

Clinical Usefulness of the Measurement of Optic Nerve Head Blood Flow in Myopic Normal-Tension Glaucoma

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ABSTRACT

AIM: Diagnosis of glaucoma is often difficult in patients with myopic changes in the optic nerve head. We investigated the clinical usefulness of measuring blood flow in myopic optic nerve heads for the diagnosis of normal-tension glaucoma.

METHODS: Forty eyes, including 20 with normal-tension glaucoma and 20 without glaucoma, of 40 patients with myopic optic nerve heads (oval and tilting to the temporal side with crescent peripapillary atrophy) and visual field defects were evaluated. Blood flow in the optic nerve head was assessed by laser speckle flowgraphy, and the mean blur rates for the entire optic nerve head and for its vessels and tissue were analyzed. The mean deviation and the circumpapillary retinal nerve fiber layer thickness were determined using the Humphrey Field Analyzer and optical coherence tomography, respectively. The mean blur rates were compared between the two groups, and their correlation with the mean deviation and circumpapillary retinal nerve fiber layer thickness were verified using simple regression analyses.

RESULTS: The mean blur rates for the entire optic nerve head and for its tissue were significantly lower in glaucomatous eyes than in nonglaucomatous eyes, and both values correlated with the mean deviation only in the former group. The mean blur rate for the optic nerve head tissue did not depend on the circumpapillary retinal nerve

fiber layer thickness in glaucomatous and nonglaucomatous eyes.

CONCLUSION: Blood flow in the optic nerve head, particularly the tissue, may be useful for the differential diagnosis of normal-tension glaucoma in patients with myopia.

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Key words: Normal-tension glaucoma; Optic nerve head; Blood flow; Myopic disc; Mean deviation

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INTRODUCTION

Glaucoma is the second leading cause of blindness according to global surveys^[1]. It is a group of optic neuropathies characterized by the death of retinal ganglion cells and loss of axons in the optic nerve head (ONH)^[2], which results in a characteristic ONH appearance and corresponding visual field defects^[3]. Although increased intraocular pressure (IOP) is the most critical risk factor^[4], a number of previous studies suggested that other factors may be involved in the pathogenesis of this glaucoma, particularly normal-tension glaucoma (NTG)^[5-7]. Other risk factors reportedly include myopia^[8-11] and dysregulation of ocular blood flow^[12,13]. Myopia has been reported to aggravate abnormalities in ocular hemodynamics in patients with glaucoma^[14,15].

On the other hand, myopic changes in eyes with glaucoma affect the appearance of the ONH and cause additional retinal nerve fiber layer defects (RNFLDs) as assessed by optical coherence tomography (OCT)^[16-18]. Consequently, the differential diagnosis of glaucoma, particularly NTG, is often difficult in patients with high myopia^[19]. Even though the OCT system for the diagnosis of glaucoma has been

improved lately^[20,21], it does not always overcome the abovementioned limitation^[22,23]. Therefore, another reliable parameter is required for the differential diagnosis of glaucoma in myopic ONHs.

Measurement of ocular blood flow using laser speckle flowgraphy (LSFG), which was developed and is clinically used in Japan, is noninvasive and completed within several seconds^[24-27]. Compared with other laser-based techniques (i.e., laser Doppler velocity and flowmetry), LSFG measurements cover a larger field and enable two-dimensional observation of the overall hemodynamic condition of the ONH tissue and vessels. ONH circulation measured using LSFG is reported to be significantly poorer in myopic eyes with glaucoma than in those without visual field defects^[28,29].

The present study aimed to verify whether blood flow in the ONH correlates with visual field defects and whether its measurement is useful for the differential diagnosis of glaucoma in patients with myopia and visual field defects.

MATERIALS AND METHODS

Subjects

The procedures of this study followed the tenets of the Declaration of Helsinki and were approved by the Institutional Review Board of Nakano Eye Clinic. Japanese adults with myopic ONHs and a refractive error of more than -3 diopters were enrolled in this study. A myopic ONH was diagnosed from its oval shape and tilt to the temporal side with crescent peripapillary atrophy. Inclusion criteria: patients with any ocular diseases except myopia, NTG, and mild cataract; those with advanced-stage NTG and/or diabetes; those who were taking systemic medications that could affect the ocular blood flow; and those with a history of smoking were excluded. NTG was diagnosed from all of the following findings: (1) presence of glaucomatous ONH changes (cupping enlargement, rim thinness etc.) and glaucomatous visual field defects confirmed by an accurately performed visual field test using the 30-2 Swedish interactive threshold algorithm (SITA) program of the Humphrey Field Analyzer (HFA, Carl Zeiss Meditec, Dublin, CA), according to the Anderson-Patella classification^[30], as well as by Goldmann perimetry; (2) an abnormal decrease in the circumpapillary retinal nerve fiber layer thickness (cpRNFLT); (3) a normal open angle as determined by gonioscopy; (4) absence of a history of IOP more than 21 mmHg; and (5) absence of a history of systemic disease (including intracranial diseases) that can cause visual field defects. Consequently, 20 eyes of 20 patients diagnosed with NTG and 20 eyes of 20 age-matched controls with no diagnosis of glaucoma despite the presence of visual field defects indicative of other causes were included in this cross-sectional study. The worse eyes were selected if both eyes were applicable for this study. Figure 1 shows a representative patient with NTG (A) and a patient without glaucoma (B). Nine out of 20 patients with NTG were using anti-glaucoma eyedrops (3: tafluprost, 3: timolol, 2: latanoprost, 1: carteolol).

Assessment of ONH blood flow

The principles of LSFG-NAVI (Softcare Co., Ltd., Fukuoka, Japan), illustrated in Figure 2, have been described in detail elsewhere^[27]. Briefly, this instrument comprises a fundus camera equipped with a diode laser (wavelength, 830 nm) and an ordinary charge-coupled device (CCD) camera (750×360 pixels). The mean blur rate (MBR) represents the blurring of the speckle pattern formed by the interference of a laser scattered by blood cells moving in the ocular fundus. A previous study suggested that absolute MBR values for the

ONH correlate with capillary blood flow (CBF) and linearly change with it, indicating the quantifiability of these values at least under certain conditions, i.e., in the absence of large topographical or color differences in the ONH induced by races, diseases, etc., which affect absorption and reflection of the laser beam^[31]. LSFG measurements were conducted a month after the withdrawal of all anti-glaucoma eyedrops in patients who were using them. The measurement time of the day was set between 1 p.m. and 4 p.m. After the pupil was dilated with 0.4% tropicamide (Midrin-M, Santen Pharmaceutical Co. Ltd., Osaka, Japan) and subjects kept sitting position for more than 15 minutes, MBR images were continuously acquired at the rate of 30 frames per second over 4 s. The LSFG Analyzer software (Softcare Co., Ltd.) synchronized all captured MBR images with each cardiac cycle, and the averaged MBR of a heartbeat was displayed as a composite map. After the margin of the ONH was identified using a round band, the software segmented out the vessels using the automated definitive threshold (Figure 2A and 2B) and analyzed the mean MBR for the entire ONH (MA), that for the ONH large vessels (MV), and that for the ONH tissue (MT).

Measurement of clinical parameters

IOP was measured using the Goldmann applanation tonometer just before blood flow measurement. The mean deviation (MD) was obtained by the SITA strategy of the 30-2 program of the HFA. CpRNFLT was assessed using the Retina Scan (RS-3000, Nidek, Co., Ltd., Gamagori, Japan) OCT device. Cup/disc ratio was obtained by the stereo fundus camera (nonmyd WX, Kowa, Company, Ltd., Nagoya, Japan) and its software (VK-2 WX, Kowa). To reduce inter-examiner variability, 3 data of cup/disc ratio by different examiners was averaged for each subject.

Statistical analysis

Each result is expressed as the mean \pm standard deviation (SD). Statistical comparisons between the two groups were evaluated by Student's t-test for unpaired data or Fisher exact test. Differences were considered statistically significant at $p < 0.05$. Correlations between two parameters, including ONH blood flow, MD, and cpRNFLT, were verified by simple regression analyses.

RESULTS

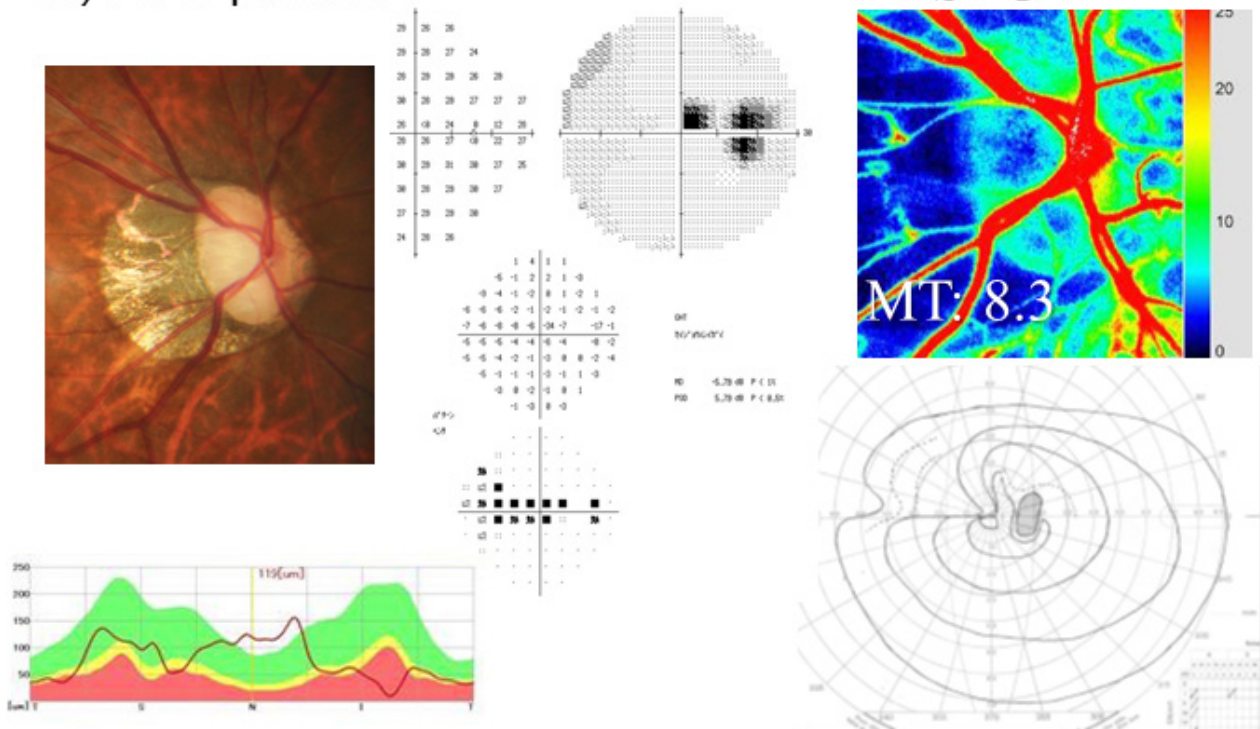
The demographic characteristics of patients with and without glaucoma are shown in Table 1. There were no significant differences in ages, gender distribution, refractive errors, visual acuity, and IOP between the two groups, whereas there were significant differences in the cup/disc ratio, MD, and cpRNFLT.

The MBR values for the two groups are shown in figure 3. MA and MT were significantly lower in the NTG group than in the nonglaucoma group, while there was no significant difference in MV between the two groups. In addition, the overlap of MT in the two groups was relatively small compared to that of MA (Figure 4).

There were significant correlations between MA and MD and between MT and MD only in the NTG group (Figures 5 and 6). On the other hand, there was no correlation between MT and cpRNFLT in both groups, although MA correlated with cpRNFLT only in the NTG group (Figures 7 and 8). In addition, MD correlated with cpRNFLT in both groups (Figure 9).

In addition, no significant correlations were found between refractive error and MBR values (MA, MV and MT) in both groups (data not shown).

A) NTG patient



B) Nonglaucomatous patient

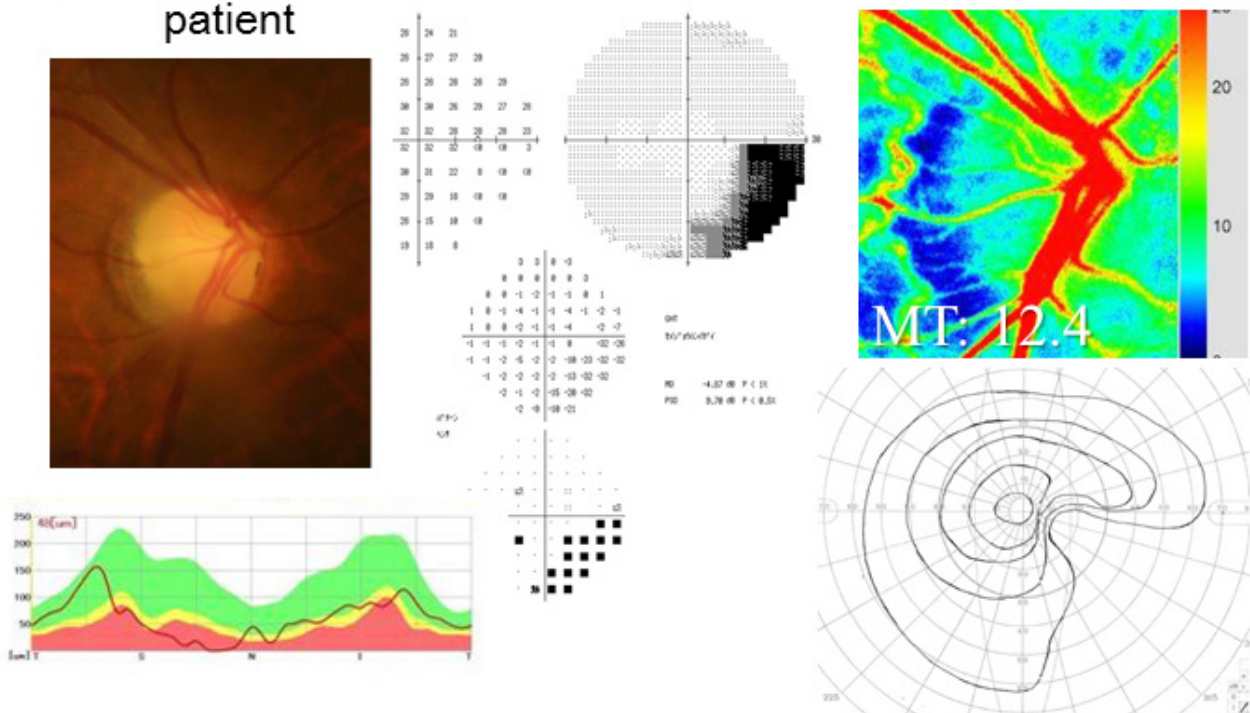


Figure 1 Representative patients with normal-tension glaucoma (NTG) and without glaucoma. A: The clinical findings of the right eye of a 32-year-old woman with NTG (Its refractive error was -15 diopters) B: The clinical findings of the left eye of a 56-year-old woman without glaucoma (Its refractive error was -9 diopters). Her visual field defect was stable during 5-year observation. LSFG: laser speckle flowgraphy. Explanation of MT is shown in the legend of Figure 2.

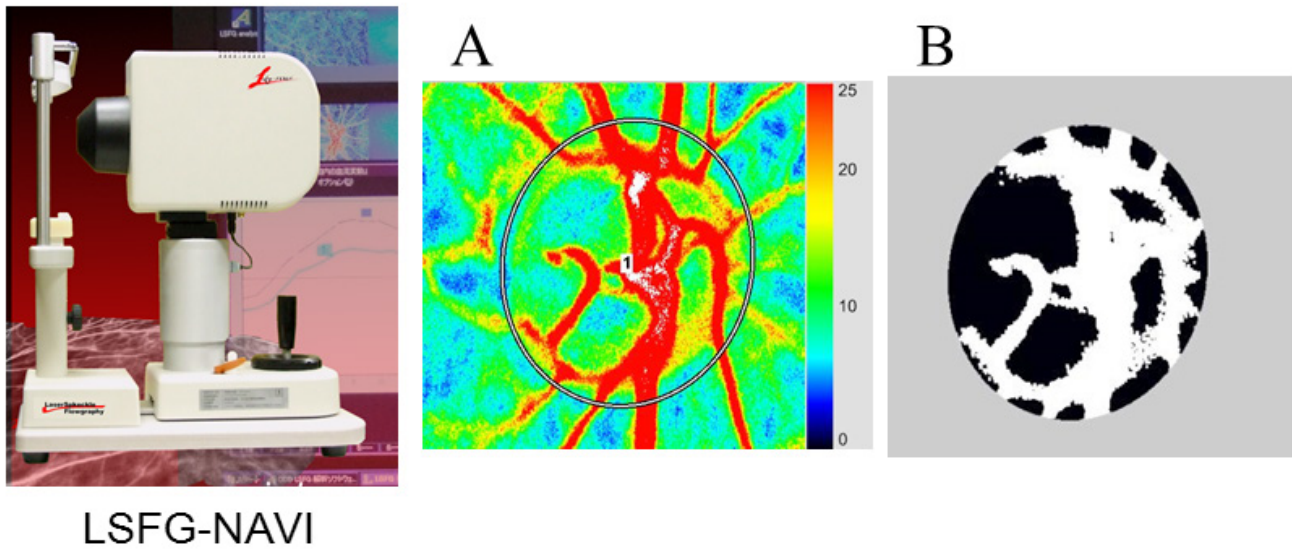


Figure 2 Appearance of the LSFG-NAVI device and assessment of blood flow within the optic nerve head (ONH) (A, B). The margin of the ONH is identified using a round band according to the color photograph of the fundus (A). The software segments out the retinal vessels using the automated definitive threshold and analyzes the mean blur rates (MBRs) for the entire ONH (MA), for the ONH large vessels (MV, shown in white), and for the ONH tissue (MT, shown in black) (B).

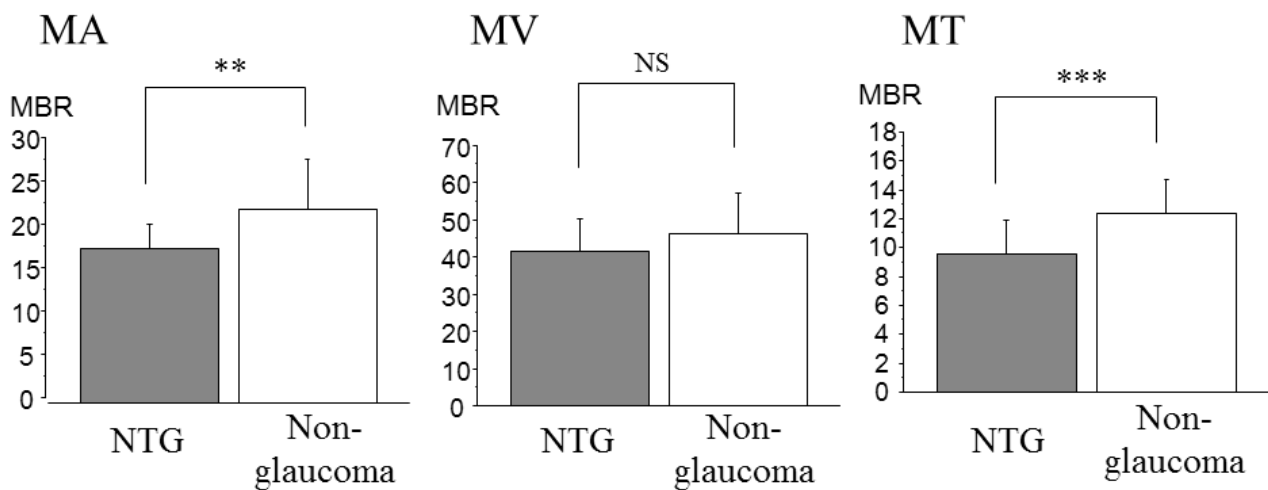


Figure 3 Comparisons of MA, MV and MT in patients with and without NTG. Data are shown as the mean \pm SD for 20 subjects, respectively. ** $P < 0.01$, *** $P < 0.001$, NS: non-significant (unpaired t test).

Table 1 Demographic characteristics of patients with and without glaucoma.

	NTG	Non-glaucoma	P value
Number	20	20	-
Age (years)	50.6 \pm 10.0	53.5 \pm 14.0	0.45
Gender (Male: Female)	5 : 15	7 : 13	0.73
Refractive error (diopter)	-7.1 \pm 3.2	-6.5 \pm 2.8	0.55
Visual acuity (logMAR)	-0.06 \pm 0.08	-0.05 \pm 0.06	0.85
IOP (mmHg)	13.3 \pm 2.1	14.1 \pm 2.6	0.27
Cup/disc ratio	0.69 \pm 0.08	0.59 \pm 0.13	0.01
Mean deviation (dB)	-6.4 \pm 2.7	-4.5 \pm 2.5	0.03
cpRNFL	66.0 \pm 10.4	77.2 \pm 15.5	0.01

Each value is expressed as the mean \pm SD; NTG: normal-tension glaucoma; logMAR: logarithm of the minimal angle resolution; OP: intraocular pressure; cpRNFL: circumpapillary retinal nerve fiber layer thickness; Statistical comparisons were evaluated by Fisher exact test for gender and Student's t-test for the others.

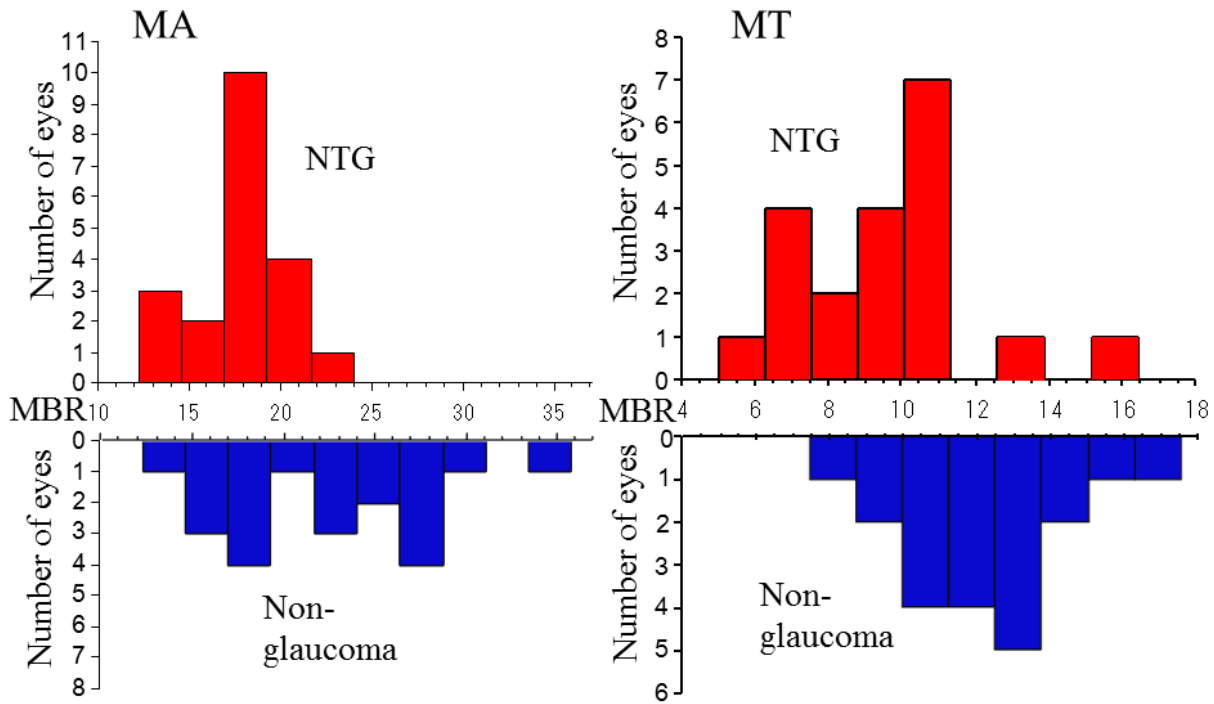


Figure 4 Histograms of MA and MT in patients with and without NTG.

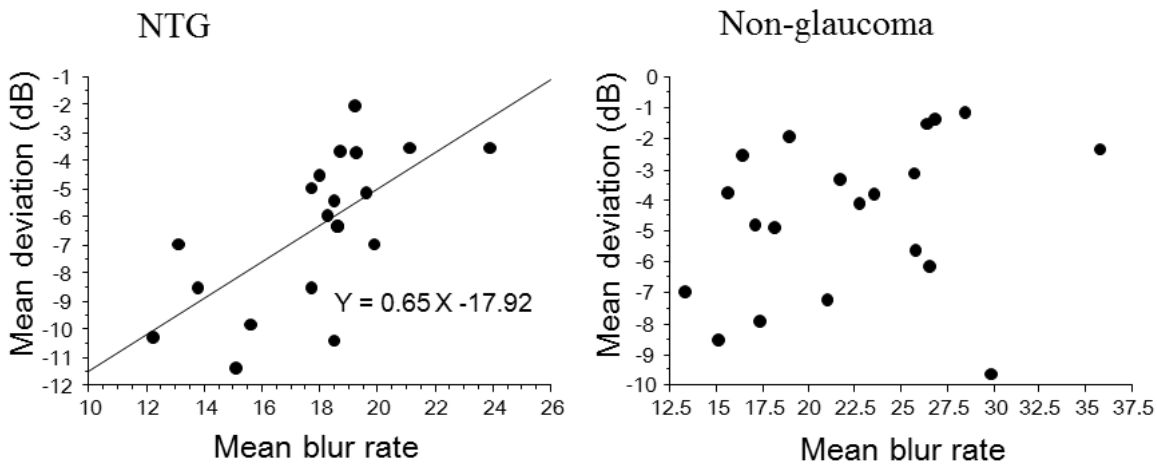


Figure 5 Relationship between MA and mean deviation (MD) in patients with and without NTG. MD was correlated with MA in glaucoma patients ($p=0.0014$, $r=0.66$), but not in those without glaucoma ($p=0.22$).

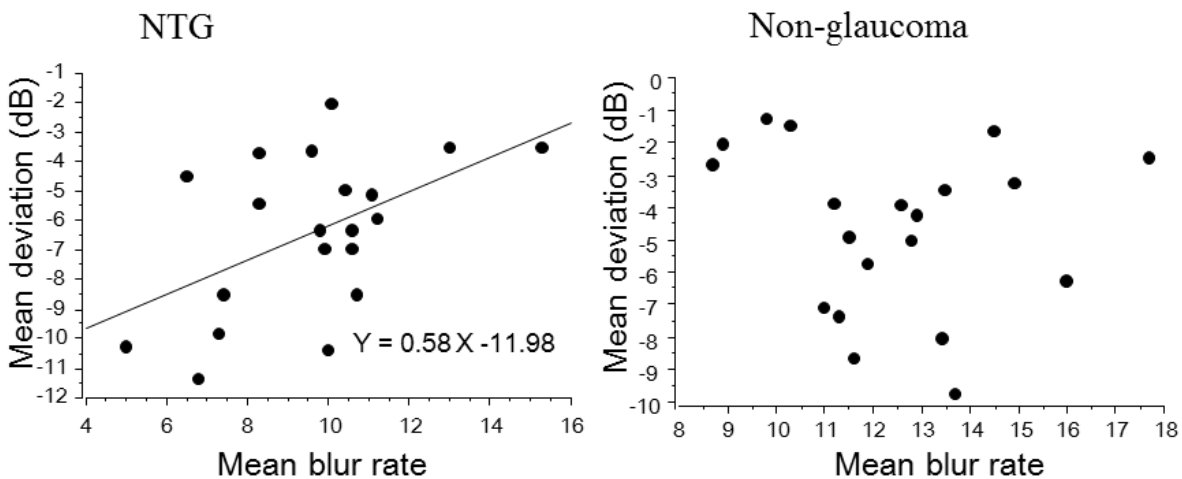


Figure 6 Relationship between MT and MD in patients with and without NTG. MD was correlated with MT in NTG patients ($p=0.021$, $r=0.51$), but not in patients without glaucoma ($p=0.56$).

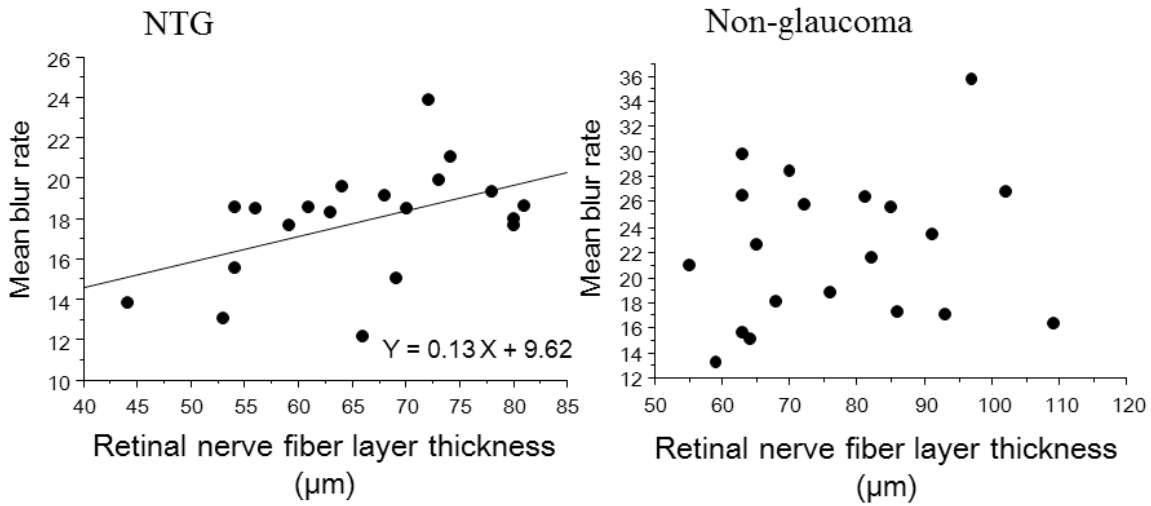


Figure 7 Relationship between MA and cpRNFLT in patients with and without NTG. MA was correlated with cpRNFLT in NTG patients ($p=0.035$, $r=0.47$), but not in patients without glaucoma ($p=0.45$).

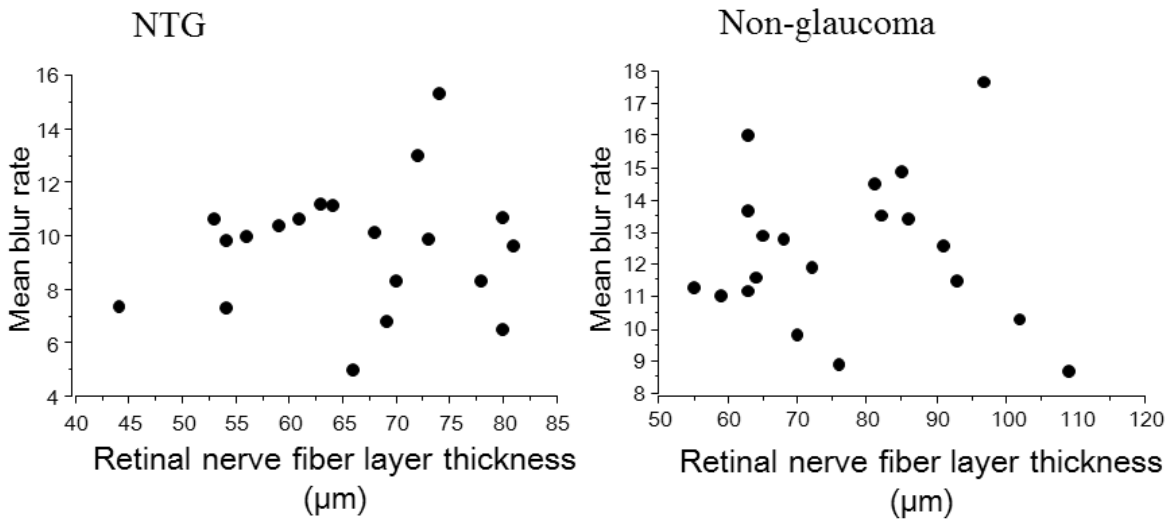


Figure 8 Relationship between MT and cpRNFLT in patients with and without NTG. MT was not correlated with cpRNFLT in both NTG patients and patients without glaucoma ($p=0.65$, 0.95 , respectively).

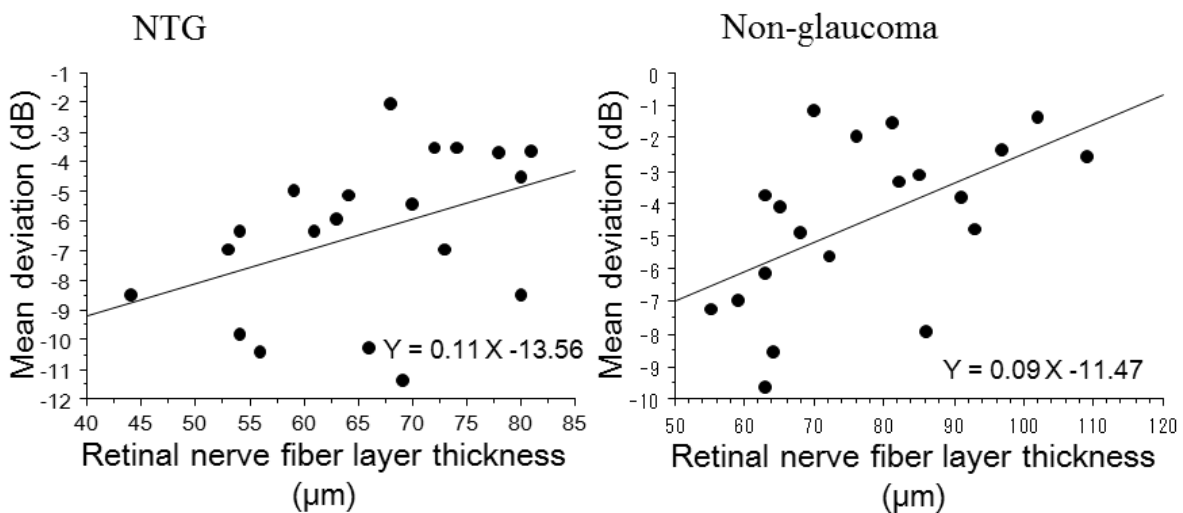


Figure 9 Relationship between cpRNFLT and MD in patients with and without NTG. MD was correlated with cpRNFLT in both NTG patients and patients without glaucoma ($p=0.049$, 0.013 ; $r=0.42$, 0.55 , respectively).

DISCUSSION

In the present study, we compared ONH blood flow between myopic glaucomatous eyes and myopic nonglaucomatous eyes to verify whether the measurement of this parameter is useful for the differential diagnosis of glaucoma in eyes with myopic ONHs and visual field defects. The results revealed that the ONH blood flow, particularly in the ONH tissue, was significantly poorer in glaucomatous myopic ONHs than in nonglaucomatous myopic ONHs. Furthermore, it correlated with MD in the glaucomatous myopic eyes, but not in the nonglaucomatous myopic eyes. Blood flow in the ONH tissue of the glaucomatous myopic eyes was not associated with cpRNFLT.

We used LSFG for assessment of ONH blood flow in the current study because its validity and reproducibility have been previously demonstrated^[31,32]. In addition, our recent studies suggested that absolute MBR values for the ONH correlated with CBF, indicating the quantifiability of these values in the absence of large topographical and color differences in the ONH^[31,33]. This condition was probably observed in the present study because we compared MBR values among eyes with myopic ONHs, which have similar topographical and color appearances.

According to our results, MA and MT were significantly lower in myopic glaucomatous eyes than in myopic nonglaucomatous eyes, whereas MV did not show any difference, suggesting a selective decrease in blood flow in the ONH tissue, not the ONH large vessels, in glaucomatous eyes. A similar result was reported only for MA in previous studies, which compared myopic glaucomatous eyes with myopic control eyes^[28,29]. In addition, the current study indicated a relatively small overlap of MT distribution in the glaucomatous and nonglaucomatous eyes, compared to that of MA. Furthermore, myopic glaucomatous eyes showed a strong correlation between MA and MD ($p=0.0014$, $r=0.66$), similar to the findings in previous studies ($p<0.001$, $r=0.58$ or 0.63)^[28,29], and between MT and MD. In addition, there was a significant correlation between MA and cpRNFLT, as reported in previous studies^[28,29], while MT showed no correlation with cpRNFLT. Therefore, MT may be relatively independent of a decrease in cpRNFLT, at least in a certain stage of glaucoma, suggesting, for the first time as per our knowledge, that a decreased MT can be a potential critical parameter for the development of glaucoma, apart from a decreased cpRNFLT.

Significant correlations between cpRNFLT and MD were detected not only in myopic glaucomatous eyes but also in myopic nonglaucomatous eyes, suggesting that cpRNFLT is also a critical parameter, though reduced ONH blood flow is not such a critical parameter in nonglaucomatous eyes. Myopic nonglaucomatous eyes in the current study showed various types of optic nerve hypoplasia; one of the representative types is superior segmental optic nerve hypoplasia (SSOH). A recent study also suggested that LSFG measurements, in addition to the analysis of cpRNFLT, may be useful to differentiate SSOH and NTG because of differences in ONH hemodynamics caused by different pathophysiologies between the two conditions^[34].

The significant intergroup differences in MD and cpRNFLT were possibly related to the difference in ONH blood flow in this study. Nevertheless, the decreased ONH blood flow may be involved in the pathology of glaucoma in myopic eyes because a significant correlation between MD and ONH blood flow was found only in glaucomatous eyes. Furthermore, it remains unclear whether the difference in ONH blood flow caused or resulted from glaucomatous impairment in ONH.

This study had several limitations. First was the small sample size. The results in the current study should be verified in a multicenter study in the future. Second, MD could not be matched between the two groups. If MD was matched, the results of this study would be more justified. Third, this study included no normal controls since it did not seem proper to compare MBR values between ONHs with normal or abnormal configuration. Fourth, we did not use the data from multiple measurements of blood flow and IOP in the day. Instead, we standardized the measurement time of the day to avoid diurnal fluctuation. Fifth, we could not examine the correlation between cpRNFLT and blood flow in each quadrant of the ONH because all patients had tilted discs, which made accurate division into superior, inferior, temporal, and nasal quadrants difficult.

In conclusion, assessment of blood flow in the ONH tissue, in addition to the evaluation of cpRNFLT, may be useful for the differential diagnosis of NTG in patients with myopic ONHs. Further studies with a larger sample size and MD-matched groups are needed to verify the present conclusions.

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CONFLICT OF INTERESTS

The author has no conflicts of interest to declare.

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