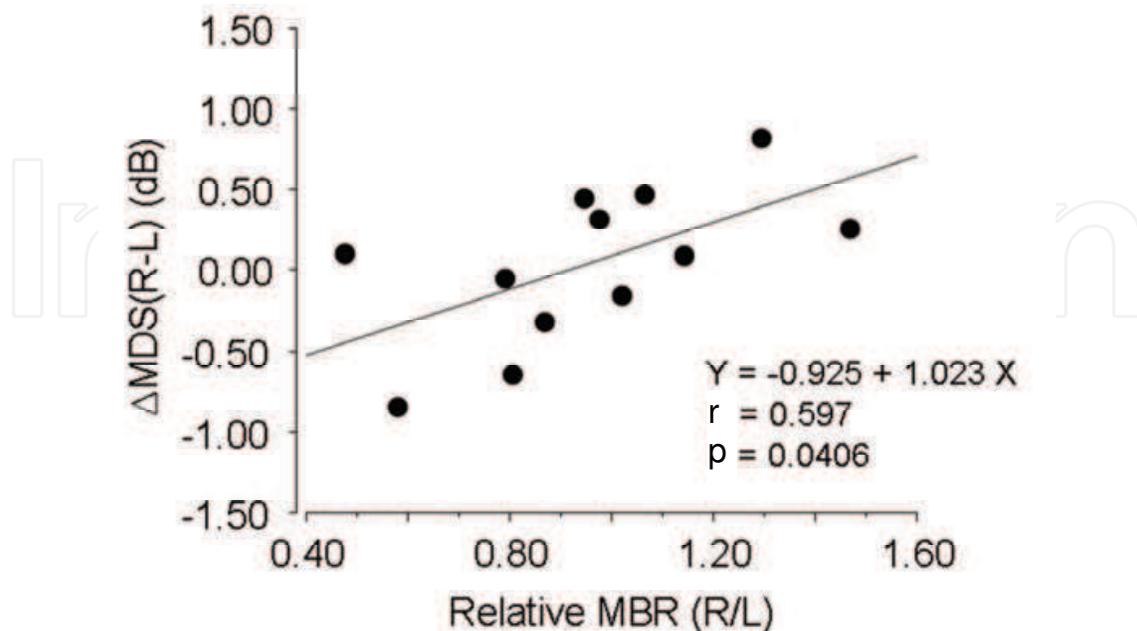


Fig. 3. The relationship between the relative MBRs and the differences of MD slopes, obtained from both eyes in 12 NTG patients.

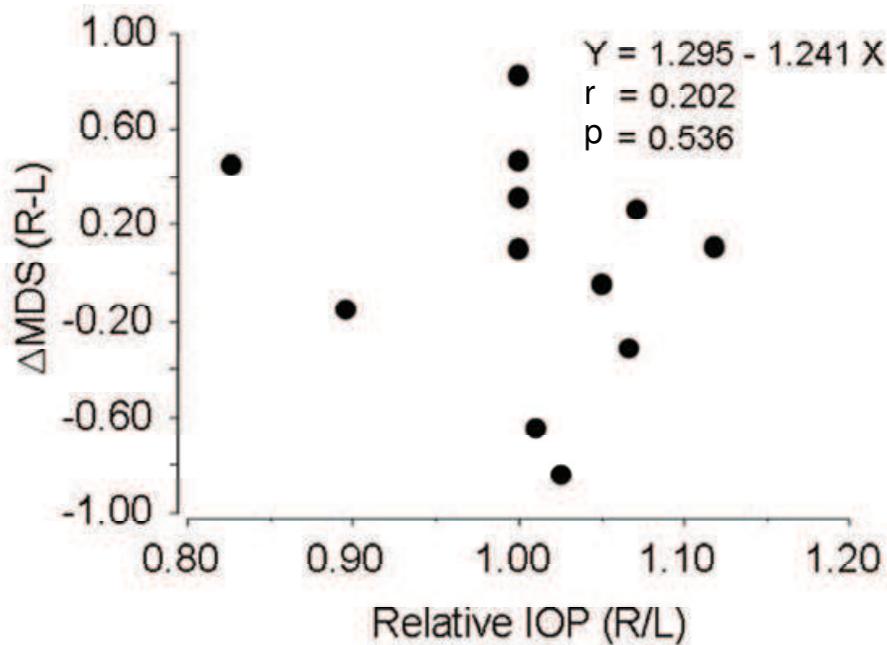


Fig. 4. The relationship between the relative IOP (intraocular pressure) and the differences of MD slopes, obtained from both eyes in 12 NTG patients.

2.3 Changes in ONH blood flow induced by PG derivatives (Clinical study 3)

The effect of tafluprost, a novel prostaglandin analogue, on the ONH blood flow was investigated in a randomized comparative study involving 24 patients with POAG. The IOPs of the subjects were 25 mmHg or less without any treatment for glaucoma. They were in the initial or middle stages of glaucoma according to Anderson & Patella (1999). They had no serious ocular or systemic diseases except for glaucoma as well as no present or past history of smoking. They were not on any systemic medications that could alter the ocular blood flow, such as calcium channel blockers or beta blockers. After random assignment, the tafluprost and latanoprost treatment groups included 11 patients and 13 patients, respectively. There were no significant differences between the subjects' ages, gender ratios or pretreatment IOPs. The IOP, blood flow in the rim of ONH, and blood pressure were measured before and 1, 3, and 6 months after treatment. ONH blood flow was measured as the MBR value using LSFG. Ocular perfusion pressure (OPP) was calculated as $2/3$ of the mean blood pressure minus the IOP. The analyzed eyes were selected at random.

As a result, the IOP decreased significantly at 1, 3, and 6 months compared to the levels measured at the start of tafluprost or latanoprost treatment. Both groups had almost the same degree of IOP reduction (Fig. 5). Blood flow in the rim of ONH, except on the nasal side, increased significantly compared with the initial levels in the tafluprost-treated group, but not in the latanoprost-treated group (Fig. 6). OPP did not change significantly in either group (data not shown).

2.4 Changes in ONH blood flow induced by beta blockers (Clinical study 4)

We have already reported the effects of combined therapy with latanoprost and beta blockers on the ONH blood flow in NTG patients. In the present study, the effects of combined therapy with latanoprost and long-acting ophthalmic solutions of beta blockers

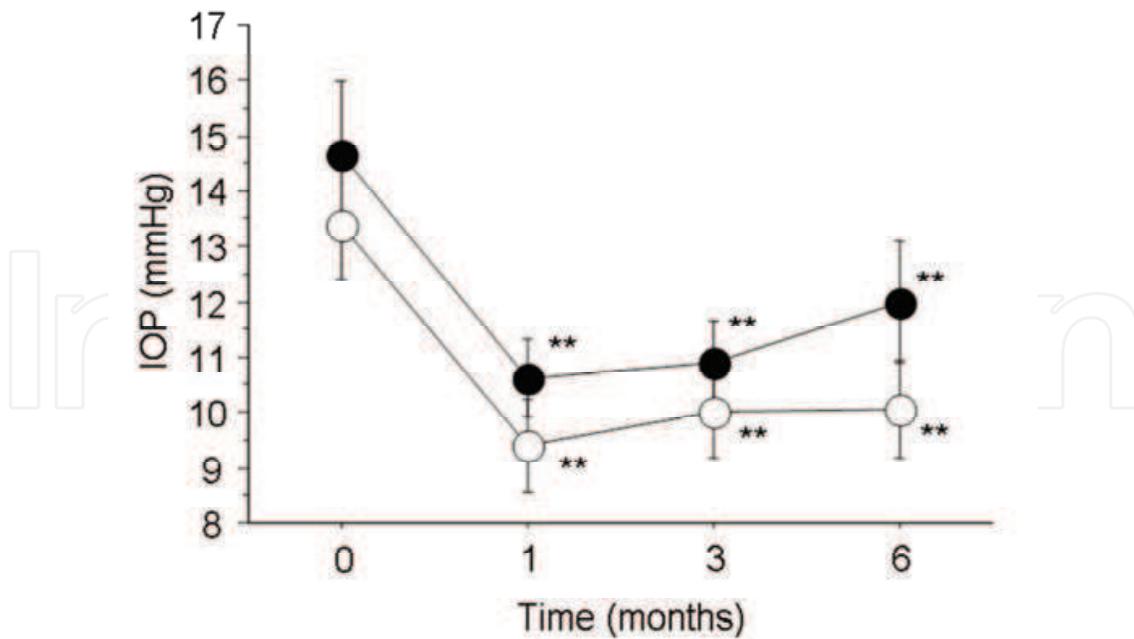


Fig. 5. IOP changes induced by tafluprost (closed circles, $n=11$) and latanoprost (open circles, $n=13$) in POAG patients. Data are expressed as mean \pm SEM. Asterisks indicate significant differences when compared with initial levels (paired t-test, $**p < 0.01$).

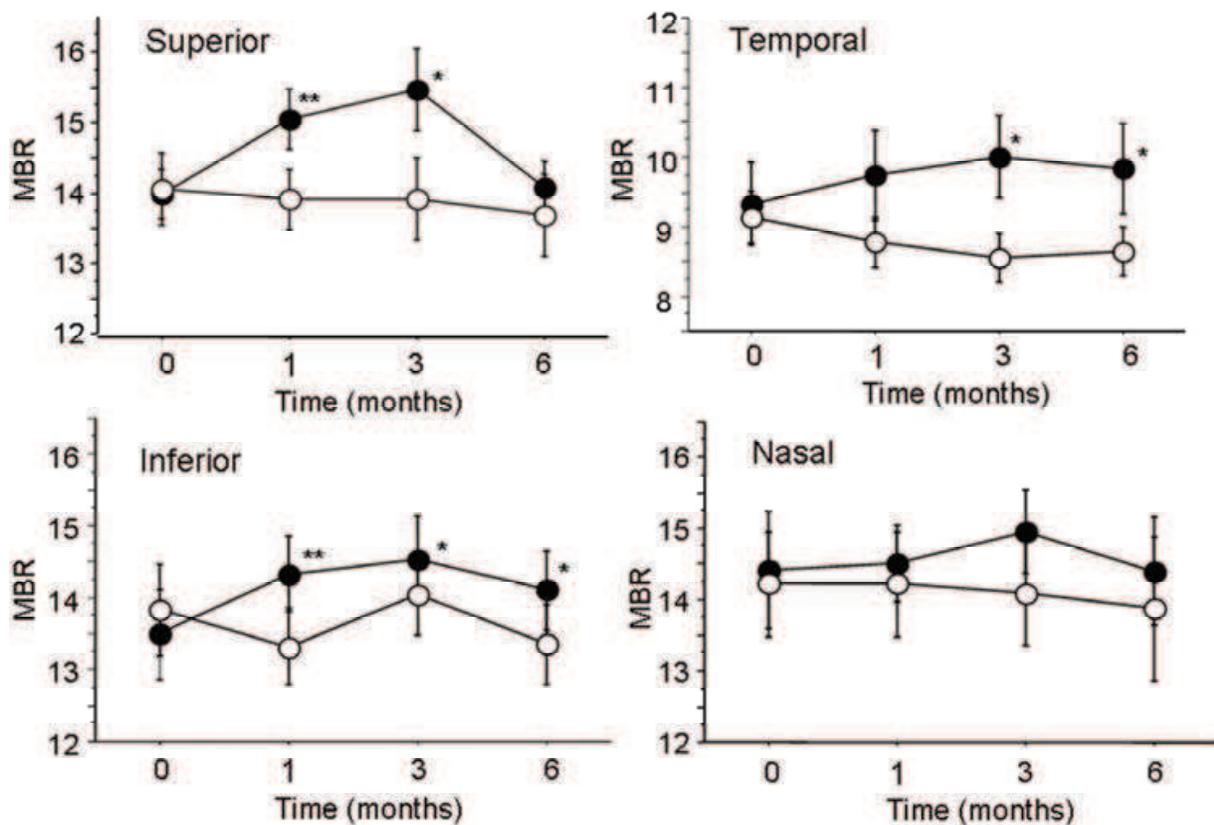


Fig. 6. MBR changes induced by tafluprost (closed circles, $n=11$) and latanoprost (open circles, $n=13$) in superior, inferior, temporal and nasal sectors of the ONH rim in POAG patients. Data are expressed as mean \pm SEM. Asterisks indicate significant differences when compared with initial levels (paired t-test, $*p < 0.05$, $**p < 0.01$).

on the ONH blood flow were investigated in a crossover study involving 10 patients with POAG. They had been receiving treatment with latanoprost for 4 weeks or more. Patients with serious ocular or systemic diseases and those who were smokers were excluded from the study. The mean \pm SD of their ages and IOPs at the start of this study were 59.3 \pm 13.3 years and 15.7 \pm 1.4 mmHg, respectively, and the male-to-female ratio was 4:6. One of the long-acting ophthalmic solutions of beta blockers, Timoptol-XE (timolol) and Mikelan-LA (carteolol), was prescribed for these patients for 2 months each. Since the order of the beta blockers was decided randomly, the Timoptol-XE-preceding group included 5 patients, and the Mikelan-LA-preceding group included 5 patients. The IOP, blood flow in the rim of ONH, and blood pressure were measured before and at 2 and 4 months after treatment. ONH blood flow was measured as a MBR value using LSFG. OPP was calculated as mentioned above. The analyzed eyes were selected at random.

The results of the current study showed that IOP decreased significantly at 2 months after combined therapy with a beta blocker (either Timoptol-XE or Mikelan-LA) compared to the levels before the combined therapy. There was no significant difference between the IOP reductions induced by the two beta blockers (Fig. 7). Blood flow in the rim of ONH, except on the nasal side, was significantly higher with the coadministration of Mikelan-LA, but not with that of Timoptol-XE, compared to the administration of latanoprost alone (Fig. 8). OPP did not change significantly after the combined therapy with either beta blocker (data not shown).

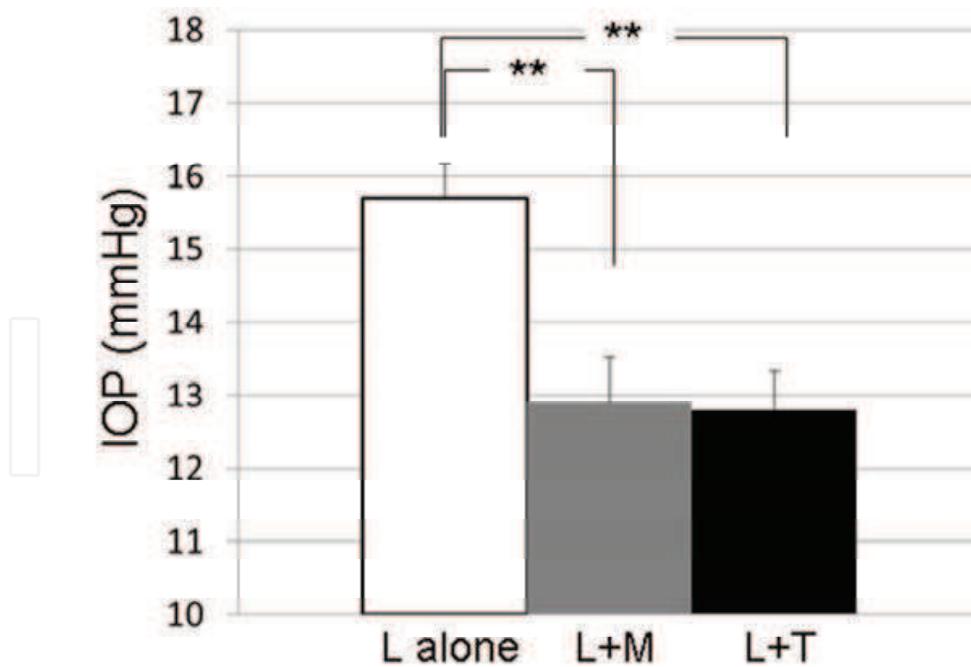


Fig. 7. IOP before and 2 months after the combined therapies with latanoprost (L) and a long-acting beta blocker (M: Mikelan-LA, T:Timoptol-XE) in 10 POAG patients. Data are expressed as mean \pm SEM. Asterisks indicate significant differences between the bracketed groups (Dunnett's test, ** $p < 0.01$).

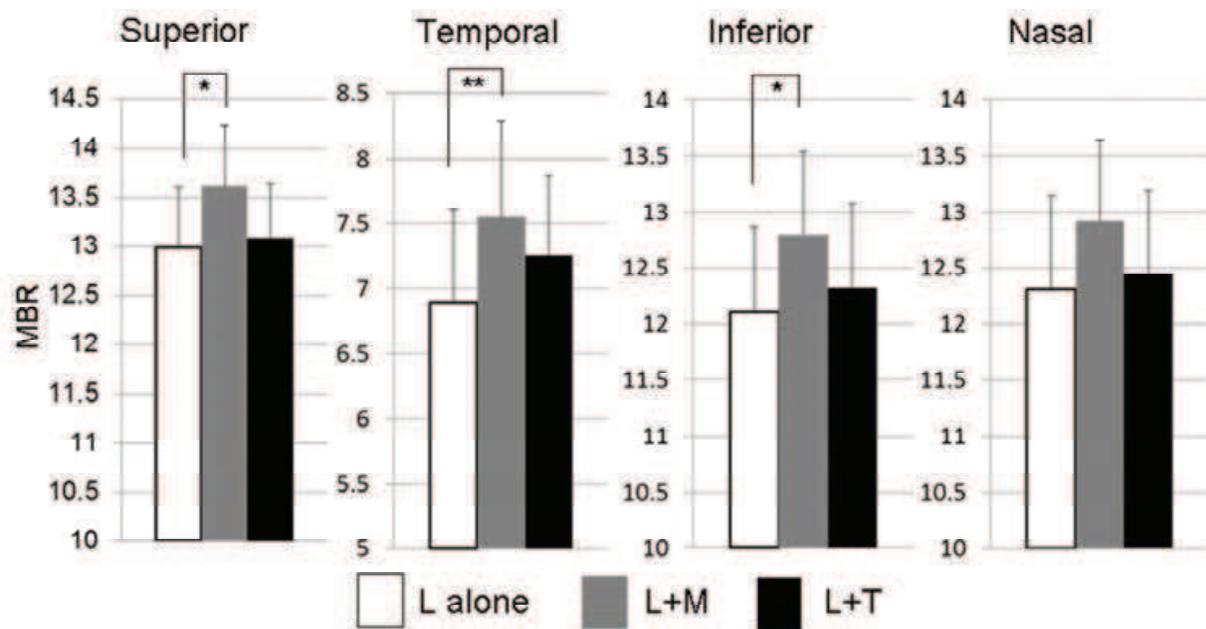


Fig. 8. MBR in superior, inferior, temporal and nasal sectors of the ONH rim before and 2 months after the combined therapies with latanoprost (L) and a long-acting beta blocker (M: Mikelan-LA, T:Timoptol-XE) in 10 POAG patients. Data are expressed as mean \pm SEM. Asterisks indicate significant differences between the bracketed groups (Dunnett's test, * $p < 0.05$, ** $p < 0.01$).

2.5 Discussions of clinical studies 1-4

Clinical study 1, a retrospective study, revealed that the blood flow was reduced in some sectors of the ONH rim even in preperimetric glaucoma. In addition, it was reduced in the other sectors in accordance with the progression of POAG. Clinical study 2, a prospective study, showed that the less blood flow there was in the ONH rim, the more the visual field defect progressed in NTG. Although it has been controversial whether the reduced ocular blood flow is only a result of the progression of optic neuropathy, our results show that reduced ONH blood flow is surely an important risk factor in the progression of open-angle glaucoma. Therefore, maintaining the ONH blood flow might be an effective therapy for POAG including NTG. Prospective clinical studies should be performed to verify the effects of agents that increase the ONH blood flow in POAG, even though such studies may be costly and time-consuming.

There are several methods for increasing the ocular blood flow. Anti-glaucoma eye drops usually reduce IOP, and OPP is then increased. Generally speaking, the following equation is valid:

$$\text{Ocular blood flow} \propto \text{OPP} / \text{Vascular resistance}$$

If vascular resistance does not vary significantly, ocular blood flow is directly proportional to OPP. Therefore, anti-glaucoma eye drops might increase ocular blood flow including ONH blood flow. Glaucoma surgeries might have similar effects on ocular blood flow through the reduction of IOP. On the other hand, there are some medications that can reduce vascular resistance, including calcium channel blockers (Koseki et al, 2008; Mayama & Araie, 2011), ROCK inhibitors (Sugiyama et al, 2011), statins (Ozkiris, 2007; Nagaoka et al, 2007), ET-1 antagonists (Resch et al, 2009; Rosenthal & Fromm, 2011) and others. These

kinds of medications might increase ocular blood flow if OPP is not changed significantly. There have also been several reports that stellate ganglion block might increase ocular blood flow mainly by reducing vascular resistance (Nagahara et al, 2001; Yu et al, 2003).

As mentioned above, reduction in IOP might lead to an increased OPP, which might result in enhancement of ocular blood flow. But Clinical studies 3 and 4, described in the present report, demonstrated that there might be a difference in the effect of anti-glaucoma medications on the ONH blood flow even though they have similar effects in terms of IOP reduction. In our study the difference was verified in the cases of some PG derivatives and beta blockers, but the difference also might be applied to other cases. These differences in the effects on the ONH blood flow, not only on the IOP, might be an important factor in the selection of anti-glaucoma medications for each glaucoma patient in the future. In addition, since there might be inter-individual differences in the effects of the same medications on the ONH blood flow, monitoring the changes in the ONH blood flow during the treatment for glaucoma would be helpful. For that purpose, more precise and easily usable instruments for measuring the ONH blood flow are needed in the near future.

3. Conclusion

The results of our clinical studies indicated that reduced ONH blood flow is an important risk factor for the progression of open-angle glaucoma including NTG, and that there might be a difference in the effect of anti-glaucoma medications on the ONH blood flow even though they have similar effects on IOP reduction. In conclusion, monitoring the changes in the ONH blood flow would be helpful in the treatment of glaucoma.

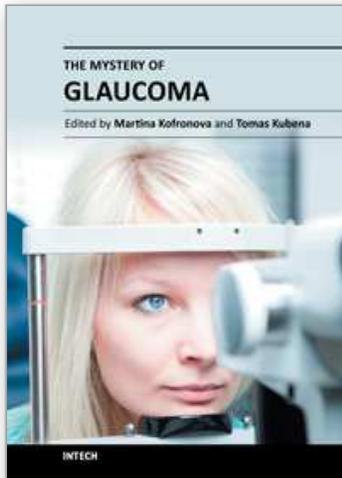
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Since long ago scientists have been trying hard to show up the core of glaucoma. To its understanding we needed to penetrate gradually to its molecular level. The newest pieces of knowledge about the molecular biology of glaucoma are presented in the first section. The second section deals with the clinical problems of glaucoma. Ophthalmologists and other medical staff may find here more important understandings for doing their work. What would our investigation be for, if not owing to the people's benefit? The third section is full of new perspectives on glaucoma. After all, everybody believes and relies – more or less – on bits of hopes of a better future. Just let us engage in the mystery of glaucoma, to learn how to cure it even to prevent suffering from it. Each information in this book is an item of great importance as a precious stone behind which genuine, through and honest piece of work should be observed.

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University Campus STeP Ri
Slavka Krautzeka 83/A
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Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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