parameters could not be obtained in 34 (12%), 41 (15%), and 71 (25%) of 282 eyes for the small, medium, and large circles, respectively, because of poor image quality score (<8) or extrusion of the circle from the measurement area. Those frequencies were significantly different among the circles ($P<0.001$, χ^2 test) and the frequency with the large circle was significantly larger than that with the small or medium circle ($P<0.001$, $P=0.002$, respectively).

Reproducibility of the measurements using the three circles

Coefficients of reproducibility of the GDx parameters in normal or OAG eyes are shown in Table 1. These were not significantly different among the three circles in normal eyes for each parameter ($P>0.05$, Friedman's test), 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.

Mean values of the GDx parameters and detection of glaucoma

Mean values of the GDx parameters are shown in Table 2. All parameters in OAG eyes were significantly smaller than in normal eyes ($P<0.05$, Wilcoxon's signed-rank test). Between the small and medium circles, all of the GDx parameters significantly correlated (Spearman's rank correlation coefficients >0.8, $P<0.001$).

The ROC curves for dividing OAG eyes from normal eyes using each parameter obtained with the small and medium circles were determined. The area under the ROC curves is shown in Table 3. Ninety-five percent confidence interval was overlapping each other between the small and medium circles, suggesting there was no apparent difference in the ability to detect OAG eyes between these circles. Among the indices, the nerve fiber indicator (NFI) had the largest area under the ROC curve. ROC curves regarding TSNIT average and NFI are drawn in Figure 2.

Table 3 Area under the ROC for dividing glaucomatous from normal eyes using the small and medium circles

	Small circle	*Medium circle*
TSNIT average	0.90 (0.85, 0.96)	0.83 (0.74, 0.91)
Superior average	0.86 (0.78, 0.93)	0.86 (0.78, 0.93)
Inferior average	0.91 (0.86, 0.97)	0.85 (0.78, 0.92)
TINIT SD	0.80 (0.71, 0.88)	0.84 (0.76, 0.91)
NFI	0.94 (0.90, 0.99)	0.93 (0.88, 0.98)

NFI, nerve fiber indicator; ROC, receiver operating curve; SD, standard deviation.
Data (area under the ROC) are shown with 95% confidence interval in the parentheses.

Table 2 Differences and correlation of the GDx parameters between normal and OAG eyes

	Small circle		*Medium circle*		*Small vs medium circles*	
	Mean (95% CI)	P-*values*[a]	*Mean (95% CI)*	P-*values*[a]	*Correlation (P-value)*	P-*values*[b]
TSNIT average						
Normal	56 (54, 57)	<0.001	49 (48, 51)	<0.001	0.89 (<0.001)	<0.001
OAG	46 (44, 48)		42 (40, 43)		0.86 (<0.001)	<0.001
Superior average						
Normal	68 (67, 70)	<0.001	59 (58, 61)	<0.001	0.89 (<0.001)	<0.001
OAG	55 (52, 59)		48 (45, 50)		0.93 (<0.001)	<0.001
Inferior average						
Normal	66 (63, 68)	<0.001	59 (57, 61)	<0.001	0.94 (<0.001)	<0.001
OAG	49 (46, 53)		47 (44, 50)		0.85 (<0.001)	<0.001
TSNIT SD						
Normal	23 (22, 24)	<0.001	21 (20, 23)	<0.001	0.96 (<0.001)	<0.001
OAG	19 (16, 22)		16 (15, 17)		0.90 (<0.001)	<0.001
NFI						
Normal	18 (16, 20)	<0.001	17 (15, 18)	<0.001	0.82 (<0.001)	0.027
OAG	44 (39, 49)		42 (37, 47)		0.82 (<0.001)	0.008

CI, confidence interval; NFI, nerve fiber indicator; SD, standard deviation.
Data are shown with 95% confidence interval (95% CI) in the parentheses.
[a]*P*-value for the difference of the means between normal and OAG eyes (Mann–Whitney *U*-test). Correlation = Spearman's rank correlation coefficient (with *P*-value) between small and medium circles.
[b]*P*-value for the difference of means between small and medium circles (Wilcoxon's signed-rank test).

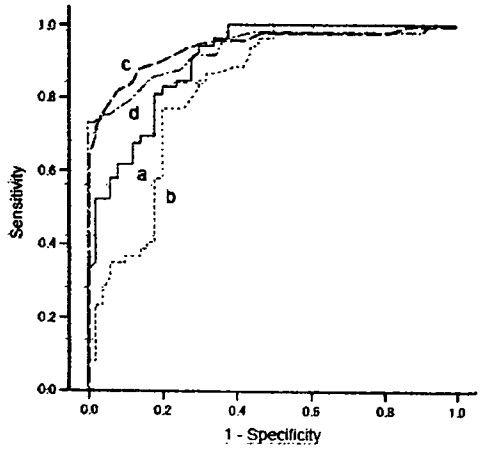

Figure 2 The ROC curves for discriminating between normal and glaucomatous eyes regarding TSNIT average of the small circle (a), that of the medium circle (b), the NFI of the small circle (c), and that of the medium circle (d).

Discussion

Frequency of PPA falling on circles on OAG eyes

The presence of PPA reduces the accuracy of the RNFL measurement using a SLP. Bowd *et al*[4] reported that in five of 73 (7%) eyes the circle fell on PPA and they used the expanded circle (20% horizontally and 20% vertically) for the analysis of those eyes. PPA is more frequently and more extensively observed in patients with glaucoma than in normal subjects in Caucasians[10,11] (no data available in Japanese) and associated with glaucomatous damage.[12–14] Because myopia is more likely associated with PPA,[5,6] and more frequent in Japan,[7] the influence of PPA on the measurement of the RNFL is of practical concern, especially in Japanese patients with OAG. In the current study, PPA fell on the small circle (default setting) in 119 (43%) of 280 OAG eyes, suggesting that accurate GDx measurement may be often disturbed because of PPA in Japanese OAG eyes when using the small circle.

When using optical coherence tomography (OCT), Lai *et al*[15] reported good agreement between the automated and manual tracing results in eyes with PPA, and the authors concluded that automated optic nerve head analysis using OCT may be used in the clinical setting in eyes with PPA. In contrast, the accuracy of GDx VCC when measuring the RNFL thickness decreases in the presence of PPA (Figure 1), and alternative measurement methods should have clinical value.

In the current study, the GDx parameters for the small, medium, and large circles could not be obtained in 34 (12%), 41 (15%), and 71 (25%) of 282 OAG eyes, respectively, because of poor image quality score (<8) or deviancy of the circle from the measurement area. Unless the optic disc was successfully located at the centre of the measurement area, the large circle easily extrude from the area. Moreover, the measurement using the large circle should be unstable because of the influence of the thinner RNFL, which was reported to often show atypical retardation pattern (ARP).[16–18]

Reproducibility of the measurements using the three circles

Good intraoperator and interoperator measurement reproducibility using an SLP has been reported by several investigators.[19–21] In the present study, we evaluated the difference in intraoperator reproducibility among the circles (Table 1). The coefficients of reproducibility in normal eyes were 8% or less, except NFI, and there was no significant difference among the three different sized circles. On the other hand, in the glaucomatous eyes, the reproducibility of some parameters was worse for the larger circles than the small ones. The sensitivity of GDx VCC is reported to be reduced in the retinal area with ARP.[16–18] This should be at least partially responsible for the poor reproducibility of the measurements with the outer circles. And besides, the influence of ARP owing to the outer and thinner retinal area should be involved with the performance in diagnosing glaucoma or assessing glaucoma progression described below.

Mean values of the GDx parameters and detection of glaucoma

Varma *et al*[22] measured histologically the thickness of the RNFL in normal human eyes and reported that the thickness decreased with increasing distance from the disc margin. In this study, the RNFL thickness obtained with the small circle was greater than that with the medium circle in normal and glaucomatous eyes, which is consistent with histologic results.

To determine the ability of each parameter to differentiate glaucomatous from normal eyes, we analysed the ROC curves. The largest area under the curve (AUC) was the NFI (0.94 with the small circle, 0.93 with the medium circle), which was similar to a previous study. Medeiros *et al*[23] reported that the AUC for NFI using GDx VCC was 0.91. There was no apparent difference between the small and medium circles when differentiating glaucoma from normal eyes. In the present version of GDx VCC, the NFI has been trained on data measured along the small circle. If a newly trained NFI, which is specially designed for the medium circle, is available, performance to detect glaucoma using the medium circle would be improved. Moreover, the

potential for the assessment of glaucoma progression may differ among the different circle sizes.

Not only beta zone of PPA but also alpha zone often shows ARP and can assert influence on GDx VCC measurements. However, because the precise determination of alpha area was difficult in some of the eyes as reported previously,[14] alpha area was not included in the present analyses. Therefore, in the current study, even if the larger circles were used and beta zone was not involved in the SLP measurement area, the disturbance of alpha zone of PPA might be still remained. Recently, a new software version, named the enhanced corneal compensation (ECC), was published.[16–18] It is reported to significantly diminish the artefacts owing to ARP. This new software may improve the performance of GDx in eyes with PPA even when using the small circle. However, whether the influence of PPA can be completely diminished with ECC is still unclear and further investigation on ECC measurements using the different measurement circles should deserve future investigation.

In conclusion, measurements with the medium circle may be a useful alternative, especially in Japan[7] and other East-Asian countries where the prevalence of myopia with PPA is higher than in Western countries.[24,25]

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Correlation Between Hemifield Visual Field Damage and Corresponding Parapapillary Atrophy in Normal-Tension Glaucoma

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• PURPOSE: To evaluate the correlation between the superior or inferior half area of parapapillary atrophy (PPA) and the corresponding hemifield visual field damage (VFD) in normal-tension glaucoma.

• DESIGN: Cross-sectional study.

• METHODS: PATIENTS: One hundred nine eyes of 109 consecutive patients with normal-tension glaucoma. OBSERVATION PROCEDURES: Topography parameters of the optic nerve head and PPA (zone β) area were obtained with the Heidelberg Retina Tomograph (HRT), and VFD was evaluated with the 30 to 2 program of Humphrey Field Analyzer. The HRT parameters and PPA area were determined separately in superior and inferior half regions. MAIN OUTCOME MEASURES: Partial correlation coefficients of the superior and inferior areas of PPA with refractive error, axial length, HRT parameters, and corresponding hemifield VFD.

• RESULTS: In simple correlation analyses, significant correlation was found between the inferior PPA area and the superior hemifield VFD (Spearman rank correlation coefficient; $Rs = -0.32$; $P < .001$) but not between the superior PPA area and the inferior hemifield VFD ($Rs = 0.05$; $P = .6$). Age, refractive error, axial length, and height variation contour were associated significantly with the total, superior, and inferior areas of PPA, respectively ($P < .01$). Multiple regression analyses showed that the superior PPA area was associated significantly with only axial length ($P < .001$), and the inferior PPA area was associated significantly with the axial length and the superior hemifield VFD ($P < .001$).

• CONCLUSIONS: In patients with normal-tension glaucoma, only the inferior half area of PPA correlated significantly with glaucomatous VFD. Axial length and myopia were associated with both the superior and inferior half areas of PPA. (Am J Ophthalmol 2006; 142:40–45. © 2006 by Elsevier Inc. All rights reserved.)

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PARAPAPILLARY ATROPHY (PPA) IS RELATED CLOSELY to the development and progression of open-angle glaucoma. PPA develops more frequently and is more extensive in eyes with glaucoma[1–3] than in eyes with ocular hypertension[4] or eyes with a so-called glaucoma-like disk,[5] compared with normal eyes; a significant correlation exists between the extent of PPA and glaucomatous damage in the optic nerve head (ONH)[4,6–8] and visual fields.[6,9–12] In addition, several longitudinal studies have reported that PPA seems to be associated with the progression of glaucomatous visual field damage (VFD).[13–17] One study reported that an increase in the extent of PPA paralleled the exacerbation of glaucomatous VFD,[14] and other studies showed the correlation between PPA and the development of glaucoma in eyes with ocular hypertension.[18–21]

In glaucomatous eyes, some differences have been found between the superior and inferior regions of the VFD, ONH morphologic condition, or PPA. For example, as to the VFD, more vulnerability was observed in the superior hemifield in eyes with normal-tension glaucoma (NTG),[22] patients with open-angle glaucoma and diabetes mellitus,[23,24] or patients with NTG with ischemic changes on cerebral magnetic resonance imaging.[25] Early glaucomatous changes are found more often in the inferior region of the ONH,[26] and PPA spreads more widely in the inferior area in healthy or glaucomatous eyes.[10] To our knowledge, however, whether the association among VFD, ONH morphologic condition, and PPA is different between the superior and inferior regions has never been investigated. The purpose of this cross-sectional study was to evaluate VFD, ONH morphologic condition, and PPA in the superior and inferior areas separately and to estimate the correlation of the superior or inferior half areas of PPA with the corresponding hemifield VFD.

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METHODS

ONE HUNDRED NINE CONSECUTIVE PATIENTS WITH NTG who met the inclusion criteria were enrolled in this cross-sectional study between January 2001 and December 2002 at the Department of Ophthalmology, University of Tokyo, Graduate School of Medicine. The study was approved by the Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients. The inclusion criteria consisted of NTG that had been diagnosed before this study, age ≤60 years, refractive error (spheric equivalent) within ±8 diopters, absence of fundus abnormalities or media opacities except slight cataract, availability of reliable visual field test results (that is, <20% fixation errors, <33% false-positive results, and <33% false-negative results) with the full-threshold or Swedish interactive threshold algorithm (SITA)-standard strategy of the 30 to two program of the Humphrey field analyzer (Carl Zeiss Meditec, Dublin, California, USA), a mean deviation obtained with Humphrey field analyzer better than −25 decibels (dB), the ability to obtain reliable measurements of the Heidelberg Retina Tomograph (HRT; Heidelberg Engineering GmbH, Dossenheim, Germany; that is, a topography standard deviation of ≤30 μm), inclination of the longest meridian of the ONH within 10 degrees of the vertical meridian on the HRT image, and PPA not exceeding the HRT imaging area. If both eyes of a patient met the inclusion criteria, the data from the right eye were used. A diagnosis of NTG was made according to the typical glaucomatous findings in the ONH and corresponding VFD in eyes with consistently normal intraocular pressure levels and the absence of any contributing ocular or systemic disorders. Normal intraocular pressure was defined as that never exceeding 21 mm Hg, including 24-hour fluctuations, without the use of ocular hypotensive medication during the follow-up period.

Visual field and ONH topography were obtained within an interval of ≤three months. The visual fields were tested with the full-threshold or SITA-standard strategy of the 30 to 2 program of the Humphrey field analyzer. The total deviation (TD) values, except the four uppermost edge values that are more vulnerable to the upper lid artifact,[27] were averaged in the superior and inferior hemifields to obtain the superior TD_{mean} and inferior TD_{mean}, respectively.

ONH topography was obtained with the HRT (version 1.11). The HRT parameters that were studied were disk area, cup area, rim area, height variation contour, cup-shape measure, and mean retinal nerve fiber layer thickness. These parameters were first determined for the global disk region. The parameters corresponding to the superior (185 degrees to 5 degrees in a right eye) and inferior (5 degrees to 185 degrees) regions of the ONH, then were determined separately with software provided by the manufacturer.[28]

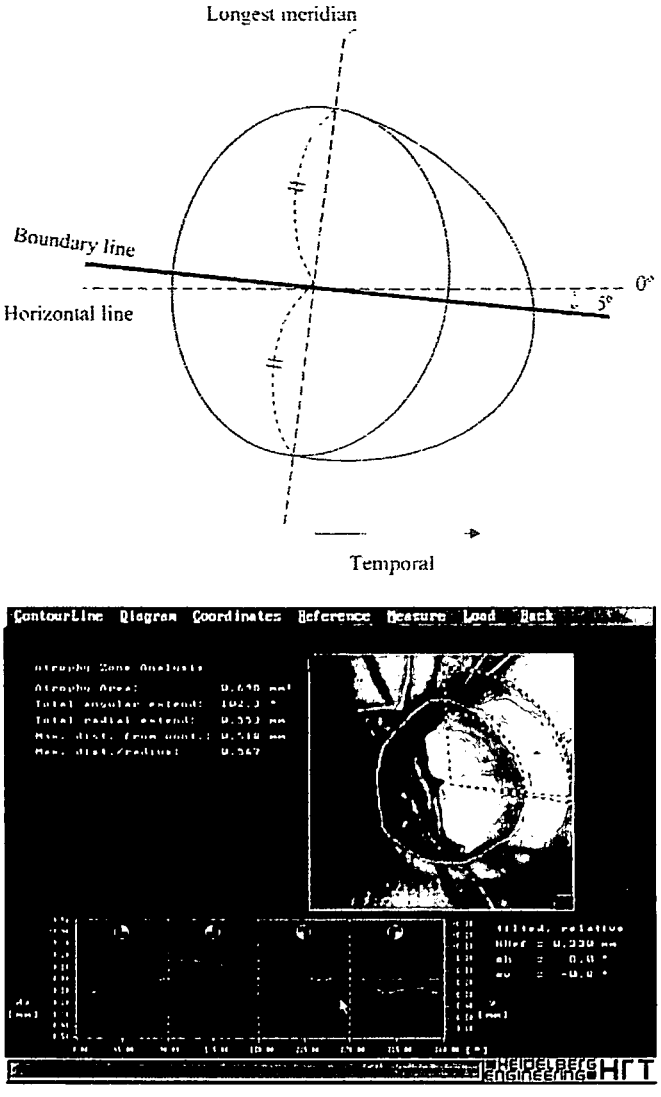

FIGURE 1. Measurement of the superior and inferior areas of parapapillary atrophy.[10] First, the central point of the longest meridian of the disk is determined, and a line is drawn through the central point 5 degrees inferior (temporal side) to the horizontal line (Top). The area of parapapillary atrophy is determined for the superior and inferior half regions, respectively. An example of the measurement of the superior area of parapapillary atrophy in a left eye of a patient with normal-tension glaucoma on a Heidelberg retina tomograph image is shown (Bottom). The superior area of parapapillary atrophy is drawn manually and is shown in blue line on the image. The area of the superior parapapillary atrophy is determined as 0.698 mm^2.

PPA usually is divided into zone α (located peripherally and characterized by irregular hypopigmentation, hyperpigmentation, or both) and zone β (located more centrally with visible large choroidal vessels and visible sclera; Figure 2). It is often difficult to draw the shape of zone α clearly on a fundus photograph or a HRT display, so poorer reproducibility and weaker correlation with VFD has been reported to be a comparison between zone α and zone

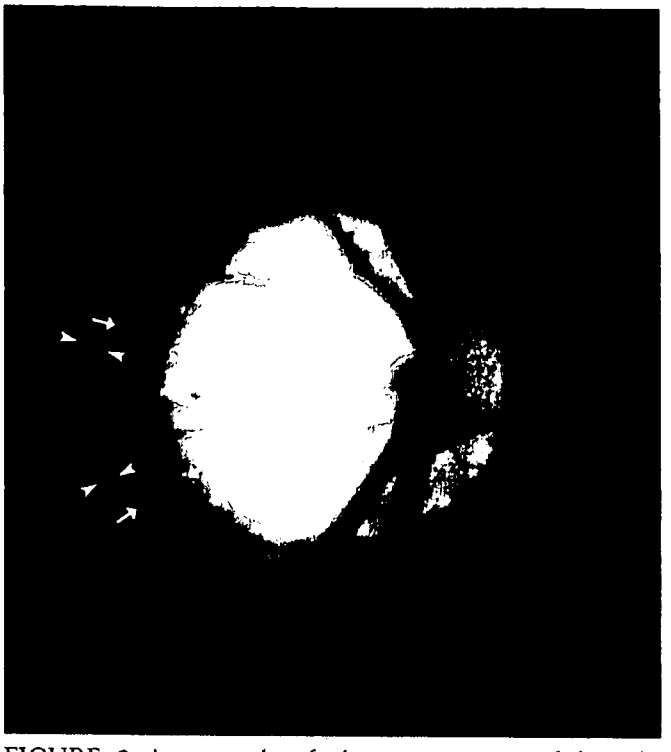

FIGURE 2. An example of glaucomatous optic disk with parapapillary atrophy area of an eye with normal-tension glaucoma. Parapapillary atrophy is divided into "zone α" (white arrow heads), which is located peripherally and characterized by irregular hypopigmentation, hyperpigmentation, or both, and "zone β" (white arrows), which is located more centrally with visible large choroidal vessels and visible sclera.

β.[6,10] Therefore, we measured the area of zone β alone in the current study. The total, superior half, and inferior half areas of zone β were determined on the HRT images as reported previously[10] with the help of color fundus photographs, if necessary (Figure 1). The axial length and refractive error were evaluated with A-scan ultrasonography (AL-2000; Tomey Corporation, Nagoya, Japan) and automated refractometry (ARK-900; Nidek, Aichi, Japan), respectively.

Statistical analyses were carried out with SPSS software for Windows (version 11.01J; SPSS Japan Inc, Tokyo, Japan). The Wilcoxon signed rank test was used to compare the mean values of the superior and inferior regions of the ONH and PPA. Spearman's rank correlation coefficient (Rs) was used to assess the simple correlations between the areas of PPA and age, refraction, axial length, visual field indices, or the HRT parameters. Multiple regression analysis was performed to assess the factors that related to the PPA area in which the dependent variable was the superior or inferior area of PPA; the independent variables were age, axial length, the corresponding disk area obtained with the HRT, and the corresponding VFD indices (superior TD_{mean} or inferior TD_{mean}). Refractive error was not included in the multiple regression model because it was correlated strongly with the axial length (Rs = −0.73).

RESULTS

IN THE 109 EYES FROM 109 PATIENTS WITH NTG, AGE, refractive error, and axial length averaged 48.7 ± 9.2 (mean ± SD) years, −3.41 ± 2.76 diopters, and 25.03 ± 1.41 mm, respectively. The mean deviation, pattern standard deviation, superior TD_{mean}, and inferior TD_{mean} were −6.53 ± 4.74, +9.00 ± 5.04, −8.42 ± 8.51, and −4.81 ± 5.74 dB, respectively. The superior TD_{mean} was significantly lower than the inferior TD_{mean} ($P = .002$).

There were no significant differences in cup area ($P = .37$), rim area ($P = .89$), and cup-shape measure ($P = .39$) between the superior and inferior regions of the ONH, whereas the disk area ($P < .001$), height variation contour ($P = .007$), and mean retinal nerve fiber layer thickness ($P < .001$) were significantly greater in the superior regions than in the inferior regions. The inferior area of PPA was significantly larger than the superior area ($P < .001$; Table 1).

Simple correlation analyses showed significant correlation between the inferior PPA area and the superior hemifield VFD (Rs = −0.32; $P < .001$) but not between the superior PPA area and the inferior hemifield VFD (Rs = 0.05; $P = .6$). Age, refractive error, axial length, and height variation contour were associated significantly with the total, superior, and inferior areas of PPA, respectively ($P < .01$; Table 2).

The multiple regression analyses showed that the superior PPA area was associated significantly with only axial length ($P < .001$) and that the inferior PPA area was associated significantly with the superior hemifield VFD and the axial length ($P < .001$; Table 3).

DISCUSSION

SOME PPA IS THOUGHT TO REPRESENT MISALIGNMENT OF the retinal pigment epithelium, the choroid, and the sclera, which might occur developmentally or might be due to ocular stretching as axial myopia develops.[29] PPA is also thought to result from the age-related changes in the peripapillary retinal pigment epithelium or acquired atrophy of the choroid, retinal pigment epithelium, or both because of ocular diseases that include glaucoma.[30,31] Thus, PPA in glaucomatous eyes might consist of both misalignment because of developmental or myopic factors and pathologic or acquired factors that include glaucoma, although a definitive delineation may be impossible. In the current study, the superior PPA area was correlated significantly with axial length alone, whereas the inferior PPA area was correlated significantly with axial length and the superior hemifield VFD. It suggests that factors that relate

TABLE 1. Heidelberg Retinal Tomography and Parapapillary Atrophy Parameters of the Optic Nerve Head of 109 Eyes With Normal-tension Glaucoma

Parameter	Global	Superior	Inferior	*P* value*
Heidelberg retinal tomography				
Disk area (mm^2)	2.21 ± 0.57	1.12 ± 0.28	1.10 ± 0.30	<.001
Cup area (mm^2)	1.07 ± 0.57	0.57 ± 0.29	0.55 ± 0.31	.37
Rim area (mm^2)	1.14 ± 0.33	0.56 ± 0.19	0.56 ± 0.20	.89
Height variation contour (mm)	0.39 ± 0.14	0.36 ± 0.13	0.34 ± 0.14	.007
Cup-shape measure	−0.088 ± 0.074	−0.054 ± 0.081	−0.064 ± 0.082	.39
Mean retinal nerve fiber layer thickness (mm)	0.225 ± 0.091	0.250 ± 0.099	0.207 ± 0.099	<.001
Parapapillary atrophy				
Area (mm^2)	0.84 ± 0.63	0.37 ± 0.32	0.48 ± 0.38	<.001
Angular extent (degree)	114 ± 60	—	—	—
Radial extent (mm)	0.49 ± 0.31	—	—	—

The data are expressed as the mean ± SD.
*For comparison of mean values of the superior half and inferior regions (Wilcoxon's signed rank test).

TABLE 2. Correlation Coefficients With Parapapillary Atrophy Areas in Simple Correlation Analyses in Patients With Normal-tension Glaucoma

Variable	Total PPA Area	Superior PPA Area	Inferior PPA Area
Age	−0.33 (<.001)	−0.29 (.002)	−0.33 (<.001)
Refractive error	−0.52 (<.001)	−0.46 (<.001)	−0.49 (<.001)
Axial length	0.53 (<.001)	0.50 (<.001)	0.49 (<.001)
Corresponding Heidelberg retinal tomography parameters*			
Disk area	NS (.50)	NS (.75)	NS (.77)
Cup area	NS (.22)	NS (.67)	NS (.71)
Rim area	NS (.12)	NS (.67)	NS (.56)
Height variation contour	0.35 (<.001)	0.43 (<.001)	0.24 (.013)
Cup shape measure	NS (.19)	NS (.22)	NS (.64)
Mean retinal nerve fiber layer thickness	0.26 (.007)	0.29 (.003)	NS (.096)
Visual field indices			
Mean deviation	NS (.07)	—	—
Superior total deviation$_{mean}$	—	—	−0.32 (<.001)
Inferior total deviation$_{mean}$	—	NS (.93)	—

NS = not significant ($P \geq .05$); PPA = parapapillary atrophy.
*The global, inferior, and superior Heidelberg retinal tomography parameters for the comparison with the total, superior, and inferior areas of parapapillary atrophy, respectively. Values indicate Spearman's rank correlation coefficients with the probability values in parentheses.

to the development of glaucoma may be associated dominantly with the inferior area of PPA and that factors that relate to myopia may be associated with both of the superior and inferior areas of PPA.

We estimated the total area of PPA to be 0.84 ± 0.63 mm^2 in the NTG eyes, which was greater than that reported by Park and associates[10] (0.52 ± 0.41 mm^2). As mentioned earlier, the area of PPA should be associated with VFD and the refractive error. Because the mean deviation in the study of Park and associates (−6.00 ± 5.80 dB) was similar to ours (−6.53 ± 4.74 dB), the differences in the refractive errors (−0.30 ± 2.68 vs −3.41 ± 2.76 diopters) between the studies might be responsible for this discrepancy in the area of PPA.

Only weak and nonsignificant correlation (Rs = −0.17; $P = .07$) was found between the total area of PPA and the mean deviation of VFD in the present study. Jonas and Naumann[6] reported a significant correlation between the PPA area and VFD with a correlation coefficient of −0.36 in 582 glaucomatous and 390 normal eyes. Park and associates[10] also reported a correlation coefficient of −0.39 in 105 patients with NTG. The degrees of myopia, which were −0.07 ± 2.18 diopters[6] and −0.30 ± 2.26[10] diopters in those studies, were less than our patients (−3.41 ± 2.76 diopters). The influence of myopia on the extent of PPA[32] might have masked and weakened the correlation between PPA area and mean deviation in this study.

TABLE 3. Multiple Regression Analyses of Factors Relating to Superior or Inferior Areas of Parapapillary Atrophy in Patients With Normal-tension Glaucoma

Parameter	Superior PPA		Inferior PPA	
	Standardized β*	*P* Value	Standardized β*	*P* Value
Age (y)	−.16	.08	−.16	.07
Axial length (mm)	.44	<.001	.40	<.001
Corresponding disk area (mm^2)†	−.006	.94	.03	.70
Superior total deviation$_{mean}$	—	—	−.29	<.001
Inferior total deviation$_{mean}$	.01	.90	—	—

With these regression models, the squared correlation coefficient was 0.25 ($P < .001$) and 0.33 ($P < .001$) for the superior and inferior areas of parapapillary atrophy, respectively.

*Standardized β = Standardized partial regression coefficient.

†Superior or inferior disk area corresponding to the area of parapapillary atrophy, respectively.

PPA = parapapillary atrophy.

The superior hemifield is damaged more often in early-to-moderate open-angle glaucoma[33] or angle-closure glaucoma.[34] The superior area just above the horizontal meridian is more vulnerable, especially in NTG eyes.[22] The inferior hemifield was reportedly more likely to sustain damage in patients with open-angle glaucoma with diabetes mellitus[23,24] or in patients with NTG with ischemic changes on cerebral magnetic resonance imaging.[25] The most frequently occurring visual field defect in nonarteritic anterior ischemic optic neuropathy is an altitudinal defect that involves the inferior hemifield.[35,36] Those studies suggest the presence of different characteristics between the superior and inferior regions of visual field or the ONH regarding the vulnerability to increased intraocular pressure or other challenges. Our results (that a significant correlation with the corresponding VFD was found only for the inferior PPA area but not for the superior PPA area) suggest that PPA itself or the causes of PPA might reflect the differences in vulnerability between the superior and inferior regions of the ONH.

The importance of evaluating PPA in diagnosis and/or follow-up of glaucoma has been recognized widely.[1–21] Because only patients with NTG were included in this study, the influence of intraocular pressure on the development of PPA is hard to determine with these data, and further investigation on patients with open-angle glaucoma with elevated intraocular pressure should be necessary. The results of the current study suggest that the inferior area of PPA may have more clinical importance in association with glaucoma. The differences in correlations with VFD between the superior and inferior areas of PPA may be noteworthy when considering the vulnerability of the ONH in patients with NTG.[30]

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Frequency Doubling Technology Perimetry in Open-angle Glaucoma Eyes With Hemifield Visual Field Damage: Comparison of High-tension and Normal-tension Groups

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Purpose: To evaluate the performance of frequency doubling technology (FDT) perimetry in open-angle glaucoma eyes with hemifield visual field damage and to compare it between open-angle glaucoma with high pressure [high-tension glaucoma (HTG)] and those with normal pressure [normal-tension glaucoma (NTG)] groups.

Methods: FDT perimetry with the N-30 full threshold protocol and standard automated perimetry (SAP) using the Humphrey Field Analyzer with the 30-2 full threshold protocol were performed in 20 eyes of 20 HTG patients and 36 eyes of 36 NTG patients with visual field damage confirmed with SAP in only one hemifield.

Results: There was no significant difference in demographics, the Heidelberg Retina Tomography indices, and the Humphrey Field Analyzer indices between HTG and NTG groups. Regarding the FDT perimetry results, mean deviation in the global field ($P = 0.009$) and mean sensitivity in the SAP-spared ($P = 0.001$) and SAP-impaired ($P = 0.011$) hemifields were lower; the numbers of FDT abnormal test points (probability of abnormality $< 5\%$) in the SAP-spared hemifield were significantly greater ($P = 0.005$) in HTG than in NTG groups. Eyes in which FDT results of the SAP-spared hemifield were judged as abnormal was more frequent in HTG groups ($P = 0.007$).

Conclusions: The performance of FDT perimetry to detect early or preperimetric glaucomatous functional changes should be different between HTG and NTG eyes.

Key Words: open-angle glaucoma, hemifield visual filed damage, frequency doubling technology perimetry, intraocular pressure

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Frequency doubling technology (FDT) perimetry is reportedly a useful tool to detect early glaucomatous visual field damage (VFD) compared with such as a standard automated perimetry (SAP),[1] which hardly detects early glaucomatous functional abnormalities until 20% to 40% of the retinal ganglion cells have gone.[2] In glaucomatous eyes with hemifield VFD, functional abnormality even in the SAP-spared hemifield were often found using FDT,[3,4] also suggesting better performance of FDT for detecting early or preperimetric functional damage.

It has been reported that FDT perimetry more sensitively reflects functional abnormalities in magnocellular pathway.[5,6] Axonal transport to the magnocellular layers of the lateral geniculate body was more notably decreased than that to the parvocellular layer in a monkey glaucoma model with chronic elevated intraocular pressure (IOP).[7] Therefore, differences in the performance of FDT perimetry between open-ange glaucoma (OAG) with elevated IOP [high-tension glaucoma (HTG)] and that with normal IOP [normal-tension glaucoma (NTG)] may be suggested. In fact, Kogure et al[8] reported that greater numbers of abnormal points were found with FDT than with SAP in HTG eyes, whereas the numbers were equivalent between FDT and SAP in NTG eyes. Horikoshi et al[9] reported that mean deviation (MD) of FDT was significantly lower in HTG than in NTG, whereas MD of SAP was not different. The subjects in these studies, however, were HTG/NTG eyes with VFD already evident with SAP, and to our knowledge differences in performance of FDT to detect subclinical or very early functional abnormalities between HTG and NTG eyes have never been studied. The aim of this cross-sectional study was to evaluate the differences in the ability of FDT to detect early functional changes in the SAP-spared hemifield between HTG and NTG.

PATIENTS AND METHODS

Patients of OAG were consecutively included from the outpatient clinic of the Department of Ophthalmology of the University of Tokyo Graduate School of Medicine between May 2001 and March 2002. The diagnosis of primary OAG was made according to typical glaucomatous optic disc cupping and VFD in eyes with

normally open angles and the absence of any contributing ocular or specific systemic disorders. The inclusion criteria were: (1) presence of primary OAG, (2) well-controlled IOP with topical medication or none, (3) no history of intraocular surgeries except laser procedures, (4) corrected visual acuity ≥ 0.7, (5) refractive error $\leq \pm 8$ diopters (D), (6) no media opacities, (7) reliable (fixation loss $< 20\%$ and false positive/negative error $< 33\%$) visual field results with the Humphrey Field Analyzer (HFA, Carl Zeiss Meditec, Dublin, CA) 30-2 full threshold test, and (8) hemifield VFD in the superior or inferior field. Hemifield VFD was determined according to the Caprioli's criteria[10] based on reliable SAP results: impaired hemifield was superior or inferior hemifield with more than 2 adjacent points of which sensitivity loss was 5 dB or more in total deviation or hemifield with more than 1 adjacent point of which sensitively loss was 10 dB or more; spared hemifield had no more than 1 point of which sensitivity loss was more than 5 dB.

SAP testing using the HFA with the 30-2 full threshold test and FDT with the N-30 full threshold protocol were newly obtained for the current study with a 3 or less month interval. All of the patients had experienced the HFA testing twice or more before this study, whereas most of them did not have experience of FDT testing. Unless a patient had experience of FDT testing twice or more, he/she underwent preceding 2 examinations using the C-20 screening protocol and the N-30 full threshold protocol, respectively, to exclude unreliable FDT results during the period with the initial learning curve.[11] On another day following these preceding examinations, the N-30 testing was repeated to obtain a result which was included for this study. If the last result was unreliable (false positive/negative trials $\geq 33\%$ or fixation losses $\geq 20\%$), it could be repeated only once. If the next trial was also unreliable, the patient was excluded. Hemifields of the FDT results were evaluated according to the criteria[4] obtained by modifying those of Quigley[12] and Sponsel et al.[13] A normal hemifield had none or 1 abnormal square with probability of 5%, 2%, or 1% and no abnormal square with probability of 0.5%; and abnormal hemifield had 2 or more abnormal squares with probability of 5%, 2%, or 1%, or one or more abnormal squares with probability of 0.5%.

Data on clinical history including IOP, glaucoma medications, presence or absence of disc hemorrhage during the follow-up periods were retrospectively obtained from the clinical chart. Data of the Heidelberg Retina Tomography II (HRT II, Heidelberg Engineering, GmbH. Heidelberg, Germany) acquired within 1 year before or during this study were also reviewed. The indices included in the current study were disk area, cup area, rim area, height variation contour, cup-shape measure, and mean retinal nerve fiber layer thickness.

The OAG patients included were divided into 2 groups; those with eyes with the highest IOP higher than 21 mm Hg (HTG group) and those with eyes with the highest IOP equal to or lower than 21 mm Hg (NTG group). The highest IOP indicated the uppermost value in IOPs recorded without any glaucoma therapies. Most of the patients in the NTG group had experience of testing the 24-hour diurnal changes in IOP to confirm the diagnosis of NTG, but few of the patients in the HTG group had undergone the test. Corneal thickness was not obtained in the current patients.

Statistical Analyses

The demographic data and the results of SAP and FDT were compared between HTG and NTG groups. Because the present data were not confirmed to show normal distribution and due to the small patient sample, nonparametric statistical tests were applied for the analyses. Means of data were compared between the groups with Mann-Whitney test. Proportions between males and females or between right and left eyes were compared between the groups using χ^2 test or Fisher exact test. A P value less than 0.05 was considered statistically significant. Statistical analyses were performed using a statistical software package, SPSS 13.0J for Windows (SPSS Japan Inc, Tokyo, Japan).

RESULTS

Twenty eyes of 20 patients and 36 eyes of 36 patients were included in the HTG and NTG groups, respectively. There was no significant intergroup difference in the patients' demographics except the highest IOP and the IOP at entry. The highest IOP and the IOP at entry were significantly higher by 5.9 and 2.5 mm Hg in the HTG group compared with the NTG group ($P < 0.001$ and < 0.001, respectively, Mann-Whitney test). There was no significant intergroup difference in the prevalence of disc hemorrhage ($P = 0.16$, Fisher exact test) (Table 1). The indices of HRT II were not significantly different between the groups ($P > 0.14$, Mann-Whitney test, Table 2).

Seven eyes (35%) in the HTG group and 14 (39%) in the NTG group had hemifield defects in the lower side; and 13 (65%) and 22 (61%) had it in the upper side, respectively, in the SAP results. As to the HFA indices, there was no significant difference in MD, pattern

TABLE 1. Comparison of the Demographics Between Patients With HTG and Those With NTG

	HTG	NTG	*P*
No. eyes	20	36	—
Age (y)	59.4 ± 7.5	57.5 ± 9.3	0.44*
Male/female	12/8	18/18	0.57†
Right/left eyes	13/7	23/13	0.99†
Refraction (D)	−3.7 ± 2.6	−2.8 ± 3.7	0.32*
Highest IOP	23.8 ± 3.2	17.9 ± 2.5	< 0.001*
IOP at entry	16.7 ± 2.6	14.1 ± 2.5	< 0.001*
Presence of disc hemorrhage	6/20	4/36	0.16†

Mean ± standard deviation.
P indicates *P* value in comparison of means or frequency between the HTG and NTG groups (*with Mann-Whitney test, †with χ^2 test or Fisher exact test).

TABLE 2. Comparison of the Indices of the HRT Between Patients With HTG and Those With NTG

	HTG	NTG	*P*
No. eyes	20	36	—
Disk area (mm^2)	2.22 ± 0.34	2.27 ± 0.66	0.67
Cup area (mm^2)	1.17 ± 0.47	1.11 ± 0.63	0.57
Rim area (mm^2)	1.05 ± 0.33	1.17 ± 0.26	0.14
Height variation contour (mm)	0.39 ± 0.09	0.44 ± 0.17	0.47
Cup-shape measure	−0.09 ± 0.07	−0.11 ± 0.08	0.57
Mean RNFL thickness (mm)	0.21 ± 0.08	0.22 ± 0.10	0.91

Mean ± standard deviation.

Mean RNFL thickness indicates mean retinal nerve fiber layer thickness; *P*, *P* value in comparison of means between the HTG and NTG groups with Mann-Whitney test.

standard deviation, mean sensitivity in the SAP-spared and SAP-impaired hemifields, and mean total deviation in the SAP-spared and SAP-impaired hemifields between the HTG and NTG groups ($P > 0.1$, Mann-Whitney test) (Table 3).

Regarding the results of FDT N-30, MD in the global field ($P = 0.009$, Mann-Whitney test) and mean sensitivity in the SAP-spared ($P = 0.001$) and SAP-impaired ($P = 0.011$) hemifields were significantly lower in HTG group than in NTG group. The numbers of abnormal test points (probability of abnormality < 5%) were significantly smaller in NTG group in the SAP-spared hemifield ($P = 0.005$). Eyes in which FDT results of the SAP-spared hemifield were judged as abnormal according to the modified abnormality criteria[4] was more frequent in HTG group (65%) than in NTG group (33%) ($P = 0.007$, χ^2 test) (Table 4).

DISCUSSION

The current results showed that as to the SAP-spared hemifield the mean sensitivity of FDT perimetry was lower and FDT detected greater numbers of abnormal test points in the HTG group than in the NTG group between which the background data were identical except IOP. This finding contrasts to the fact that the mean of total deviation value in the SAP-spared hemifield tended to be better in the HTG group although the difference was not statistically significant. In OAG eyes with superior or inferior hemifield VFD, functional or morphologic abnormalities were found even in the SAP-spared hemifield using multifocal visual evoked potential technique[14] or scanning laser polarimetry[15,16] and also FDT perimetry.[3,4] In addition to these previous studies, the current study first suggested differences in functional abnormality in the SAP-spared hemifield between HTG and NTG eyes.

Most of the patients had no or little experience of FDT testing prior to this study. As to the learning effects of initial FDT perimetry, Matsuo et al[11] found significant improvement of the FDT perimetry results between the first and second tests but no significant changes between the second and third tests, suggesting the importance of at least 2 preceding tests to obtain reliable FDT perimetry results. Therefore, for the patients who had no experience of FDT perimetry in the current study, 2 sessions of FDT testing with the C-20 screening protocol and the N-30 full threshold protocol, respectively, were performed before obtaining the examination adopted for the analyses.

In the current study, eyes with refractive error less than ± 8 D were included. Because high myopic eyes are relatively common in Japanese population[17] and probably more common among glaucoma patients,[18] if moderate to high myopic eyes were excluded, the studied subjects would become relatively far from the true population of Japanese glaucoma patients. On the other hand, although the refractive error of each patient was corrected according to the manufacturers' recommendation, the influence of myopia on the results of SAP or FDT perimetry could not be ignored. However, if the eyes with myopia < −5 D were excluded from the studied eyes, the means and standard deviations of the FDT and SAP indices would be little changed. For example, the FDT mean sensitivity in the SAP-spared hemifield would be changed from 24.16 ± 3.11 to 23.93 ± 3.74 dB for HTG and from 27.28 ± 3.22 to 27.37 ± 3.14 dB for NTG. This suggests that the influence of high myopic eyes on the current results should not be so large.

TABLE 3. Comparison of the Results of the HFA With the Central 30-2 Full Threshold Test Between Patients With HTG and Those With NTG

	Hemifield	HTG	NTG	*P*
No. eyes	—	20	36	—
MD (dB)	—	−4.03 ± 3.55	−3.43 ± 2.83	0.72
Pattern standard deviation (dB)	—	8.38 ± 5.03	7.14 ± 4.04	0.54
Mean sensitivity (dB)	Spared	27.91 ± 1.66	27.57 ± 1.70	0.38
	Impaired	18.99 ± 7.06	21.42 ± 5.84	0.36
Mean total deviation (dB)	Spared	0.36 ± 1.46	−0.25 ± 1.53	0.17
	Impaired	−9.04 ± 7.45	−6.55 ± 6.03	0.53

Mean ± standard deviation.

P indicates *P* value in comparison of means between the HTG and NTG groups (Mann-Whitney test); Spared (impaired), spared (impaired) hemifields determined with the HFA results.

TABLE 4. Comparison of the Results of the FDT Perimetry With the N-30 Full Threshold Test Between Patients With HTG and Those With NTG

	Hemifield	HTG	NTG	P
No. eyes	—	20	36	—
MD (dB)	—	−5.59 ± 3.19	−4.13 ± 3.18	0.009*
Mean sensitivity (dB)	Spared	24.16 ± 3.11	27.28 ± 3.22	0.001*
	Impaired	15.33 ± 6.6	19.98 ± 6.2	0.011*
No. abnormal test points	Spared	3.20 ± 2.8	1.14 ± 0.25	0.005*
	Impaired	6.30 ± 2.1	4.89 ± 2.6	0.051*
Rate of eyes with abnormal FDT results in the HFA-spared hemifield	—	13/20	12/36	0.007†

Mean ± standard deviation.

P indicates *P* value in comparison of means or proportions between the HTG and NTG groups (* with Mann-Whitney test and † with χ^2 test); spared (impaired), spared (impaired) hemifields determined with the HFA results.

Between the HTG and NTG groups in the current study, difference in IOP at the entry averaged about 2.5 mm Hg and that in the highest IOP in their clinical charts averaged about 6 mm Hg. Because IOP varied due to medications or other factors, actual differences in mean IOP throughout their clinical history between the HTG and NTG eyes were hardly determined. However, it should be certain that eyes in the HTG group had been exposed to higher IOP for longer period than those in the NTG group. Between the HTG and NTG groups, there was no significant difference in refraction, the morphology of the optic disc evaluated with the HRT II, and prevalence of disc hemorrhage. Although difference in other important factors, including corneal thickness, and unknown factors in the patients' background between the 2 groups can not be excluded, differences in IOP should be one of main causes for discrepancy in the FDT results in the SAP-spared hemifield.

HTG and NTG should be included in the same or continuously spreading clinical entity, which is OAG. IOP is believed to be the most important risk factor for OAG. It can be speculated that IOP plays the more vital role in OAG patients with the higher IOP. On the other hand, risk factors other than IOP may be relatively more involved with the pathogenesis of OAG in patients with lower IOP. Therefore, even small differences in IOP such as 6 mm Hg between HTG and NTG groups in the current study should have possible impact on the clinical findings of OAG, and it should deserve careful investigation. In previous studies,[19,20] the reduction in IOP by approximately 5 mm Hg by medical or surgical therapies showed significant effects to halt or slow the deteriorations in visual field defects or optic disc findings in NTG, suggesting that a 6-mm Hg difference in IOP between HTG and NTG patients in the current study should have clinical implication.

One limitation of this study is the limited number of the patients. However, among the same number of the patients, the results of FDT were significantly different between the HTG and NTG patients with *P* value ranged 0.005 to 0.001 in the SAP-spared hemifield (Table 4), whereas there was no intergroup difference in the HFA indices with *P* value larger than 0.17 (Table 3). A statistical power analysis, with α of 0.05 and the power of 0.8, revealed that if we try to detect the difference in the mean sensitivity of 0.34 dB, which is the intergroup difference in the SAP mean sensitivity in the SAP-spared hemifield (Table 3), the sample size needed is calculated as approximately 760 (380 vs. 380) subjects. Another limitation of the current study is the lack of measurements of corneal thickness which possibly influence the IOP measurements.[21] If corneal thickness were obtained in the current study, some of the patients would be classified into the different group after the correction of IOP using corneal thickness. This should deserve future studies when an appropriate correction method of IOP with corneal thickness will be available.

Although it has recently become the subject of debate, the magnocellular pathway was reportedly more predominantly damaged by chronically elevated IOP in monkey eyes.[7] Magnocellular pathway is thought to play a role in abnormality in FDT perimetry.[5,6] Therefore, it is likely that the current result suggests possible association between elevated IOP and abnormality in FDT results although it should be confirmed by future studies including longitudinal follow-up of greater numbers of the patients. In other words, as to the detection of preperimetric or early functional changes in glaucomatous eyes, FDT perimetry may have higher sensitivity in OAG eyes with higher IOP.

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