cup/disc ratio ≥0.8 but with no other ophthalmoscopic and SAP findings suggestive of glaucoma (large C/D eyes) and to determine the relationship of the abnormalities to the optic disc topography results obtained using a Heidelberg Retina Tomograph (HRT, Heidelberg Engineering GmbH, Heidelberg, Germany).

SUBJECTS AND METHODS

The study protocol was approved by the ethical review committees of the individual institutes and adhered to the tenets of the Declaration of Helsinki. Subjects were recruited consecutively from those seen in the outpatient clinics of the Departments of Ophthalmology of the University of Tokyo Graduate School of Medicine, Tajimi Municipal Hospital, Nihon University, School of Medicine, and Yoshikawa Eye Clinic from October 1998 to September 2000. We recruited subjects with an eye with generalized enlargement of optic disc cupping. After obtaining informed consent from all participants, the enrolled subjects underwent a routine ocular examination, which included visual acuity testing, slit-lamp biomicroscopy, Goldmann applanation tonometry, funduscopy with pupil dilation, and automated perimetry using a Humphrey Field Analyzer (HFA) with the central 30-2 standard full-threshold strategy (HFA30-2, Carl Zeiss Meditec, Dublin, CA). All subjects enrolled in the study were familiarized with automated perimetry by undergoing at least 2 visual field examinations with the HFA 30-2 in each eye before we obtained the data used for analysis, and all had reliable visual field measurements with fixation loss, and false-positive and false-negative rates of less than 25%. Scanning laser tomography using HRT was performed according to standard procedures. Stereoscopic optic disc photographs were obtained after mydriasis using a simultaneous stereoscopic fundus camera (Topcon TRC-SS, Topcon Inc., Tokyo, Japan) with ASA 100 36-mm film (Fuji chrome 100, Fuji Film Inc., Tokyo, Japan).

Subject Selection

Eye with a Generalized Enlargement of Optic Disc Cupping (Large C/D Eyes)

One hundred twenty eyes of 60 subjects who met the following criteria were extracted from all the subjects recruited: (1) eyes with generalized enlargement of optic disc cupping with a vertical cup/disc ratio ≥0.8 and no other apparent ophthalmoscopic signs suggestive of glaucoma, such as disc hemorrhage, nerve fiber layer bundle defects, rim notching, localized rim thinning, saucerization of the rim, or bilateral asymmetry of the cup/disc ratio ≥0.2; (2) eyes with no disc anomalies such as a tilted disc; (3) recorded IOP consistently less than 21 mm Hg bilaterally; (4) best-corrected visual acuity (BCVA) equal to or greater than 20/25; (5) no media opacity; (6) refractive errors in spherical equivalents within ± 3 diopters; (7) normal open angles bilaterally; (8) no apparent history of disc hemorrhage in either eye; (9) disc area less than 4 mm^2 measured by scanning laser tomography; and (10) no visual field loss determined by the Humphrey 30-2 program (HFA30-2) in either eye (Fig. 1). The rim border was determined by graduation of color, texture, and the course of the blood vessels based on the stereoscopic optic disc photographs, and the vertical cup/disc ratio was evaluated in 0.05 units using a ruler. The visual field was considered normal if it did not meet the modified liberal criteria proposed by Caprioli[21]; that is, (a) at least 2 adjacent test points (excluding the outermost rim) having a sensitivity with a probability of less than 5% on the pattern deviation probability plot, and/or (b) a point having a sensitivity with a probability less than 1% on the pattern deviation probability plot, and/or (c) a 5-dB difference in pattern deviation value across the nasal horizontal meridian in 2 adjacent test points.

The stereoscopic optic disc photographs of the 120 eyes then were reevaluated by 3 glaucoma specialists (MA, YY, YS) who reviewed all photographs independently in a blinded manner. If all 3 agreed that the eye had generalized enlargement of optic disc cupping with vertical cup/disc ratio ≥0.8 and no other apparent signs suggestive of glaucoma in both the studied and contralateral eyes such as disc hemorrhage, nerve fiber layer bundle defects, rim notching, localized rim thinning, saucerization of the rim, or bilateral asymmetry of the cup/disc ratio ≥0.2, that eye was enrolled in the study. When both eyes of a patient met the criteria, one randomly chosen eye was included. Thirty eyes of 30 subjects (mean age, 51.4 ± 11.1; range, 28–71) were ultimately enrolled.

Eyes with Early-Stage Normal Tension Glaucoma

We reviewed stereoscopic optic disc photographs of 282 eyes of 141 consecutive patients with NTG with mild visual field loss who had been seen in the outpatient clinic of the Department of Ophthalmology of the University of Tokyo Graduate School of Medicine. We selected eyes with generalized enlargement of optic disc cupping (generalized enlargement of the optic cup discs)[22] and an HFA 30-2 mean deviation of >-5 dB. An optic disc with generalized enlargement of the optic cup disc with a vertical C/D ratio ≥0.8 was identified based on independent readings by 3 glaucoma specialists (SM, GT, NK), and the eye was enrolled in the study only when the 3 reviewers agreed (Fig. 2). Further, the enrolled eyes with NTG had to have a BCVA of at least 20/25 with no media opacities, spherical equivalent refractive errors within ±3 diopters, and no clinically significant visual field changes during the past 2 years. Seventeen eyes of 17 patients with NTG (mean age, 59.4 ± 10.3; range 28–75) were ultimately enrolled.

An abnormal visual field in the current study for selecting NTG was defined by modifying the moderate criteria of Caprioli[21]; that is, (a) 3 or more adjacent test points (excluding the outermost rim) having a sensitivity with a probability of less than 5% on the pattern deviation probability plot, and/or (b) 2 or more adjacent points having a sensitivity with a probability less than 1% on the pattern deviation probability plot, and/or (c) a 10-dB difference in pattern deviation across the nasal horizontal meridian in 2 or more adjacent test points. When both eyes of a patient met the criteria, one randomly chosen eye was included.

A diagnosis of NTG was made in eyes with the following:

1. an untreated peak IOP no higher than 21 mm Hg during follow-up that included measurement over a 24-hour period (IOP measured every 2 hours) in both eyes

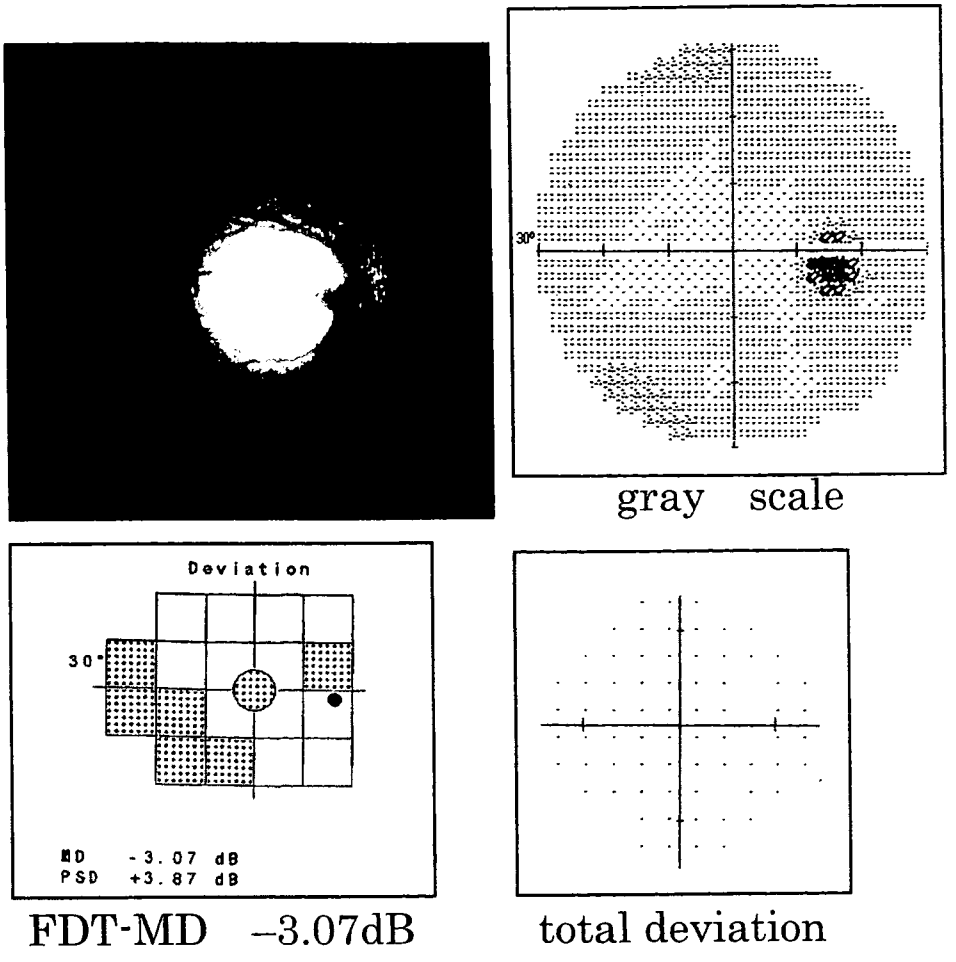

FIGURE 1. Optic disc photograph (top left), FDT printout (lower left), and HFA results (top right, gray scale; bottom right, total deviation) from a representative case of the large C/D eyes.

2. a normal open anterior chamber angles in both eyes
3. the presence of glaucomatous optic nerve head changes and corresponding visual field changes
4. no ocular, rhinologic, neurologic, or systemic disorders responsible for the optic nerve damage
5. no history of hemodynamic crisis or previous ocular surgeries or laser treatment in either eye.

Normal Eyes

The normal eyes were defined as having a BCVA of at least 20/25, refractive errors in spherical equivalents within ± 3 diopters, normal appearance of the optic disc in both eyes with a vertical cup/disc ratio ≤0.6, a normal open angle, an IOP less than 21 mm Hg in both eyes, no family history of glaucoma, no other significant ocular diseases except for a mild refractive error, no history of increased IOP or ocular trauma, and normal results with the HFA 30-2 based on the modified liberal criteria by Caprioli[21] described previously. From visual field examinations with the HFA 30-2 performed by volunteers familiar with the examination, one randomly chosen eye from 25 normal eyes (9 males and 16 females; mean age, 44.2 ± 13.5 years) were enrolled. Eyes with an apparently small optic disc were excluded.

Scanning Laser Tomography

Scanning laser tomography was performed using HRT with software version 2.01 (Heidelberg Engineering, GmBH, Heidelberg, Germany) within 3 months of the last Humphrey visual field test. The principles and description of the instrument have been reported previously.[16–20] Images with a standard deviation of less than 30 μm were used. The contour line of the optic disc margin was outlined (along the inner margin of the scleral ring) by an experienced operator (SK) while viewing photographs of the optic disc. According to software version 2.01, a reference plane was automatically set 50 μm posterior to the mean height of the disc margin contour line in a temporal segment between 350 and 356 degrees.

To analyze the configuration of the optic nerve head, we used the following HRT parameters: disc area (mm^2), cup volume (mm^3), rim volume (mm^3), mean cup depth (mm), cup shape measurement (CSM), height variation contour, and mean retinal nerve fiber layer thickness (mm).

Frequency Doubling Technology Testing

All subjects were first tested with the C-20 screening program to familiarize them with FDT using the Humphrey FDT screener (Carl Zeiss Meditec), after which they underwent the N-30 full threshold program. FDT was performed first in

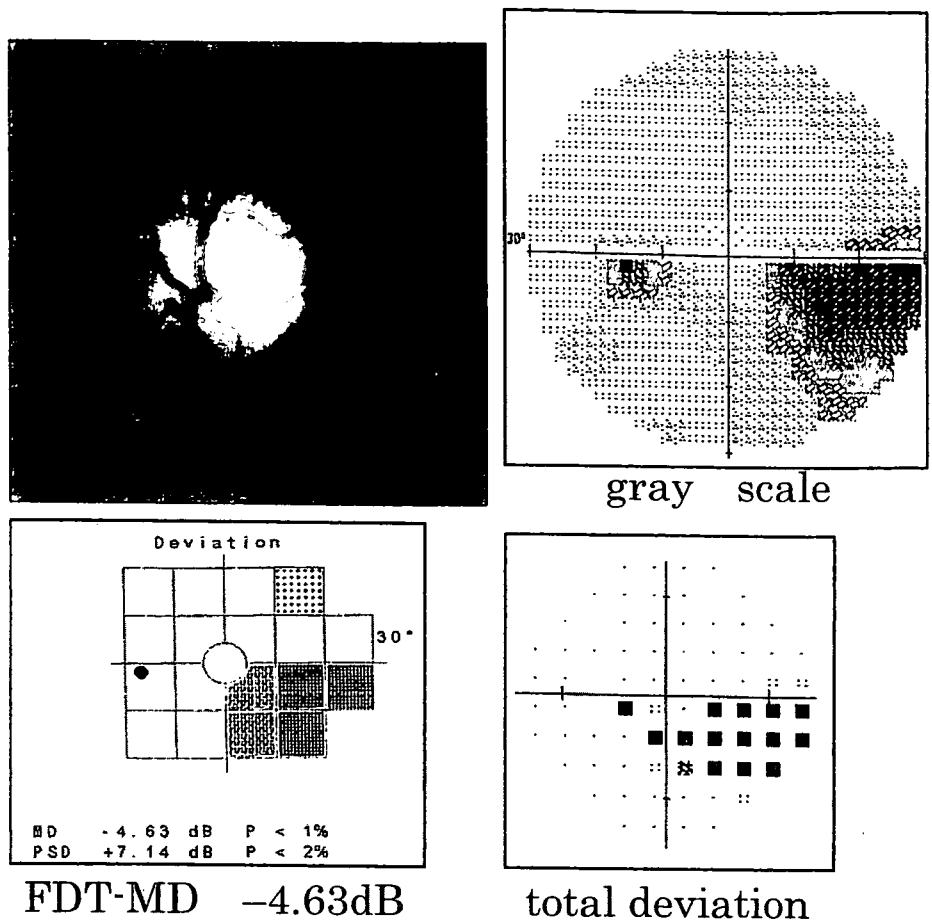

FIGURE 2. Optic disc photograph (top left), FDT printout (lower left), and HFA results (right top, gray scale; bottom right, total deviation) from a representative case with early-stage NTG.

the right eye. With the N-30 full threshold program, 19 sectors were tested, a central round sector, 16 square sectors in the periphery up to 20 degrees, and 2 more square sectors in the nasal periphery from 20 degrees up to 30 degrees. The location for each stimulus presentation was randomly selected, and the threshold value for each test location was defined by the minimal contrast of the pattern that was perceived. Patients were instructed to fixate on a small central black square on the video monitor and asked to respond when they detected a presented stimulus. There was a rest period of at least 5 minutes between the C-20 screening program and the N-30 full threshold program. The results of FDT used for analysis were obtained within 3 months of the Humphrey visual field test. To be considered reliable, a test had to have both false-positive and false-negative trials and fixation losses of less than 20%, which were calculated as in standard threshold perimetry.[23]

Wu et al[13] reported criteria for judging the N-30 results obtained from upper or lower hemifield as normal or abnormal; that is, a normal hemifield had zero or one abnormal FDT sectors at probabilities of 5%, 2%, or 1% and no abnormal sectors at a probability of 0.5%, and an abnormal hemifield had 2 or more abnormal FDT sectors at probabilities of 5%, 2%, or 1%, or one or more abnormal FDT sectors at a probability of 0.5%.

The results with the N-30 program were considered abnormal when at least one hemifield was abnormal or the result of the central round sector was abnormal (probability of <5%), and the results were considered normal when both hemifields were considered normal based on the criteria of Wu et al[13] and the results of the central round sector were normal.

Statistical Analysis

The results from large C/D eyes, early-stage NTG, and normal eyes were compared. For statistical analysis, the difference in the mean values among the 3 groups was evaluated using a two-tailed t test or a t test with Tukey's correction for multiple comparison tests (SAS software version 6.12). A difference in the observed counts between two groups was evaluated using a χ^2 test. Pearson correlation was calculated to assess the correlation between HRT parameters and the FDT mean deviation. A P value less than 0.05 was considered statistically significant.

RESULTS

Study Group Characteristics

Table 1 shows the demographics of the 31 men and 41 women included in the study. The mean age of the 30 subjects with large C/D eyes was significantly older than that of the 25 normal subjects and significantly younger than that of the 17 patients with early-stage NTG. The mean IOP was

TABLE 1. Study Population Characteristics (mean ± SD)

Variable	Large C/D Eyes (1) (n = 30)	NTG Eyes (2) (n = 17)	Normal Eyes (3) (n = 25)	1 vs 2	1 vs 3	2 vs 3
Age (years)	51.4 ± 11.1	59.4 ± 10.3	44.2 ± 13.5	*	*	*
Eye right/left	16/14	7/10	15/10			
IOP (mm Hg)	14.5 ± 2.2	16.3 ± 1.8	13.2 ± 2.3			*
Refractive error (D)	−0.91 ± 1.76	−1.08 ± 2.59	−0.46 ± 1.23			
HFA-MD (dB)	−0.87 ± 1.61	−3.49 ± 1.35	0.03 ± 1.61	*		*

HFA-MD, Humphrey field analyzer mean deviation.
*Significant difference ($P < 0.05$, t-test with Tukey's correction for multiple comparison). Large C/D eyes, eyes with generalized enlargement of optic disc cupping (vertical cup/disc ratio ≥0.8), normal intraocular pressure, normal standard achromatic automated perimetry (SAP) result, and no other ophthalmoscopic findings suggesting glaucoma. NTG eyes, eyes with early-stage normal tension glaucoma with generalized enlargement of optic disc cupping (vertical C/D ratio ≥0.8).

significantly higher in the early-stage NTG group. There was no significant inter-group difference in refraction or right/left ratio. The mean deviation of the HFA-30 program of the large C/D eyes was significantly better than that in the early-stage NTG eyes, while it was not significantly different from that in the normal eyes (Table 1).

HRT Parameters

Table 2 lists the means and standard deviations of the HRT parameters for the 3 groups of eyes. There was no significant difference in the HRT parameters between the large C/D and the early-stage NTG eyes, while the normal eyes significantly differed from the other two groups in all HRT parameters, except for the disc area. All large C/D eyes and 16 of 17 of the early-stage NTG eyes (94.1%) were classified as glaucomatous using the HRT classification program, while 1 of 25 normal eyes (4%) was classified as glaucomatous.

FDT Results

The FDT mean deviation in the large C/D eyes was significantly lower than in the normal eyes and higher than in the early-stage NTG eyes (Table 3). FDT pattern standard deviation in the large C/D eyes was not significantly different from that in the normal eyes, but it was significantly smaller than that in the early-stage NTG eyes (Table 3). Based on the criteria of Wu et al,[13] the results of FDT perimetry using N-30 program were considered abnormal in 57%, 82%, and 20% of the large C/D eyes, early-stage NTG, and normal eyes, respectively. The percentage of eyes considered abnormal by FDT was significantly higher in the large C/D eyes than in the normal eyes, but it was not significantly different between the large C/D eyes and the early-stage NTG eyes (Table 3). Among the HRT parameters examined, only the cup shape measure showed significant correlation with FDT mean deviation ($r = -0.452$, $P = 0.0140$) in the large C/D eyes, while no HRT parameters showed significant correlation with FDT mean deviation or pattern standard deviation in normal and early-stage NTG eyes.

Comparison Between Eyes With Large C/D Eyes with Normal and Abnormal FDT Results

We divided the large C/D eyes into 2 groups, FDT-normal and FDT-abnormal, using FDT mean deviation or FDT pattern standard deviation values with a probability of less than 5% as a cut-off value,[24] or the criteria of Wu et al,[13] and the HRT parameters between the two subgroups were compared. The intraocular pressure was significantly higher in the FDT-abnormal group than in the FDT-normal group when the FDT mean deviation criterion or the criteria of Wu et al[13] was applied (13.9 ± 2.5 versus 15.6 ± 1.6 mm Hg, $P = 0.045$ and 13.4 ± 2.5 versus 15.3 ± 1.6 mm Hg, $P = 0.031$, respectively).We found that only the CSM was significantly higher (ie, the cupping was steeper or more glaucomatous) in the FDT-abnormal group than in the FDT-normal group when the FDT mean deviation criterion or the criteria of Wu et al[13] was applied, while there were no significant intergroup differences in any other parameters (Tables 4–6). On the other

TABLE 2. Optic Nerve Topography in Eyes With Large C/D Eyes, NTG Eyes, and Normal Eyes (mean ± SD)

Variable	Large C/D Eyes (1) (n = 30)	NTG Eyes (2) (n = 17)	Normal Eyes (3) (n = 25)	1 vs 2	1 vs 3	2 vs 3
Disc area (mm^2)	2.88 ± 0.47	2.78 ± 0.39	2.66 ± 0.29			
Cup volume (mm^3)	0.61 ± 0.39	0.62 ± 0.42	0.19 ± 0.13		*	*
Rim volume (mm^3)	0.21 ± 0.09	0.18 ± 0.11	0.50 ± 0.12		*	*
Mean cup depth (mm)	0.38 ± 0.13	0.39 ± 0.13	0.26 ± 0.08		*	*
CSM	−0.04 ± 0.06	−0.03 ± 0.06	−0.20 ± 0.07		*	*
Height variation contour (mm)	0.35 ± 0.09	0.35 ± 0.11	0.41 ± 0.07		*	*
Mean RNFL thickness (mm)	0.17 ± 0.06	0.17 ± 0.07	0.27 ± 0.05		*	*

CSM, cup shape measure; RNFL, retinal nerve fiber layer.
*Significant difference ($P < 0.05$, t-test with Tukey's correction for multiple comparison) for explanation of large C/D eyes and NTG eyes. See footnotes for Table 1.

TABLE 3. FDT in Eyes With Large C/D Eyes, NTG Eyes, And Normal Eyes (mean ± SD)

Variable	Large C/D Eyes (1) (n = 30)	NTG Eyes (2) (n = 17)	Normal Eyes (3) (n = 25)	1 vs 2	1 vs 3	2 vs 3
FDT- MD (dB)	−2.41 ± 2.30	−3.96 ± 2.23	−0.42 ± 2.06	*	*	*
FDT-PSD (dB)	4.46 ± 2.06	6.38 ± 2.57	3.70 ± 0.55	*		*
Criterion of Wu et al[13] (abnormal/normal)	17/13	14/3	5/20		†	†

FDT, frequency doubling technique; FDT-MD, frequency doubling technique mean deviation; FDT-PSD, frequency doubling technique pattern standard deviation.
*Significant difference ($P < 0.05$, t-test with Tukey's correction for multiple comparison); †Significant difference ($P < 0.05$, χ^2 test).

hand, when the FDT pattern standard deviation criterion was used, there were no significant intergroup differences in HRT parameters, probably because only 5 eyes were judged to be FDT pattern standard deviation abnormal.

DISCUSSION

A physiologic large cup/disc ratio is a diagnostic term applied to eyes with generalized enlargement of optic disc cupping and normal IOP but no other evidences suggestive of glaucoma.[25] Clinically, however, it sometimes may be difficult to differentiate pre-perimetric stage NTG eyes with generalized enlargement of optic disc cupping from normal variant eyes with a large cup/disc ratio. The prevalence of NTG is thought to be much higher in Japan than in other countries.[26] It is possible that some eyes with a large cup/disc ratio may represent pre-perimetric-stage NTG eyes. The current study was designed to find clues to identify eyes with large C/D that appears otherwise healthy but may be actually in pre-perimetric stage of NTG. For this purpose, we included only eyes with generalized enlargement of optic disc cupping with a vertical cup/disc ratio ≥0.8 (large C/D eyes). For NTG eyes, we thought that it is more appropriate to use NTG eyes closer to pre-perimetric stage; that is, in the earlier stage of the disease, and with similar appearance of optic nerve head (generalized enlargement of optic disc cup with a vertical C/D ratio ≥0.8).

In the current study, the average age happened to be somewhat different among the 3 groups compared. We think, however, this difference has little influence on the validity of comparison performed for the following reasons:

1. The most important intergroup comparison in the current study was that between large C/D eyes with normal FDT result and those with abnormal FDT result. As long as this comparison was concerned, no intergroup age difference was found (Tables 4–6).
2. Regarding HFA and FDT results, we used age-corrected parameters.
3. In Japanese eyes, age-related differences in HRT parameters presently used should be little between the age of 44 and 59 years.[27]

Our findings suggested that FDT N-30 results are useful for differentiating the large C/D eyes as in the current study from both normal eyes and those with early-stage NTG with generalized enlargement of optic disc cupping, and that some of large C/D eyes as in the current study have functional abnormalities in the M-cell pathway that is more sensitively detected by FDT.[28,29] In both the normal and early-stage NTG eyes, no HRT parameters showed correlation with FDT mean deviation, while only CSM showed significant correlation with FDT mean deviation in the large C/D eyes. We carried out this correlation analysis for exploratory purposes. Since we calculated correlation coefficients for 6 HRT parameters excluding disc area, conservative P value may be $0.084 = 0.014 \times 6$ according to the Bonferroni correction. Being compatible with this result, when the large C/D eyes were divided into the FDT-normal and FDT-abnormal subgroups based on the FDT mean deviation or criteria of Wu et al,[13] the CSM was significantly higher (ie, cupping was steeper) and

TABLE 4. HDT Parameters in FDT-Abnormal Subgroup and FDT-Normal Subgroup in Large C/D Eyes by FDT Mean Deviation Criterion (mean ± SD)

Variable	FDT-Abnormal Group (n = 10)	FDT-Normal Group (n = 20)	P Value
Disc area (mm^2)	2.91 ± 0.41	2.85 ± 0.45	0.747
Cup volume (mm^3)	0.71 ± 0.39	0.58 ± 0.42	0.422
Rim volume (mm^3)	0.20 ± 0.09	0.23 ± 0.09	0.391
Mean cup depth (mm)	0.40 ± 0.12	0.37 ± 0.13	0.068
CSM	0.00 ± 0.05	−0.07 ± 0.05	0.002
Height variation contour (mm)	0.35 ± 0.08	0.36 ± 0.09	0.801
Mean RNFL thickness (mm)	0.17 ± 0.07	0.17 ± 0.06	0.999
Age (years)	55.6 ± 10.1	48.8 ± 5.2	0.067

CSM, cup shape measure; RNFL, retinal nerve fiber layer; HRT, Heiderberg Retina Tomograph; FDT, frequency doubling technique.

TABLE 5. HRT Parameters in FDT-Abnormal Subgroup and FDT-Normal Subgroup in Large C/D Eyes by Criterion of Wu et al[13] (mean ± SD)

Variable	FDT-Abnormal Group (n = 17)	FDT-Normal Group (n = 13)	*P* value
Disc area (mm^2)	2.96 ± 0.40	2.77 ± 0.47	0.252
Cup volume (mm^3)	0.77 ± 0.48	0.44 ± 0.19	0.028
Rim volume (mm^3)	0.21 ± 0.10	0.23 ± 0.08	0.566
Mean cup depth (mm)	0.41 ± 0.16	0.32 ± 0.07	0.271
CSM	−0.01 ± 0.05	−0.08 ± 0.05	<0.001
Height variation contour (mm)	0.36 ± 0.08	0.36 ± 0.11	0.801
Mean RNFL thickness (mm)	0.17 ± 0.07	0.18 ± 0.06	0.818
Age (years)	54.0 ± 10.7	51.6 ± 10.2	0.533

HRT, Heiderberg Retina Tomograph; FDT, frequency doubling technique; CSM, cup shape measure; RNFL, retinal nerve fiber layer.

the IOP also higher in the FDT-abnormal group. The possibility that higher IOP affected the FDT N-30 test results may not be excluded, but rather seems unlikely. The IOPs in both FDT normal and abnormal eyes were close to the normal average IOP (about 13.5 and 15.5 mm Hg, respectively).[30] CSM is a description of depth; cups with gradually sloping borders tend to have negative values and cups with steep sloping walls tend to have positive values. CSM is an important HRT parameter that indicates the degree of glaucomatous disc damage[18] (more positive CSM value). Furthermore, several investigators have suggested that CSM is the single best HRT parameter for distinguishing between normal eyes and those with early-stage glaucoma.[31–34] Taken together, the present findings suggest that FDT mean deviation, CSM, or both might be clinically useful for grading the abnormalities in eyes with generalized enlargement of optic disc cupping with vertical cup/disc ratio ≥0.8.

It is tempting to speculate that large C/D eyes as in the current study with normal SAP and IOP values but with abnormal FDT results are more likely to develop NTG in the future, but a longitudinal study is needed to evaluate this possibility.

The average disc area in the present study was 2.88 ± 0.47 mm^2 in the large C/D eyes, which is somewhat larger than the average disc in Japanese patients (2.22 mm^2).[27] Heijl and Molder[35] studied the effect of optic disc diameter on the diagnostic power of subjective disc evaluation in glaucoma. The sensitivity for recognizing glaucoma was 58% in the small disc group, 72% in the middle group, and 85% in the large disc group. Thus, the larger discs were more likely to be judged as glaucomatous. In other words, patients with large discs have a greater chance of being diagnosed with glaucoma than patients with medium-sized or small discs. It is possible that there was a similar bias in the eyes in which we detected a large cup/disc ratio. There was no significant difference in disc size, however, between the current large C/D eyes and the early-stage NTG or normal eyes in this study. The differences in the diagnosis between these three groups should not depend on disc size.

Mansberger et al[8] investigated the difference in HRT parameters in large C/D eyes (vertical C/D ≥0.8) with SAP abnormalities and those with only short-wavelength automated perimetry (SWAP) abnormalities and found that the optic nerve head appearance in the latter group was less glaucomatous. In the current study, the parallel of the former group in the study of Mansberger et al[8] would be the early-stage NTG group and that of the latter group of their study the large C/D eyes with FDT abnormalities. In the current study, however, no HRT parameters showed significant difference between the above two groups. This apparent discrepancy may be at least partly attributed to difference in the IOP of subject eyes between the two studies (high IOP subjects in the study of Mansberger et al[8] and normal IOP subjects in the current study) or difference between FDT being more sensitive to change in M-cell pathway and SWAP being more sensitive to change in short-wavelength sensitive pathway.[36] Whether SWAP result is also useful for differentiating the large C/D eyes as in the current study from normal and early-stage NTG eyes with generalized enlargement of optic disc cupping waits future studies.

In summary, there was no significant difference in the HRT parameters between the current large C/D eyes and the eyes with early-stage NTG with generalized enlargement of optic disc cupping. The results using the FDT N-30 program in the large C/D eyes were significantly different from both the early-stage NTG and normal eyes. When the HRT parameters were compared between the two subgroups of the large C/D eyes, that is, those with FDT-normal results and those with FDT-abnormal results, only the CSM was significantly higher (ie, cupping was steeper) in eyes with FDT-abnormal results. Further, among HRT parameters, only the CSM showed significant negative correlation with FDT mean deviation in this group. Therefore, a part of eyes with a large cup/disc ratio but without any other signs suggestive of glaucoma as in this study may already have functional and/or structural change that can be detected more sensitively by FDT than SAP, and by CSM. Longitudinal follow-up of these eyes will help determine the predictive value of FDT for future development of NTG.

TABLE 6. HRT Parameters in FDT-Abnormal Subgroup and FDT-Normal Subgroup in Large C/D Eyes by FDT-PSD Criterion (mean ± SD)

Variable	FDT-Abnormal Group (n = 5)	FDT-Normal Group (n = 25)	*P* Value
Disc area (mm^2)	2.88 ± 0.47	2.88 ± 0.43	0.996
Cup volume (mm^3)	0.82 ± 0.56	0.59 ± 0.38	0.240
Rim volume (mm^3)	0.23 ± 0.12	0.21 ± 0.08	0.846
Mean cup depth (mm)	0.48 ± 0.15	0.36 ± 0.11	0.080
Cup shape measure	−0.04 ± 0.04	−0.04 ± 0.09	0.805
Height variation contour (mm)	0.38 ± 0.08	0.36 ± 0.09	0.559
Mean RNFL thickness (mm)	0.18 ± 0.07	0.18 ± 0.07	0.704
Age (years)	51.4 ± 9.8	58.8 ± 11.6	0.144

HRT, Heiderberg Retina Tomograph; FDT, frequency doubling technique; RNFL, retinal nerve fiber layer.

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Intraocular Metabolites of Isopropyl Unoprostone

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ABSTRACT *Purpose*: It is still unknown which metabolite of isopropyl unoprostone is responsible for reducing intraocular pressure. This study was carried out to measure intraocular metabolites of isopropyl unoprostone in the aqueous humor of primate and human eyes. *Methods*: Nine monkeys were randomly divided into three groups, all of which received isopropyl unoprostone. In group I, the drug was scheduled to be instilled at 0 hr, in group II at 1 hr, and in group III at 2 hr, prior to aqueous humor aspiration in order to determine metabolite concentration. Furthermore, 27 patients scheduled for cataract surgery and intraocular lens implantation were divided into five groups that received isopropyl unoprostone. In group A, the drug was scheduled to be instilled at 0 hr, in group B at 1 hr, in group C at 2 hr, in group D at 3 hr, and in group E at 4 hr, prior to surgery. At the beginning of the operation, the aqueous humor was aspirated. Metabolites of isopropyl unoprostone in the aqueous humor were determined by high-performance liquid chromatography. *Results*: M1 (3-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]propionic acid) (unoprostone free acid) and M2 ((*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoic acid), an intraocular oxidized metabolite of isopropyl unoprostone, were measured. M1:M2 in monkeys was respectively 0:0 ng/ml in group I, 150.2 ± 45.1:9.5 ± 1.7 ($p < 0.05$) in group II, and 74.6 ± 31.4:19.2 ± 5.3 ($p < 0.01$) in group III. M1:M2 in humans was respectively 0:0 ng/ml in group A, 50.6 ± 22.3:3.2 ± 1.3 ($p < 0.05$) in group B, 125.0 ± 23.1:12.2 ± 3.4 ($p < 0.001$) in group C, 144.9 ± 33.8:24.5 ± 6.2 ($p < 0.01$) in group D, and 56.7±21.5:18.7±5.3 ($p < 0.05$) in group E. *Conclusions*: A free acid of isopropyl unoprostone is the major intraocular metabolite of isopropyl unoprostone that is expected to act on target tissues in the eyes of both monkeys and humans.

KEYWORDS aqueous humor; human eye; intraocular metabolism; isopropyl unoprostone; monkey eye

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INTRODUCTION

Prostaglandin (PG) F2 α-related compounds isopropyl unoprostone, latanoprost, travoprost, and bimatoprost are now widely used as antiglaucoma ophthalmic solutions because of their efficacy in reducing intraocular pressure (IOP).[1–7] Isopropyl unoprostone was developed in Japan and became

commercially available in 1994 as the first approved PG-related antiglaucoma ophthalmic solution.[1,2] This solution is, among PG F2 α-related compounds, the weakest at reducing IOP.[3] However, isopropyl unoprostone has fewer side effects with regard to hyperpigmentation and eyelash growth than other PG F2 α-related compounds.[4]

Isopropyl unoprostone is classified as a docosanoid with low affinity to all prostanoid receptors,[8] and the mechanism by which isopropyl unoprostone reduces IOP remains unclear. Sharif *et al.* suggested that isopropyl unoprostone and its free acid act as a weak FP agonist, whereas latanoprost or travoprost act as a potent FP agonist.[8,9] Thieme *et al.* reported that free acid of isopropyl unoprostone contracts trabecular meshwork cells through the maxi-K channel.[10] Kashiwagi *et al.* measured intraocular metabolites of isopropyl unoprostone in the aqueous humor of pigmented Dutch rabbits by high-performance liquid chromatography (HPLC) and found that M2 ((*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoic acid), an oxidized metabolite of isopropyl unoprostone, predominated in terms of concentration, production of PGE, and stimulation of melanocytes compared to M1 (3-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]propionic acid), a free acid of isopropyl unoprostone (Fig. 1).[11–13] Based on these results, Kashiwagi *et al.* suggested that M2 was the main pharmacological source of isopropyl unoprostone in the human eyeball. However, there may be species differences in the metabolism of PG-related compounds. Therefore, intraocular metabolites of isopropyl unoprostone in the human and primate eye remains unclear. This study was performed to measure the levels of the metabolites of isopropyl unoprostone in the aqueous humor of the primate and human eye.

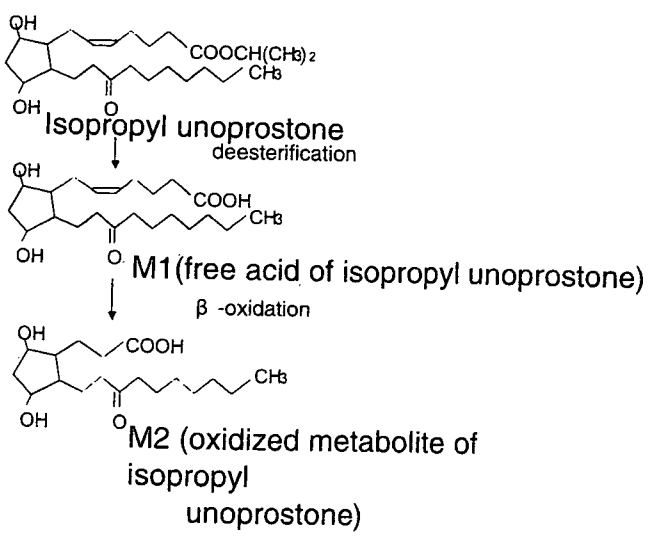

FIGURE 1 **Metabolism of isopropyl unoprostone. Metabolites in the isopropyl unoprostone cascade are abbreviated M1 and M2.**

MATERIALS AND METHODS

Cynomolgus Monkeys

The study was designed according to the time-course of the effects on IOP after isopropyl unoprostone instillation in cynomolgus monkeys,[14] and samples were collected up to 2 hr after eye drops were administered. A single instillation of 0.035 ml ophthalmic solution of isopropyl unoprostone containing 0.042 mg isopropyl unoprostone was administered to one randomly chosen eye of a cynomolgus monkey.

Nine cynomolgus monkeys (males 3–5 kg, 3–7 years old, Shinnihon Kagaku Co. Ltd., Tokyo, Japan) were randomly divided into three groups that received isopropyl unoprostone. In group I, the drug was scheduled to be instilled at 0 hr, in group II at 1 hr, and in group III at 2 hr prior to aspiration of 0.1 ml aqueous humor in order to determine isopropyl unoprostone metabolites. All samples were supplemented with 100% acetonitrile at double the sample volume and then frozen at −20°C until analysis. All procedures were carried out in compliance with the ARVO Statement for the Care and Use of Animals in Ophthalmology and Vision Research.

Humans

Twenty-seven patients (male/female: 6/21, mean age ± SD: 78.1 ± 8.1 years) scheduled for cataract surgery and intraocular lens implantation were enrolled in the study between February and November 2003 at the Tokyo Metropolitan Geriatric Hospital (Tokyo, Japan). Written informed consent was obtained from all participants, and the Ethics Committee of Tokyo Metropolitan Geriatric Hospital approved the study protocol; the study was performed according to the principles of the Helsinki Declaration. A single instillation of 0.035 ml ophthalmic solution of isopropyl unoprostone containing 0.042 mg isopropyl unoprostone was administered to a patient's eye. The patients were randomly divided into five groups that received isopropyl unoprostone. In group A, the drug was scheduled to be instilled at 0 hr, in group B at 1 hr, in group C at 2 hr, in group D at 3 hr and in group E at 4 hr prior to surgery. The pupil was routinely dilated with one drop

of tropicamide and phenylephrine hydrochloride, both given 4 times at intervals of 30 min before the surgery in all 5 groups. At the beginning of the operation, 0.1 ml of aqueous humor was aspirated for the determination of drug concentration. All samples were supplemented with 100% acetonitrile at double the sample volume and then frozen at −20°C. until analysis.

High-Performance Liquid Chromatography and Mass Spectrometry Operating Conditions

In Kashiwagi's results from rabbits, intraocular metabolites of isopropyl unoprostone other than M1 or M2 were barely detectable between 5 min and 12 hr after topical isopropyl unoprostone administration.[11] Therefore, this study measured M1 and M2 as follows. Aqueous humor samples were assayed using an HPLC-tandem mass spectrometry (LC-MS/MS) method.[15,16] The lower limit of quantitation was 5.0 ng/ml for isopropyl unoprostone and 1.0 ng/ml for M1 and M2. HPLC was performed using an 1100 series liquid chromatograph system equipped with a G1322A degaser, G1312A pump, and G1313A autosampler (Agilent Technologies Italia, Milan, Italy). The analytical column was a Develosil ODS-UG-5 cartridge with a 5-μm particle size and 50 mm × 2 mm internal diameter (Nomura Chemical Co., Ltd., Aichi, Japan); it eluted with a mixture of (A) 0.1% acetic acid in 20% acetonitrile and (B) 0.1% acetic acid in acetonitrile as the mobile phase. Separation was obtained using 0–80% linear gradients of B in A for 2 min, followed by isocratic elution with 80% B for 3 min at a flow rate of 0.25 ml/min. The LC eluate was introduced directly into an API365 MS (Sciex, Thornhill, Ontario, Canada) equipped with a Turbo Ionspray (Concord, Canada). The negative turbo-ionspray voltage (V) was −4800 mV. The dwell time was 100 ms. Total run time was 8 min, and the obtained multiple reaction monitoring chromatograms were used for quantitation. A weighted linear least-squares regression was used to generate calibration curves from standards and calculate the concentrations of quality control (QC) samples. The peak area was measured using MacQuan software (version 1.6).

Statistical Analyses

Statistical analyses were conducted using a Student's *t* test. Mean and standard error have been indicated. A p value of less than 0.05 was considered statistically significant.

RESULTS

Isopropyl unoprostone was not detected in the aqueous humor of cynomolgus monkeys. M1:M2 in the monkey was respectively 0:0 ng/ml in group I ($n = 3$), 150.2 ± 45.1:9.5 ± 1.7 ($p < 0.05$) in group II ($n = 3$), and 74.6 ± 31.4:19.2 ± 5.3 ($p < 0.01$) in group III ($n = 3$). The M1 concentration was much higher than that of M2 at every measuring time (Fig. 2) and M1 was found to be the main intraocular metabolite of isopropyl unoprostone in cynomolgus monkeys.

Isopropyl unoprostone was not detected in the aqueous humor of humans. M1:M2 in human was respectively 0:0 ng/ml in group A ($n = 5$), 50.6 ± 22.3:3.2 ± 1.3 ($p < 0.05$) in group B ($n = 5$), 125.0 ± 23.1:12.2 ± 3.4 ($p < 0.001$) in group C ($n = 6$), 144.9 ± 33.8: 24.5 ± 6.2 ($p < 0.01$) in group D ($n = 6$), and 56.7 ± 21.5:18.7 ± 5.3 ($p < 0.05$) in group E ($n = 5$). M1 concentration was much higher than that of M2 at all measuring times, and M1 was found to be the main intraocular metabolite of isopropyl unoprostone in humans (Fig. 3).

DISCUSSION

The current work indicated that after drops of isopropyl unoprostone are administered, M1, a free acid of isopropyl unoprostone, is the primary intraocular metabolite in monkeys and humans. Which of the metabolized compounds to be measured was determined according to the previous study reporting types

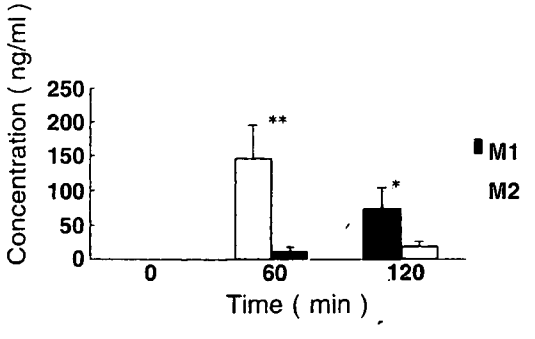

FIGURE 2 Time-course of aqueous humor concentrations of M1 and M2 in cynomolgus monkeys. M1 is (3-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]propionic acid), that is, a free acid of isopropyl unoprostone. M2 is ((*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoic acid), that is, an intraocular oxidized metabolite of isopropyl unoprostone. *$p < 0.05$, **$p < 0.01$ vs. M2, $n = 3$, mean ± SE.

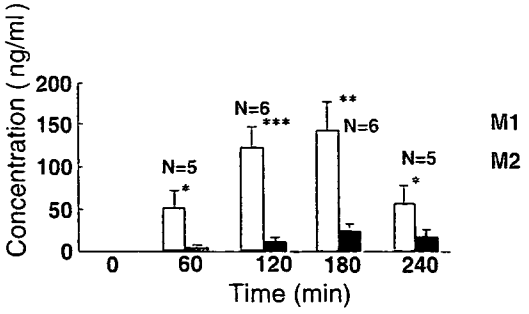

FIGURE 3 Time course of aqueous humor concentrations of M1 and M2 in humans. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. M2, $n = 5$ or 6, mean ± SE.

of isopropyl unoprostone.[11] Timepoints of measurements after instillation were determined according to the reported time-course of the IOP after isopropyl unoprostone instillation in cynomolgus monkeys and humans.[1,14,17]

In both monkeys and humans, M1 was the main intraocular metabolite, but the peak time after instillation differed. Although we do not have good explanation for the difference between monkeys and humans in the time course of aqueous M1 and M2 levels after isopropyl unoprostone instillation, there may be several possible reasons. The rate of aqueous humor production in cynomolgus monkeys is somewhat lower than that in humans,[17] while the volume of the anterior chamber is thought to be much smaller than that in humans.[18] Therefore, the turnover rate of the aqueous and isopropyl unoprostone-derived materials in the aqueous is expected to be higher in cynomolgus monkeys than that in humans, resulting in an earlier peak in these materials in this species. Another possibility that cannot be excluded is that repeated instillation of mydriatics before cataract surgery affected the intracameral isopropyl unoprostone delivery in humans (cataract patients). Additionally, cynomolgus monkeys have thinner corneas than humans,[19] which might also have affected the peak time of instilled substances in the anterior chamber. Kashiwagi's study showed that M2 was dominant in the aqueous humor of rabbits.[11] Differences with Kashiwagi's results with rabbits are thought to be at least partly attributed to a species difference in the metabolism of PG-related compounds. While the current authors actually performed the same experiment using rabbits, M1 predominated within an hour of drop administration; by 2 hr, M2 was predominant, which was roughly compatible with the results of Kashiwagi *et al.*[11] Time changes in IOP after topical isopropyl unoprostone was administered were similar to those M1 levels in both primate and human aqueous, which may support that the free acid of isopropyl unoprostone, M1, is mainly responsible for ocular hypotensive effects of isopropyl unoprostone.[14] Based on the current results, isopropyl unoprostone's action on intraocular tissues such as human or primate trabecular meshwork cells, iris melanocytes, and ciliary muscle examined using M1 rather than unchanged isopropyl unoprostone or M2, an oxidized metabolite of isopropyl unoprostone, should have clinical relevance. Using the iris and ciliary bodies of rabbits and cows, Kashiwagi *et al.* suggested[12] the possibility that M2 induces a drop in IOP through PGE production. This possibility is rather unlikely at least in primates and in humans. Whether M1 lowers IOP in humans through action on maxi-k channels of trabecular meshwork (TM) cells[10] or acts as an FP agonist[8,9] awaits future studies. In pigs, isopropyl unoprostone is metabolized to M1 only by the corneal epithelial cells, while in the iris and ciliary bodies, isopropyl unoprostone underwent little metabolism.[20] If metabolism of isopropyl unoprostone in pigs is similar to that in humans and monkeys, the unchanged isopropyl unoprostone should be used rather than M1 or M2 to examine its effects on extraocular tissue (i.e., ciliary arteries, epidermal cells, and fibroblasts).[21,22] It is of interest that Yoshitomi *et al.* reported that unchanged isopropyl unoprostone, but not its metabolites M1 and M2, relaxed precontracted rabbit ciliary arteries.[21] Tamaki *et al.* reported that blood flow of the optic nerve head was increased after isopropyl unoprostone instillation in humans only in the treated site.[23] Taken together with the results reported by Yoshitomi *et al.*[21] and Babiole *et al.*[20], the result reported by Tamaki *et al.*[23] may suggest that isopropyl unoprostone relaxed short ciliary arteries also in humans.

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Optic Disc Topography and Peripapillary Retinal Nerve Fiber Layer Thickness in Nonarteritic Ischemic Optic Neuropathy and Open-Angle Glaucoma

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Objective: To evaluate the results of scanning laser tomography and scanning laser polarimetry (SLP) and the correlations with visual field damage (VFD) in eyes with nonarteritic ischemic optic neuropathy (n-AION) compared with eyes with open-angle glaucoma (OAG).

Design: Cross-sectional study.

Participants: Thirty-three eyes of 33 patients with n-AION and 33 eyes with OAG whose age and VFD evaluated with the Humphrey field analyzer were matched to those of the n-AION eyes.

Main Outcome Measures: The parameters of optic disc topography obtained with the Heidelberg Retina Tomograph II (HRT II) and retinal nerve fiber layer (RNFL) thickness with GDx with variable corneal compensation and the correlation to VFD.

Results: The cup area, cup-to-disc area ratio, and mean cup depth were significantly smaller, and the cup shape measure more negative, in the n-AION eyes than in the OAG eyes ($P<0.001$), whereas rim area was significantly greater ($P<0.001$). Multivariate analyses showed that none of disc area, rim area, and mean cup depth in the n-AION eyes and only rim area ($P = 0.029$) in the OAG eyes was significantly associated with mean deviation (MD). Ellipse average of RNFL thickness significantly correlated with MD in the n-AION eyes ($P = 0.045$) and in the OAG eyes ($P = 0.022$).

Conclusions: Disc topography of eyes with n-AION was quantitatively characterized by small and shallow cupping and a relatively large rim area compared to eyes with OAG matched for age and VFD. In eyes with n-AION, significant correlation with VFD was found only for the RNFL thickness evaluated with SLP but not for the HRT II parameters. *Ophthalmology 2006;113:1340–1344 © 2006 by the American Academy of Ophthalmology.*

Nonarteritic anterior ischemic optic neuropathy (n-AION) is thought to result from acute perfusion insufficiency around the optic nerve head (ONH). Although the exact etiology of ischemia in n-AION is unknown, decreased circulation to the posterior ciliary arteries is thought to be the main cause of the disease.[1,2] Unlike arteritic AION, complete occlusion of posterior ciliary arteries is not mandatory and circulation resumes after the acute phase.[1] Systemic diseases such as ischemic heart disease,[3] hypercholesterolemia,[3] diabetes mellitus,[3–5] hypotension,[6,7] and possibly hypertension[4] are thought to be risk factors for n-AION.

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In patients who develop n-AION, the ONHs have anatomic characteristics such as small disc area, no to minimal physiologic cupping, and an increased number of branches of the central retinal vessels within the disc; they are often referred to as the "disc at risk."[8] In addition to empirical and qualitative knowledge, some quantitative studies using fundus photographs have reported small discs, small cup-to-disc ratios, or both.[9–12] Three-dimensional and quantitative methods of evaluation of the ONH morphology and retinal nerve fiber layer (RNFL) thickness using confocal scanning laser ophthalmoscopy, the Heidelberg Retina Tomograph II (HRT II, Heidelberg Engineering, Dossenheim, Germany), and scanning laser polarimetry (SLP), the GDx Nerve Fiber Analyzer with Variable Corneal Compensation (GDx VCC, Laser Diagnostic Technologies, Inc., San Diego, CA), have been developed recently but have not been used to study n-AION eyes, with the exception of a few studies.[13–15] Moreover, the relationship between the morphologic changes and visual field damage (VFD) in n-AION eyes has never been investigated.

The aims of this cross-sectional study were to (1) evaluate the OHN topography and the RNFL thickness in

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n-AION eyes and (2) assess the correlation of these parameters with VFD and compare with eyes with OAG matched by age and VFD.

Materials and Methods

Thirty-three consecutive patients (33 eyes) with n-AION who met the inclusion criteria between January 2002 and December 2003 at the Inouye Eye Hospital or the outpatient clinic of the Department of Ophthalmology, University of Tokyo Graduate School of Medicine, were included after providing informed consent. The study was approved by the Institutional Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Inclusion criteria were as follows: (1) eyes with a history of acute onset of n-AION ≥4 months before enrollment in the study, (2) eyes in which reliable assessments of visual field, HRT II, and GDx VCC were available, and (3) eyes without ocular diseases, except n-AION and slight cataract, that could affect the results of visual field testing, GDx VCC, and HRT II.

n-AION was diagnosed based on a history of an acute event of optic disc swelling, superficial hemorrhage at the optic disc border and adjacent retina, or both as the cause of an acute, painless, and incomplete visual loss. Because most of the patients in the current study were referred from other hospitals or clinics, the objective symptoms of the acute phase of n-AION were confirmed by ourselves in 11 of the 33 eyes studied. In the other 22 eyes, we reconfirmed the existence of objective symptoms in the acute phase by asking the referring ophthalmologists. We also conducted detailed interviews of the patients to confirm the sudden visual loss or other symptoms at the onset of the disease. No patient had findings suggestive of arteritic-AION described by Beck et al[12] that includes systemic symptoms of giant cell arteritis, sudden marked visual loss to the level of hand motions or less, a chalky-white swollen optic disc, occlusion of 1 or the other posterior ciliary artery observed on fluorescein fundus angiography, and a high erythrocyte sedimentation rate (>50 mm/hour). Fluorescein angiography had been performed in 25 of the 33 patients, excluding those with a history of drug allergy or renal or hepatic dysfunctions. Erythrocyte sedimentation rate testing was performed in 15 patients in whom possibility of inflammatory vascular diseases or temporal arteritis could not be excluded. No patients underwent biopsy of the temporal artery. Because ≥4 months had passed after the acute onset, the swelling and hemorrhages of the disc had subsided, and the disc borders were clearly delineated at the time of this study.

The 3-dimensional features of the ONH were determined using the HRT II. For each patient, 3 topographic images were obtained, combined, and automatically aligned to create a single mean topographic image used for analysis. Magnification errors were corrected using the patients' corneal curvature measurements. An experienced examiner outlined the optic disc margin on the mean topographic image while viewing color photographs of the optic disc. Good-quality images required focused reflectance with a standard deviation ≤50 μm. The topographic parameters studied were disc area, cup area, rim area, cup-to-disc area ratio, cup volume, rim volume, mean cup depth, and cup shape measure for the comparison between the n-AION and OAG eyes, and disc area, rim area, and mean cup depth for the multivariate analysis of the correlation with VFD.

The thickness of the peripapillary RNFL was evaluated by an experienced examiner with GDx VCC, which is a modified SLP system with a variable corneal compensator. A SLP macular image first was obtained to determine the eye-specific corneal polarization axis and magnitude. A polarimetry image around the optic disc then was obtained by compensating for the eye-specific corneal polarization. The quality of the polarimetry image was evaluated with the Q-score provided by the GDx VCC standard software, and images with a Q-score of ≤7 were not used in this study. The GDx VCC parameters investigated in this study were ellipse average (TSNIT average), superior average, and inferior average.

Visual field testing was performed with the 30-2 program of the Swedish Interactive Threshold Algorithm standard strategy of the Humphrey Visual Field Analyzer (HFA; Carl Zeiss Meditec, Oberkochen, Germany). Only reliable results (fixation loss <20%, false-positive error <33%, or false-negative error <33%) were used. For each patient with n-AION or OAG, the visual field examination and ocular imaging with the HRT II and GDx VCC were completed within 1 month of each other. The HFA parameters investigated were mean deviation (MD), average of total deviation in the superior hemifield (TD_{sup}), and average of total deviation in the inferior hemifield (TD_{inf}).

From the stored data of patients with OAG from whom reliable HFA, GDx VCC, and HRT II measurements had been obtained in the same 2 clinics and during the same time period, 33 OAG eyes were randomly chosen with age and MDs that matched to those of the AION eyes. For each pair of eyes, the differences in the age and MD did not differ by >3 years and >2 dB, respectively. However, the location of VFD and the degree of damage in each superior or inferior hemifield was not matched between the 2 groups.

OAG was diagnosed based on normal open angles, typical glaucomatous optic disc appearances corresponding to VFD, the absence of apparent pale color of the optic disc, and the absence of any contributing ocular or specific systemic disorders. The typical glaucomatous optic disc appearance included enlargement of the vertical cup-to-disc ratio, apparent difference of the vertical cup-to-disc ratio between both eyes, local narrowing of the neural rim, splinter hemorrhage, and/or visible nerve fiber layer defect.

Statistical Analysis

Means of the data were compared between the n-AION eyes and the OAG eyes using Student's *t* test. According to the Bonferroni's method, $P<0.05$/the number of the comparisons was considered statistically significant with consideration for the multiple comparisons. The prevalence of dominant superior or inferior hemifield damage in the HFA results was compared between the 2 groups using the Fisher exact test. Because disc area, rim area, and mean cup depth were correlated with each other, their correlation with MD was calculated using the multiple regression analysis in which the dependent variable was MD and independent variables were disc area, rim area, and mean cup depth. The multiple regression analyses in which dependent variable was MD, TD_{sup}, or TD_{inf} and the independent variables disc area and the corresponding RNFL thickness (TSNIT average, inferior average, or superior average, respectively) were performed. Statistical analyses were performed using a statistical software package, SPSS 13.0J for Windows (SPSS Japan Inc., Tokyo, Japan).

Results

There were no statistically significant differences between the n-AION eyes and the OAG eyes in gender, refractive error, or VFD ($P>0.05/6$ with Bonferroni's correction) except visual acuity, which was significantly worse in the n-AION eyes ($P = 0.003<0.05/6$) (Table 1).

Beside the 33 eyes with n-AION included in the current study, 16, 8, and 5 eyes were excluded because of unreliable results on the HRT II, GDx VCC, or both, respectively. There was no significant difference in age (61.8±10.4 vs. 63.8±11.7 years, $P =$

Table 1. Patient Demographic Data

	n-AION	OAG	P Value*
Men/women	17/16	18/15	0.6
Age (y)	61.8±10.4	61.8±10.3	—
Best-corrected visual acuity (log MAR)	0.31±0.54	0.04±0.38	0.003†
Refractive error (diopters)	−1.1±3.4	−3.1±3.5	0.022
Mean deviation (dB)	−12.3±8.3	−12.3±8.2	—
Pattern standard deviation (dB)	10.6±5.8	10.8±4.6	0.9
TD_{sup} (dB)	−8.20±9.22	−14.5±10.4	0.011
TD_{inf} (dB)	−13.9±10.4	−9.6±8.6	0.077

log MAR = logarithm of the minimal angle of resolution; dB = decibels; n-AION = nonarteritic anterior ischemic optic neuropathy; OAG = open-angle glaucoma; TD_{inf} = average of total deviation in the inferior hemifield; TD_{sup} = average of total deviation in the superior hemifield. Values are expressed as the mean ± standard deviation.
*Unpaired *t* test except for men/women, for which the chi-square test was used.
†Statistically significant with consideration for the multiple comparisons ($P<0.01$).

0.5, unpaired *t* test), visual acuity (0.31±0.54 vs. 0.81±1.58 in logarithm of the minimal angle of resolution, $P = 0.1$), and VFD (−12.3±8.3 vs. −11.8±9.9 dB in MD, $P = 0.4$) between the 33 included eyes and 29 excluded eyes.

TD_{inf} was significantly worse than TD_{sup} ($P<0.05$, unpaired *t* test) in 16 of 33 eyes with n-AION and in 7 of 33 eyes with OAG, respectively. TD_{sup} was significantly worse than TD_{inf} ($P<0.05$) in 7 of 33 eyes with n-AION and in 16 of 33 eyes with OAG, respectively. These figures were significantly different between n-AION and OAG ($P = 0.009$, Fisher exact test).

The cup area, cup-to-disc area ratio, cup volume, and mean cup depth were significantly smaller, and the cup shape measure more negative in the n-AION eyes than in the OAG eyes, whereas the rim area was significantly greater in the n-AION eyes (all $P<0.001$). The superior average of RNFL thickness obtained with GDx VCC was smaller in the n-AION eyes ($P = 0.001$), whereas

Table 2. HRT II and GDx VCC Parameters

Parameter	n-AION	OAG	P Value*
HRT II			
Disc area (mm^2)	1.94±0.38	2.20±0.56	0.031
Cup area (mm^2)	0.41±0.45	1.09±0.67	<0.001†
Rim area (mm^2)	1.49±0.55	1.04±0.32	<0.001†
Cup-to-disc area ratio	0.21±0.20	0.48±0.19	<0.001†
Cup volume (mm^3)	0.07±0.13	0.30±0.29	<0.001†
Rim volume (mm^3)	0.37±0.20	0.28±0.17	0.053
Mean cup depth (mm)	0.13±0.07	0.29±0.10	<0.001†
Cup shape measure	−0.18±0.07	−0.07±0.06	<0.001†
GDx VCC			
TSNIT average (μm)	40.7±11.0	44.9±10.1	0.1
Superior average (μm)	42.6±12.7	53.0±12.0	0.001†
Inferior average (μm)	46.7±16.2	45.4±12.3	0.7

GDx VCC = GDx Nerve Fiber Analyzer with Variable Corneal Compensation; HRT II = Heidelberg Retina Tomograph II; n-AION = nonarteritic anterior ischemic optic neuropathy; OAG = open-angle glaucoma; TSNIT average = ellipse average.
Values are expressed as mean ± standard deviation.
*Unpaired *t* test.
†Statistically significant with consideration for multiple comparisons.

Table 3. Results of the Multiple Regression Analyses for the HRT Parameters Associated with Mean Deviation

	n-AION		OAG	
HRT II Parameter	*Standardized β*	*P Value*	*Standardized β*	*P Value*
Disc area	−0.042	0.871	0.012	0.949
Rim area	−0.016	0.967	0.433	0.029
Mean cup depth	0.389	0.277	0.384	0.061

HRT II = Heidelberg Retina Tomograph II; n-AION = nonarteritic anterior ischemic optic neuropathy; OAG = open-angle glaucoma.

no significant difference was seen in the TSNIT average and inferior average of RNFL thickness between the 2 groups ($P = 0.1$ and 0.7, respectively) (Table 2). The superior average was significantly smaller than the inferior average in the n-AION eyes ($P = 0.001$, paired *t* test), whereas the superior average was significantly greater in the OAG eyes ($P = 0.002$). But the absolute differences between the superior and inferior averages were not significantly different between the n-AION and OAG eyes ($P = 0.090$).

The multiple regression analyses showed that disc area, rim area, and mean cup depth in the n-AION eyes were not associated with MD ($P>0.2$); only rim area ($P = 0.029$) in the OAG eyes were significantly associated with MD (Table 3). TSNIT average and MD were correlated in both the n-AION ($P = 0.045$) and OAG ($P = 0.022$) eyes, respectively. Superior ($P<0.001$) and inferior ($P = 0.003$) averages in the n-AION eyes and superior ($P = 0.039$) average in the OAG eyes were significantly correlated with the corresponding VFD (Table 4).

Discussion

In the typical clinical course of n-AION, disc swelling and hemorrhages on the disc or at the margins are seen at the time of onset. The disc swelling tends to resolve within 2 months; pallor appears earlier, frequently by 1 month.[16] Colen et al[14] report a case of n-AION in which the RNFL thickness obtained by SLP with fixed corneal compensation (FCC) decreased from 62 to 49 μm within the first month after onset and then remained unchanged. Considering these factors, in the current study we included only eyes with follow-up periods of ≥4 months after the onset of n-AION.

The ONHs in n-AION eyes are characterized by a small disc area, no or minimal cupping, and an increased number of branches of the central retinal vessels within the disc.[8] Studies using quantitative measures on fundus photographs revealed a smaller disc size of 2.74±0.45 mm^2 in n-AION eyes (vs. 3.34±0.73 mm^2 in normal eyes),[9] 2.31±0.26 mm^2 (vs. 2.71±0.68 mm^2 in normal eyes),[10] and smaller cup-to-disc ratios of 0.154±0.117[11] and 0.16±0.15 (vs. 0.31±0.19 in normal eyes).[12] We could not demonstrate this finding, but our study was not sufficiently powered to do so. Moreover, in the current study, small and shallow cupping in eyes with n-AION, compared to eyes with OAG matched for age and MD, was demonstrated quantitatively. The cup area, mean cup depth, and cup-to-disc area ratio were approximately half and the cup volume one fourth of the values in the OAG eyes.

Table 4. Results of the Multiple Regression Analyses for the GDx VCC Parameters Associated with the Corresponding Visual Filed Damage

Parameter	n-AION		OAG	
	Standardized β	*P Value*	*Standardized β*	*P Value*
TSNIT average for MD	0.41	0.045	0.42	0.022
Inferior average for TD_{sup}	0.67	<0.001	0.31	0.102
Superior average for TD_{inf}	0.59	0.003	0.38	0.039

GDx VCC = GDx Nerve Fiber Analyzer with Variable Corneal Compensation; MD = mean deviation; n-AION = nonarteritic anterior ischemic optic neuropathy; OAG = open-angle glaucoma; TSNIT average = ellipse average; TD_{sup} = average of total deviation in the superior hemifield; TD_{inf} = average of total deviation in the inferior hemifield.

The current study is also the first documentation of RNFL thickness measured using SLP with VCC in eyes after n-AION. Banks et al[13] measured the RNFL thickness in eyes with n-AION or AION using SLP with FCC.[13] Those authors reported the average thicknesses as 59±7 and 51±9 μm in the acute (n = 18 eyes) and chronic (n = 20 eyes) phases, respectively. Colen et al.[14] reported the follow-up of 1 case of n-AION using SLP with FCC, in which the RNFL thickness (the "superior average") decreased from 62 μm 10 days after onset to 48 μm 9 months later. Compared to those reports, the TSNIT averages in 33 n-AION eyes of the current study (40.7±11.0 μm) were relatively smaller. Because anterior segment birefringence varies widely in human eyes, SLP with FCC often provides inappropriate data on RNFL thickness.[17,18] Moreover, the RNFL thickness values tend to be higher with FCC than with VCC,[18] possibly explaining the discrepancy in RNFL thickness in n-AION eyes between the current and previous studies.[13,14]

In the n-AION eyes of this study, the superior average of RNFL thickness was significantly smaller than the inferior average. This is contrary to the results in normal[19,20] or OAG[19] eyes and the current results on OAG, and suggested that the superior region of the ONH was more commonly affected in n-AION. Although the HRT parameters did not significantly correlate with VFD, the results of GDx VCC were significantly associated with the corresponding VFD with regression coefficients of 0.41 to 0.67 (Table 3).

Eyes with slight cataract were included in the current study. Even slight cataract can possibly affect the results of visual field testing. However, Carrillo et al[21] recently reported that the average change in MD after extraction of cataract in OAG patients whose preoperative log MAR visual acuity averaged 0.24 (between 20/30 and 20/40) was <0.1 dB and not statistically significant, suggesting that at least slight or mild cataract should not have apparent effects on the average of MD in a group of patients. Moreover, in the current study, because age of the n-AION patients and that of the OAG patients were matched (61.8±10.4 vs. 61.8±10.3 years), the total amount of the influence of (slight) cataract should be similar between the 2 groups, if it existed.

Most of the patients with n-AION had no experience with visual field testing using the HFA prior to this study, whereas the patients with OAG had several experiences. According to Heijl et al,[22] improvement of MD between the initial and second tests of the HFA in newly diagnosed glaucoma patients averaged 2.81 dB, which corresponded to 23% of the average of MD of the current n-AION eyes (−12.3 dB). Therefore, differences in the HRT parameters between the n-AION eyes and the OAG eyes, which ranged 30% to 320% (Table 2), cannot be explained completely by the influence of learning effects in the HFA testing.

In conclusion, the ONH topography in n-AION eyes was quantitatively characterized by small and shallow cupping and a relatively larger rim area compared to the age- and MD-matched OAG eyes. In n-AION eyes, the RNFL thickness evaluated with GDx VCC showed a good correlation with VFD, whereas the HRT results did not significantly correlate with VFD.

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CLINICAL STUDY

Performance of GDx VCC in eyes with peripapillary atrophy: comparison of three circle sizes

S Kunimatsu, A Tomidokoro, H Saito, M Aihara, G Tomita and M Araie

Abstract

Purpose **A scanning laser polarimetry (GDx VCC) equips three different sized measurement circles. In eyes with peripapillary atrophy (PPA), the GDx measurement becomes inaccurate when the circle falls on PPA. The aim of this study was to evaluate performance of the three circles of GDx measurement in eyes with PPA.**

Methods **Three different sized circles were compared regarding frequency of PPA, which fell on each circle in 282 open-angle glaucoma (OAG) eyes, reproducibility of GDx parameters in 24 normal and 22 OAG eyes, and ability to detect glaucoma in 50 normal and 50 OAG eyes.**

Results **PPA was observed in 230 (82%) of 282 OAG eyes. PPA fell on the small circle (default setting), medium, and large circles in 119 (43%), 38 (14%), and 12 (4%) of the 280 OAG eyes. Reproducibility of GDx parameters was not significantly different among three circles in normal eyes ($P > 0.05$), whereas coefficients of reproducibility of TSNIT average ($P = 0.006$) and superior average ($P = 0.035$) were smaller in the smaller circles in OAG eyes. GDx parameters significantly correlated ($P < 0.001$), but were significantly different ($P < 0.05$) between the small and medium circles. The area under receiver operating characteristic curves for dividing OAG from normal eyes using GDx parameters was similar between the small and medium circles.**

Conclusions **If the medium circles were used, obstructing influences of PPA on GDx measurement could be avoided more often in Japanese OAG eyes with similar reproducibility and comparable ability to detect glaucoma compared to those with the default small circle.**

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Keywords: peripapillary atrophy; GDx; VCC; open-angle glaucoma; scanning laser polarimetry

Introduction

Accuracy of measurements of the retinal nerve fiber layer (RNFL) thickness using a scanning laser polarimetry (SLP), GDx (Carl Zeiss Meditec, Dublin, CA, USA), has been improved after the introduction of the variable corneal compensation (VCC) system, which reduces the influence of the anterior segment birefringence in an individual eye.[1–4] However, one of the remaining drawbacks of SLP is that RNFL measurements are inaccurate when peripapillary atrophy (PPA) fell on the measurement circle (Figure 1). As PPA is more frequent in myopic eyes[5,6] and myopia is much more common among Japanese,[7] it is supposed that PPA is commonly accompanied with Japanese patients of open-angle glaucoma (OAG).

With new software (GDx VCC version 5.3.2.), two different sizes of circles (medium and large) are available in addition to the default size circle (small). The inner diameters are 2.4, 3.2, and 4.0 mm for small, medium, and large circles, respectively, in eyes with normal refraction, although the actual sizes will be altered according to the refractive error of each eye. Using the medium or large circle instead of the default small circle, the obstructing influence of PPA on the RNFL measurement would be often avoided. To our knowledge, however, no report is available on the clinical usefulness of the medium or large circle. The aim of this study was to estimate the frequency of PPA in Japanese OAG eyes and to assess the reliability and usefulness of the RNFL measurements

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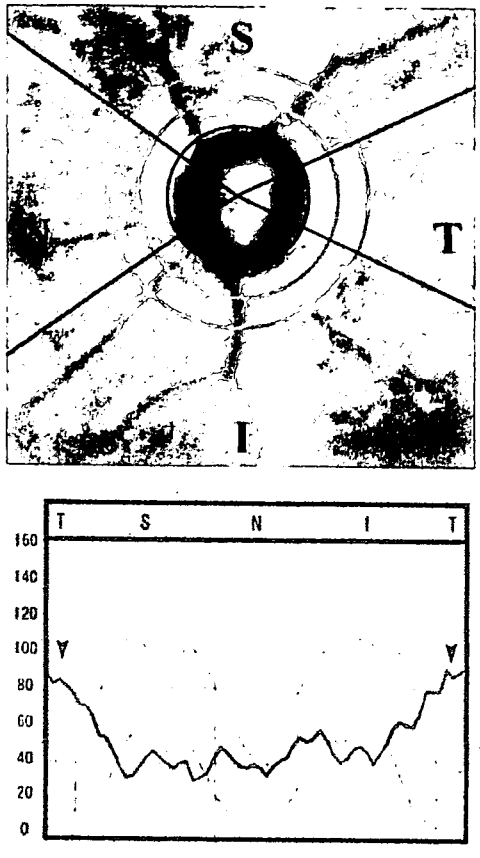

Figure 1 An example of GDx VCC measurements in eyes with PPA. This eye has a large PPA and the temporal portion of the PPA falls on the measurement circle (small circle) (a). As the consequence, retinal neve fiber layer thickness is measured abnormally thicker in the temporal area (arrowheads, b).

using medium or large circle for those eyes in which the small circle would fall on the area with PPA.

Methods

The studies below were carried out at the Department of Ophthalmology of the University of Tokyo, Graduate School of Medicine. Written informed consent to use their clinical data for this study was obtained from all subjects. The study was approved by the Institutional Review Board for Human Research of the University of Tokyo, Graduate School of Medicine and was conducted according to the tenets of the Declaration of Helsinki.

Measurement of GDx VCC

SLP images were obtained using GDx VCC with a software version 5.3.2. The general principles of SLP have been described in detail elsewhere.[8,9] Imaging was obtained under dim light and with undilated pupils. For each eye, the macula was imaged without compensation, and the eye-specific corneal polarization axis and corneal polarization magnitude were recorded. Corneal birefringence-compensated SLP images then were acquired using the eye-specific corneal polarization axis and magnitude by adjusting the VCC retarder. Determination of the GDx VCC parameters was performed with regard to the small (default), medium, and large circles, respectively, on each acquired image with quality score of 8 or more.

Frequency of PPA falling on circles in OAG eyes

The frequency of eyes in which PPA fell on each of the GDx circles was determined using the stocked data of 282 eyes of 141 OAG patients continuously obtained between September 2003 and May 2004. A diagnosis of OAG was made according to the typical glaucomatous optic disc findings, the corresponding visual field damage, and the absence of any contributing ocular or systemic disorders in disregard of intraocular pressure (IOP). Eyes with refractive errors (spherical equivalent) larger than 8 D and eyes had history of intraocular surgery including laser were not included. The patients studied included 81 male and 60 female patients and age averaged 55.4 ± 12.3 (mean ± SD) years, refractive error −3.9 ± 3.5 D, IOP with or without medication 18.3 ± 3.9 mmHg, and mean deviation (MD) of the Humphrey Field Analyzer 30-2 SITA standard (Carl Zeiss Meditec, Dublin, CA, USA) −6.0 ± 5.4 dB.

The GDx VCC results of each patient were reloaded from the hard disc drive of the instrument and the small, medium, and large circles were drawn. Beta zone of PPA, which was identified by choroidal atrophy with visible large choroidal vessels and sclera, was determined and judged whether each of the measurement circles fell on the PPA or not on the display of GDx VCC instrument with the help of colour fundus photographs if necessary. Alpha zone of PPA, which located peripherally and characterized by irregular hypopigmentation, hyperpigmentation, or both, was not included in the current study.

Reproducibility of the GDx measurements using the three circles

Reproducibility of GDx VCC parameters obtained with three circles was evaluated in 24 eyes of 16 ophthalmologically healthy subjects (mean age, 35.1 ± 6.2 years) and 22 eyes of 14 patients with OAG (mean age, 53.8 ± 13.6 years) in whom the data were newly obtained. The criteria of the diagnosis of OAG were same as above. In the OAG patients, refractive error averaged −3.3 ± 3.7 D, IOP with or without medication 14.1 ± 3.1 mmHg, and MD −5.6 ± 5.5 dB.

Ophthalmologically healthy subjects had IOP not exceeding 21 mmHg, the optic disc with a normal appearance, a normal open angle, a normal visual field defined, and had no history of ocular diseases or a family history of glaucoma. In the ophthalmologically healthy subjects, refractive error averaged -1.0 ± 1.4 D.

Each eye was scanned twice on separate days within a 1-month period. Eyes were excluded when any of the three circles fell on PPA or image quality fell below 8. The coefficient of the reproducibility for each parameter was calculated as follows: $|V_1-V_2|/(V_1+V_2)/2 \times 100\%$, where V_1 is the first and V_2 the second measurement obtained.

Mean values of the GDx parameters and detection of glaucoma

As the fraction of poor-quality images is rather high for the large circle (see Results section), the performance of the GDx was not determined for this circle size. Comparison of the GDx parameters between 50 ophthalmologically normal eyes of 50 subjects (mean age, 50.6 ± 8.7 years) and 50 OAG eyes of 50 patients (mean age, 49.4 ± 9.1 years), of whom data were newly obtained for this part of the current study, and ability to detect glaucomatous eyes using GDx VCC was evaluated. The criteria of ophthalmologically healthy subjects and the diagnosis of OAG patients were same as above. In the OAG patients, refractive error averaged -3.6 ± 2.5 D, IOP with or without medication 14.2 ± 3.3 mmHg, and MD -4.2 ± 2.9 dB. In the ophthalmologically healthy subjects, refractive error averaged -0.8 ± 1.6 D.

Statistical analysis

Statistical analyses were performed using a statistical software package, SPSS 13.0J for Windows (SPSS Japan Inc., Tokyo, Japan). Friedman's test was used to compare the averages among three groups. The difference between two groups was evaluated using the Wilcoxon's signed-rank test or the χ^2 test. Statistical correlation was evaluated by Spearman's rank correlation coefficient.

Receiver operating characteristic (ROC) curves were used to describe the ability to differentiate OAG eyes from normal eyes. A P-value less than 0.05 was considered statistically significant.

Results

Frequency of PPA falling on circles in OAG eyes

PPA could not be determined owing to expanded chorioretinal atrophy around the optic disc in two eyes. PPA was observed in 230 (82%) of the remaining 280 OAG eyes. PPA fell on the small, medium, and large circles in 119 (43%), 38 (14%), and 12 (4%) of the 280 eyes, respectively. The frequency with small circle was significantly greater than that with medium circle ($P<0.001$), and that with medium circle was greater than that with large circle ($P<0.001$). The GDx VCC

Table 1 Coefficient of reproducibility for the GDx parameters obtained with small, medium, and large circles in normal and OAG eyes

	Small circle	*Medium circle*	*Large circle*	*P-values**
TSNIT average				
Normal	3.3 (1.6, 5.1)	4.3 (1.9, 6.6)	5.0 (2.1, 8.0)	0.14
OAG	4.5 (0.7, 8.3)	6.2 (1.1, 11.2)	7.8 (2.8, 12.9)	0.006
Superior average				
Normal	3.7 (2.3, 5.1)	4.6 (2.5, 6.7)	5.2 (2.5, 7.9)	0.5
OAG	2.2 (0.7, 3.8)	3.1 (0.2, 6.0)	4.6 (1.1, 8.1)	0.035
Inferior average				
Normal	4.6 (2.5, 6.6)	4.8 (2.3, 7.3)	5.7 (2.9, 8.6)	0.080
OAG	7.5 (2.6, 12.4)	14.2 (1.5, 27.0)	14.9 (5.5, 24.2)	0.078
TSNIT SD				
Normal	7.4 (4.4, 10.4)	7.2 (4.3, 10.0)	7.0 (4.1, 9.9)	0.9
OAG	8.2 (4.1, 12.3)	7.4 (3.6, 11.1)	10.7 (5.8, 15.6)	0.060
NFI				
Normal	13.3 (8.2, 20.3)	19.5 (13.4, 29.2)	20.8 (10.9, 29.1)	0.054
OAG	17.6 (9.0, 26.2)	19.4 (7.8, 30.9)	16.7 (5.9, 27.5)	0.6

NFI, nerve fiber indicator; OAG, open-angle glaucoma; SD, standard deviation.
Data are shown with 95% confidence interval in the parentheses.
*P-value for difference among three circles (Friedman's test).